

An Overview of Achalasia Cardia

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ABSTRACT

Achalasia is one of the most studied esophageal motility disorders. However, the pathophysiology and reasons that patients develop achalasia are still unclear. Patients often present with dysphagia to solids and liquids, regurgitation, and varying degrees of weight loss. There is significant latency prior to diagnosis, which can have nutritional implications. The diagnosis is suspected based on clinical history and confirmed by esophageal high-resolution manometry testing. Esophagogastroduodenoscopy is necessary to rule out potential malignancy that can mimic achalasia. Recent data presented in abstract form suggest that patients with type II achalasia may be most likely, and patients with type III achalasia may be least likely, to report weight loss compared to patients with type I achalasia. Although achalasia cannot be permanently cured, palliation of symptoms is possible in over 90% of patients with the treatment modalities currently available (pneumatic dilation, Heller myotomy, or peroral endoscopic myotomy). This article reviews the clinical presentation, diagnosis, and management options in patients with achalasia, as well as potential insights into histopathologic differences and nutritional implications of the subtypes of achalasia.

Keywords: Achalasia, histopathology, weight loss, nutrition

INTRODUCTION:

Achalasia is a rare esophageal motility disorder characterized by esophageal aperistalsis and impaired relaxation of the lower esophageal sphincter (LES) during deglutition. The annual incidence of achalasia is approximately 1 in 100,000 people worldwide, with an overall prevalence of 9 to 10 in 100,000 people.¹⁻⁴ Patients often present with progressive dysphagia to solids and liquids, heartburn, chest pain, regurgitation, and varying degrees of weight loss or nutritional deficiencies.^{5,6} Table 1 outlines the prevalence of various presenting symptoms in patients with achalasia. Patients with suspected achalasia based on clinical presentation should always undergo an upper esophagogastroduodenoscopy (EGD) to rule out pseudoachalasia from an obstructing mass. The diagnosis of achalasia is confirmed with high-resolution manometry (HRM), which is the current gold standard test.⁷

Prevalence of Symptoms in Patients With Achalasia

Presenting Symptom	Patients Reporting the Symptom
Dysphagia	82%-100%
Regurgitation	76%-91%
Weight loss	35%-91%
Chest pain	25%-64%

Presenting Symptom	Patients Reporting the Symptom
Heartburn	27%-42%
Nocturnal cough	37%
Aspiration	8%

Achalasia is a heterogeneous disease categorized into 3 distinct types based on manometric patterns: type I (classic) with minimal contractility in the esophageal body, type II with intermittent periods of panesophageal pressurization, and type III (spastic) with premature or spastic distal esophageal contractions (Figure 1). These subtypes have subtle differences in clinical presentation but have distinct responses to various treatment modalities, including pharmacologic, endoscopic, and surgical methods.

This article provides an overview of the clinical presentation, pathogenesis, diagnosis, and management of achalasia, as well as the potential nutritional implications among manometric subtypes I, II, and III.

Clinical Presentation:

Achalasia can initially present with a variety of symptoms (Table 1) that impair a patient's quality of life, work productivity, and functional status. Classically, achalasia presents as progressive dysphagia to solids and liquids. Heartburn may present in 27% to 42% of patients with achalasia, and, thus, patients are frequently misdiagnosed with gastroesophageal reflux disease (GERD) and treated with proton pump inhibitor (PPI) therapy. An incorrect GERD diagnosis often leads to a significant delay in diagnosing achalasia, until patients have persistent symptoms that eventually lead to the correct diagnostic studies. Dysphagia and regurgitation are common among all ages, but younger patients are more likely to have chest pain and heartburn.¹¹ Obese patients (body mass index [BMI] ≥ 30) may have more frequent choking or vomiting symptoms. Women and patients with type III achalasia are more likely to present with chest pain. Furthermore, studies show that 35% to 91% of patients report weight loss during initial presentation. The degree of weight loss is widely variable, with an average weight loss of 20 ± 16 lbs.

Achalasia and Weight Loss:

Due to the paucity of data, it is currently unknown why some patients with achalasia lose weight and other patients do not. One of the pioneer studies evaluating clinical response in patients with achalasia who underwent pneumatic dilation (PD) in the 1970s noted weight loss in approximately 91% of patients (n=264), with 16 patients reporting over 20 kg of weight loss and 18 patients reporting 5 kg of weight loss.¹⁵ However, a significant number of patients in this study had diagnostic latency, with the noted duration of their symptoms ranging from 2 to over 20 years prior to diagnosis and treatment. This delay in diagnosis is fairly common in patients with achalasia. Most patients post-PD are noted to rapidly regain weight; in the aforementioned study, weight loss was only observed in less than 6% of patients at 3 to 13 years of follow-up.¹⁵ Since that study, no further insight into weight loss in achalasia has been made.

In a retrospective study assessing clinical, radiologic, and manometric profiles of 145 patients with untreated achalasia, 31% of patients with classic achalasia reported weight loss compared to 43% of patients with vigorous achalasia. Both groups reported approximately 20 ± 16 lbs of weight loss, but there was a significantly higher percent of patients with vigorous achalasia who had normal LES pressure (49% vs 13%). Thus, it is unclear whether LES physiology is related to the presence or absence of weight loss, as it would be expected that patients with higher baseline LES pressure report more weight loss. Further research evaluating differences in clinical presentation based on sex did not note any differences in the mean duration of symptoms, age at diagnosis, or mean weight loss between men and women.

Nutritional Implications:

Nutrition in patients with achalasia is often overlooked because it is presumed that treatment of LES restrictive physiology should resolve dysphagia and normalize oral intake. There are currently no published studies evaluating nutrition in this population and whether treatment truly improves overall nutrition. Two studies in this area have been performed by our group, but the findings have been reported only in abstract form to date and have not yet been published in full after a peer review process. In one study, we prospectively evaluated the nutritional status of 19 patients with untreated achalasia; 80% of patients reported having altered their diet due to swallowing difficulties, and 90% reported consuming less than usual. Furthermore, 80% of patients in this cohort reported an estimated weight loss of approximately 40 lbs over the course of 6 months.¹⁶ More importantly,

laboratory data showed that 75% of patients had low prealbumin levels, which is a marker of poor nutrition.¹⁶ In a subsequent retrospective study of 100 patients with achalasia, we assessed demographic, clinical, and manometric characteristics to determine potential correlates of weight loss in this population. Weight loss was reported in 51% of patients, with a mean weight loss of 28 lbs (14-40 lbs); as expected, BMI was significantly lower in patients with a reported weight loss (median BMI, 25 vs 31; $P < .001$).¹⁷ There were no significant differences in age at diagnosis, sex, or symptom presentation (dysphagia, regurgitation, or chest pain) between the groups. However, a significant percentage of patients with type II achalasia (63%) reported weight loss compared to other subtypes. Seventy-three percent of patients with type III achalasia denied having any weight loss. Thus, patients with type II achalasia may be most likely, and patients with type III achalasia may be least likely, to have weight loss compared to type I achalasia.¹⁷

Interestingly, patients who denied having any weight loss were noted to have symptoms for a significantly longer time (24 vs 12 months; $P < .01$), which might be suggestive of a lack of dietary adaptations in patients with a shorter duration of symptoms. Furthermore, patients with weight loss did have higher mean residual LES pressure (30 vs 20 mm Hg; $P = .006$).¹⁷ Postintervention, 43% of patients denied regaining their weight even after undergoing therapy for achalasia (PD or surgical myotomy), with a median follow-up period of 22 months (range, 6-90 months). There were no differences in the postintervention modified achalasia dysphagia score between patients with and those without weight loss.¹⁷ However, it should be noted that this study was primarily a descriptive retrospective study aimed at finding potential correlates of weight loss in patients with achalasia. Thus, prospective longitudinal studies are needed to better evaluate potential implications of weight loss in this population.

There are currently no studies evaluating dietary modification as adjunctive treatment in patients with achalasia (pre- or postintervention). Physiologically, a low-fiber diet (defined as a maximum of 10 g of fiber/day) could be considered in these patients, similar to patients who have small bowel strictures. Soluble fiber increases the viscosity of the bolus, which reduces absorption, and insoluble fiber possesses high water-binding capacity and increases the bulk of the bolus.⁸ Thus, in the setting of high LES pressure (physiologic obstruction) in patients with achalasia, a low-fiber diet would potentially allow easier passage through a small narrowing. Some patients with significant weight loss and severe malnutrition may need to switch to high-calorie and -protein liquids, which should be coordinated under the guidance of a registered dietitian due to the potential risk of refeeding syndrome.⁸ However, it should be noted that despite concerns of significant weight loss in this population, refeeding syndrome has been rarely reported in the literature, with only 1 case report of new-onset Wernicke encephalopathy in a pregnant woman with achalasia.¹⁸ There is also significant overlap between clinical presentations of eating disorders and achalasia, which can often lead to misdiagnosis, especially in young women.¹⁹ Research is currently underway to develop an evidence-based dietary recommendation in patients with achalasia.

Pathophysiology:

Despite achalasia initially being described nearly 300 years ago, the underlying etiology and molecular pathology of why patients develop this disease are still vastly unclear. This lack of clarity is the primary reason that the treatment of achalasia has not evolved significantly over the years from primarily using brute force (PD), surgical myotomy, or peroral endoscopic myotomy [POEM]) to mechanically disrupting the LES. The primary etiology of achalasia is thought to be selective loss of inhibitory neurons in the myenteric plexus of the distal esophagus and LES resulting in a neuronal imbalance of excitatory and inhibitory activity. Excitatory neurons release acetylcholine while inhibitory neurons primarily release vasoactive intestinal peptide (VIP) and nitric oxide (NO).²⁰ A localized decrease of VIP and NO with unopposed excitatory activity causes failure of LES relaxation and loss of esophageal peristalsis.²¹

Multiple studies have suggested a possible association between achalasia and infections, including parasitic and viral ones. Patients with Chagas disease (*Trypanosoma cruzi*) have a pathophysiology similar to that of primary achalasia. Some studies have found an increased prevalence of serum viral antibodies in patients with achalasia, specifically for herpes simplex virus (HSV), human papilloma virus, and the measles virus, compared to control patients. Other studies have detected HSV-1 DNA (viral infection), RNA (active replication), and virus in surgical myotomy samples from patients with achalasia. In addition, multiple case-control studies and a volume genetic association study have shown the contribution of human leukocyte antigen class II genes in the susceptibility of achalasia.

More recently, a newer focus in evaluating the molecular pathology of patients with achalasia has strengthened the consideration of achalasia as an autoimmune inflammatory disorder. This is supported by the presence of

myenteric antibodies in the circulation and inflammatory T-cell infiltrates in the myenteric plexus of patients with achalasia. Furthermore, patients with achalasia are 3.6 times more likely to have other autoimmune diseases, including uveitis, type I diabetes, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome. Serum from patients with achalasia, but not from patients with GERD, can induce phenotypic and functional changes in myenteric neurons, which reproduce the characteristics of the disease. A recent cross-sectional study compared immunohistochemical stains of 26 LES muscle specimens from patients with achalasia to those of controls (5 esophagectomy biopsies from patients with proximal esophageal cancer). Histopathologic analysis showed capillaritis (51%), plexitis (23%), nerve hypertrophy (16%), venulitis (7%), and fibrosis (3%). More importantly, tissue from patients with achalasia had increased expression of proteins involved in extracellular matrix turnover, apoptosis, proinflammatory cytokines, and profibrogenic cytokines. Patients with type III achalasia exhibited the highest inflammatory response vs types I and II. Patients with type I achalasia did have higher profibrogenic cytokines (transforming growth factor- β) compared to type II or III. Both myenteric antibodies and HSV-1 infection (determined by in situ hybridization) were found in 100% of patients with achalasia. Another study showed that the myenteric plexus ganglion cell loss was greater in type I achalasia specimens than in type II achalasia specimens, suggesting that type I achalasia likely represents disease progression from type II achalasia. More research, particularly prospective, is needed to determine whether differences in underlying inflammatory cascade might also contribute to weight loss in addition to restrictive LES physiology.

Diagnosis:

Every patient with clinical suspicion of achalasia should undergo an EGD to evaluate for pseudoachalasia. A barium swallow is useful for assessing esophageal morphology and motility, and at times is the test in which the diagnosis of achalasia is initially suspected. However, endoscopic and radiologic studies alone may identify only up to 50% of achalasia; thus, the gold standard diagnostic test is HRM, which can classify achalasia into its 3 subtypes.

Endoscopy:

Approximately 2% to 4% of patients with suspected achalasia have pseudoachalasia from infiltrating malignancy or stricture. Potential risk factors for malignancy-associated pseudoachalasia include older age at the time of diagnosis, shorter duration of symptoms, and more weight loss (12 vs 5 kg) on presentation. Patients with 2 or more of these risk factors on presentation should undergo careful investigation to rule out malignancy. Classic visual findings include a dilated esophageal body with a puckered LES and proximally retained food and saliva. However, the esophagus may appear normal or with sequelae of stasis, including superficial ulcers, esophagitis, or candidiasis. The LES may remain closed with insufflation, but the endoscope should pass with gentle pressure. An excessively tight LES may indicate infiltration, and one study showed that the LES was difficult or impossible to pass during endoscopy in 61% of patients with pseudoachalasia compared with 23% of patients with achalasia. A high suspicion of malignancy should be evaluated with biopsy, endoscopic ultrasound, or chest/abdominal computed tomography scan.

Barium esophagram:

A barium esophagram is a noninvasive radiologic study that can assist with initial diagnosis or response to treatment with graded PD. A barium swallow evaluates the morphology of the esophagus and classically shows a dilated or tortuous esophagus with a narrowed LES and "bird's beak" appearance. A timed barium esophagram may help predict the effectiveness of treatment. By taking radiographs at 1, 2, and 5 minutes postbarium, it is possible to evaluate esophageal emptying. Although symptoms may not correlate directly with column height, the rate of barium emptying is predictive of long-term success after treatment.

Manometry:

HRM is the gold standard test for the diagnosis of achalasia. Conventional manometry tracings in patients with achalasia show the absence of esophageal peristalsis and incomplete LES relaxation with residual pressures of over 10 mm Hg. HRM with esophageal pressure topography is more sensitive and specific than conventional manometry and is able to classify achalasia into 3 distinct subtypes, which can have treatment implications.⁷ Type II achalasia has the best response to treatment, followed by type I achalasia, whereas type III achalasia is the most difficult to treat. Clinical success in achalasia trials is often defined using the Eckardt score (maximum score of 12), which is the sum of symptom scores for dysphagia, regurgitation, chest pain, and weight loss. A

postintervention Eckardt score of less than 3 is defined as clinical remission, but there has been a lack of objective measures used as markers of remission in patients with achalasia (such as weight gain postintervention). In one study evaluating treatment outcome implications with either PD or laparoscopic Heller myotomy (LHM) in 176 patients with achalasia, the Eckardt score was 3 or less postintervention in 96% of patients with type II achalasia, 81% with type I achalasia, and 66% with type III achalasia, but there were no significant differences between reported weight loss scores within the subtypes. Future clinical trials using objective pre- and postintervention weight are needed to understand the relationship between improvement in dysphagia and postintervention weight changes.

Management:

There is no cure for achalasia. Thus, treatment is aimed at relieving symptoms by improving LES physiology, which leads to reduced functional obstructions and facilitates esophageal emptying. This may be achieved through pharmacologic, endoscopic, or surgical methods. The choice of treatment depends on patient comorbidities, symptom severity, patient preference, and provider expertise (Figure 6). In general, the most effective and long-term treatments are PD or myotomy via laparoscopy or endoscopy.⁵ High-risk surgical patients may temporarily benefit from noninvasive management with oral medications or localized botulinum toxin (BT) injection.

Pharmacologic Treatment:

Oral therapies are the least effective treatment option for achalasia. The 2 most commonly utilized classes of oral medications include calcium channel blockers (CCBs) and nitrates. CCBs such as nifedipine (10-30 mg; given 30-45 min before meals) decrease LES resting pressure by 13% to 49% and improve symptoms in up to 75% of patients.⁵ Effectiveness varies, as absorption is unpredictable and limited by side effects (including headaches, orthostatic hypotension, and lower extremity edema) in up to 30% of patients. Sublingual nitrates may be slightly more effective than sublingual nifedipine, with one study showing a 65% vs 49% response rate. However, sublingual nitrates are very short-acting and must be taken 10 to 15 minutes before eating. Side effects include tachycardia, and many patients develop tachyphylaxis. Less commonly used medications include anticholinergics (atropine, cimetropium bromide), β -adrenergic agonists (terbutaline), and theophylline. More recently, sildenafil has also been shown to decrease LES tone and residual pressure in patients with achalasia.⁴⁸ However, due to transient effectiveness, the inability to halt disease progression, and the likelihood of side effects, oral medications should be used only in patients who need a bridge to more effective therapy, in nonsurgical candidates, or in patients who have failed BT injections.

BT injection for achalasia is an effective short-term therapy. BT injection into the LES locally inhibits the release of acetylcholine, causing relaxation of the smooth muscle, which allows for easier passage of food bolus into the gastric body. Multiple studies have identified certain factors that predict a prolonged and favorable response; these factors include age greater than 40 years and type II or III achalasia. Most patients (as high as 90%) have symptom relief within the first month of BT injection. However, over 50% of these patients will experience a return of their symptoms within 1 year, requiring repeat injections. As shown in multiple randomized, controlled trials, BT injections are less efficacious and have a shorter duration of effectiveness when compared directly to PD or surgical myotomy. This treatment should be used only for high-risk surgical patients and should not be used prior to PD or surgical myotomy because of the increased risk of perforation from the potential development of fibrosis.

Pneumatic Dilation:

The most effective nonsurgical treatment option for achalasia is PD.⁵ A polyethylene balloon is endoscopically deployed and filled with air to apply 7 to 15 psi across the LES for 15 to 60 seconds. The radial force disrupts the muscularis propria of the LES, thus decreasing the hypertonicity. Patients benefit most from a graded approach with increasing diameters (3.0-4.0 cm), which may provide a 90% response rate at 6 months and 44% response rate at 6 years. Predictors of favorable clinical response include older age (>45 years), female sex, a narrow esophagus, and type II pattern of achalasia on HRM. Using this graded approach, many patients can remain in remission for 5 to 10 years. If patients continue to have symptoms, surgical options should be explored, particularly in younger patients who may respond more favorably.⁵

Myotomy:

The primary surgical goal in the treatment of achalasia is a myotomy of the circular muscle fibers of the LES to create a long-lasting decrease in residual LES pressure. The 2 accepted strategies are LHM with a possible

concurrent fundoplication and POEM. Both methods are very effective and should be considered with PD as first-line therapies in appropriate surgical candidates. All therapies, including POEM, should only be done in medical centers with providers who have experience performing the procedures and managing potential complications.

Laparoscopic Heller Myotomy:

LHM performed with or without antireflux fundoplication (Dor vs Toupet) is a highly effective treatment for achalasia. Originally performed as an open thoracotomy and laparotomy, the less-invasive laparoscopic approach has similar efficacy rates but decreased morbidity.^{4,5} LHM provides excellent symptom relief, with efficacy rates ranging from 88% to 95% and lasting for 6 to 10 years.^{7,8} It is recommended that the myotomy extends 4 to 5 cm in the distal esophagus and 2 to 3 cm into the stomach.⁹ Intraoperative complications include esophageal perforation, which may occur in approximately 6.9% of patients, although most of these complications may be repaired immediately during the surgery.⁶ The most common side effect post-LHM is the development of GERD. Fundoplication can reduce the chance of developing GERD from 41.5% to 14.5%. Both Dor and Toupet fundoplications are similarly effective in reducing the risk of GERD after a LHM.

Favorable patient characteristics for LHM include younger men, a tortuous esophagus, an esophageal diverticulum, or previous esophageal surgery. As with PD, patients with type II achalasia respond better (93%) than patients with type I (81%) or III (86%).³

Peroral Endoscopic Myotomy:

POEM is one of the most recent advances in the treatment of achalasia. This method was first described in the 1980s, but underwent extensive revision and development in the 2000s.³ Over 5000 patients have now undergone the procedure.⁴ A submucosal tunnel is created in the esophagus approximately 10 cm proximal to the gastroesophageal junction, and a myotomy of circular muscle layers is distally extended to 2 cm into the cardia. Two large European and US multicenter trials have reported short-term efficacy rates similar to those of LHM and a response rate of over 90%. Furthermore, long-term follow-up in a cohort of 500 patients showed excellent symptom control over a 3-year period, and POEM has similar efficacy in all 3 types of achalasia. Recently, it has been hypothesized that the ability of POEM to create a longer myotomy proximal to the LES may especially benefit patients with type III achalasia, although this has yet to be confirmed by additional trials.⁸ Furthermore, a retrospective study comparing clinical outcomes of POEM to those of standard LHM with a minimum postoperative follow-up of 3 years showed similar treatment success, reflux rates, and quality-of-life measures.⁹ POEM was also found to be safe and effective in patients with persistent symptoms after LHM, although the rate of clinical success was lower (81% vs 94%) than in patients without prior LHM.⁷

The most common complication post-POEM is the development of GERD, which occurs in as many as 44% of patients.¹ However, a prospective study showed that most of these patients are responsive to PPI therapy.¹ Major complications of POEM are rare but include bleeding, pneumothorax, thoracic effusion, and transmural perforation.² However, randomized, controlled studies comparing the long-term efficacy and safety of POEM vs LHM or PD are needed.

CONCLUSION:

Achalasia is one of the most studied esophageal motility disorders and is characterized by impaired LES relaxation and esophageal aperistalsis. Most patients present with dysphagia to solids and liquids, regurgitation, and varying degrees of weight loss. Recent data suggest that patients with type II achalasia may be most likely, and patients with type III achalasia may be least likely, to report weight loss compared to patients with type I achalasia. Furthermore, molecular pathology studies have shown differences in markers of extracellular matrix turnover, pro inflammatory cytokines, and profibrogenic cytokines among the types of achalasia. Although achalasia cannot be permanently cured, excellent palliation of symptoms is possible in over 90% of patients with the treatment modalities currently available (PD, LHM, or POEM). However, more studies need to be conducted on the adequacy of well-balanced nutrition in this population pre- and post-intervention and to see whether dietary modification can be used as an adjunctive treatment to help improve weight post-intervention, especially in patients who are not candidates for definitive treatments.

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