Laryngopharingeal reflux disease: from pathophysiology to treatment

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Summary

Many patients experience ear, nose and throat symptoms associated with their gastroesophageal reflux disease. These symptoms are purportedly caused by reflux of gastroduodenal contents into the larynx, which leads to laryngopharyngeal reflux (LPR).
Various modalities are used to diagnose LPR, including ambulatory pH monitoring, laryngoscopy, and esophagogastroduodenoscopy, as well as a few new emerging diagnostic tests. However, there are no yet established diagnostic criteria or gold standard methods which can reliably distinguish LPR from other conditions.
Numerous studies have investigated the role of proton pump inhibitor therapy in this patient population, but the results were disparate and often inconsistent. While only a subgroup of patients with LPR appears to respond to PPI therapy, most patients show no symptomatic improvement, particularly with regard to extraesophageal symptoms. Thus, there is a vital need to explore alternative treatment options, including anti-reflux surgery, lifestyle changes, and other classes of medications to better address LPR management.
This review will evaluate currently available diagnostic tests and therapeutic options for patients with laryngeal signs and symptoms of chronic reflux disease.

KEY WORDS: gastroesophageal reflux, laryngopharyngeal reflux, chronic cough, impedance and pH monitoring, proton pump inhibitors.

Introduction

Gastroesophageal reflux is defined as the reflux of gastric content into the esophagus causing troublesome symptoms and complication (1). According to the Montreal Consensus Conference, the manifestations of GERD have been classified into either esophageal or extraesophageal syndromes and, among the latter ones, the existence of an association between LPR and GERD has been established. Laryngopharyngeal reflux (LPR) may be manifested as laryngeal symptoms such as cough, sore throat, hoarseness, dysphonia and globus, as well as signs of laryngeal irritation at laryngoscopy (2). Laryngopharyngeal symptoms are increasingly recognized by general physicians, lung specialists and ear, nose and throat (ENT) surgeons (3). In particular, there is a large number of data on the growing prevalence of laryngopharyngeal symptoms in up to 60% of GERD patients (4-6). In addition, some studies support the notion that GERD, as well as smoking and alcohol use, are risk factors for laryngeal cancer (7, 8).

The prevalence of extraesophageal reflux is difficult to determine due to the lack of a gold standard diagnostic criteria.

The prevalence of extraesophageal reflux is difficult to determine due to the lack of a gold standard diagnostic criteria. There are no common pH testing values predicting causal link between reflux and the extraesophageal symptoms. However, it is estimated that 1/3 of patients with GERD may have extraesophageal symptoms (4). Locke et al. reported that prevalence of hoarseness was 14.8% and globus 7.0% (9).
According to a prospective study (the ProGERD study) from Europe, involving 6215 patients with heartburn, the prevalence of laryngeal disorders was 10.4% (4). Approximately 20-60% of patients with GERD have head and neck symptoms without any

considerable heartburn. Micklefield et al. revealed that 56% of patients with chronic hoarseness and laryngeal lesions had at least one esophago-pharyngeal reflux episode (10). De Bortoli et al. reported that MII-pH analysis confirmed GERD diagnosis in less than 40% of patients with previous diagnosis of LPR, most likely because of the low specificity of the laryngoscopic findings (11).

Extraesophageal symptoms can present in isolation but most often occur concomitantly with typical GERD symptoms. In fact, the existence of so-called "silent reflux" is highly controversial, so much so that recent American Gastroenterological Association (AGA) guidelines recommend against using acid suppressive medications for treatment of extraesophageal symptoms in the absence of typical symptoms (12). However, it is also established that physiologic reflux of gastroduodenal contents may occur without perceived symptoms. Despite increasing literature over the past two decades on LPR, this condition can be difficult to diagnose and treat. The main reason for this difficulty is the lack of specificity of symptoms for reflux and poor sensitivity of currently available diagnostic testing for LPR. Many patients with possible LPR may have refractory symptoms involving voice, swallowing, or breathing problems and are often referred to a plethora of specialists – including otolaryngologists, pulmonologists, allergists, and gastroenterologists – for treatment. As such, it is estimated that providing medical care for LPR patients costs over 50 billion US dollars, five times that of GERD alone (13). Therefore, LPR is a significant medical problem that deserves additional attention.

The aim of this review is to evaluate currently available diagnostic tests and therapeutic options for patients with laryngeal signs and symptoms of chronic reflux disease.

Pathophisiology

While the exact pathogenesis of extraesophageal reflux is not fully understood, there are two hypothesised mechanisms of action: a direct and indirect exposure to gastroduodenal reflux of the laryngopharyngeal mucosa. Acidity of gastric juice alone may cause tissue damage at the upper airway level (14), but several studies demonstrated that this is not the only etiologic factor involved in the pathogenesis of LPRD. Indeed, Pearson et al. (15) highlighted that, although acid can be controlled by proton pump inhibitor (PPI) therapy, all the other damaging factors (i.e. pepsin, bile salts, bacteria and pancreatic proteolytic enzymes) remain potentially resistant to PPI therapy and may have their damaging ability enhanced. Particularly, pepsin can damage all extra-gastric tissues at a pH value up to 6 (16). Noticeably, Johnston et al. showed a detectable level of pepsin remaining on the laryngeal epithelia surface after a reflux event (17). The same Authors described that pepsin is taken up by laryngeal epithelial cells by receptor-mediated endocytosis (17), thus it may represent a novel mechanism, besides its proteolytic activity alone, by which pepsin could cause GERD-related cell damage independently of the pH of the refluxate (15).

There are two main mechanisms involved into laryngopharyngeal reflux: the acid gastric reflux causing direct tissue damage at the upper airway level, and a vagal response resulting in bronchoconstriction and cough.

The second proposed mechanism hypothesizes that reflux of gastroduodenal contents into the distal esophagus stimulates a vagal response that in turn results in bronchoconstriction and cough. Subsequent pressure gradient changes in the abdomen and thorax during coughing are then thought to trigger a vicious cycle of cough and promote additional reflux events (18, 19). Upper esophageal sphincter dysfunction is also thought to also contribute direct exposure of reflux to laryngeal mucosa (20). While the deleterious effects of pepsin and acid on esophageal mucosa are often reversible, some evidence suggests that direct exposure to laryngeal mucosa can lead to irreparable injury. That is to say, while esophageal mucosal damage may heal with time, laryngopharyngeal damage may be permanent (21). It is important to recognize that the current treatment options in patients with LPR are predominantly targeted at the direct exposure model of pathogenesis.

Diagnosis

The diagnosis of LPR is a very difficult task and several controversies remain regarding how to confirm LPRD. Laryngoscopic findings, especially edema and erythema, are often used to diagnose LPR by ENT surgeons (2). However, it should be pointed out that, in a well-performed prospective study, laryngoscopy revealed one or more signs of laryngeal irritation in over 80% of healthy controls (22). Moreover, it has been demonstrated that accurate clinical assessment of LPR is likely to be difficult because laryngeal physical findings cannot be reliably determined from clinician to clinician, and such variability makes the precise laryngoscopic diagnosis of LPR highly subjective (23). The sensitivity and specificity of ambulatory pH monitoring as a means for diagnosing GERD in patients with extraesophageal reflux symptoms have been challenged (1). Furthermore, the sensitivity of 24-h dual-probe (simultaneous esophageal and pharyngeal) monitoring has ranged from 50 to 80% (20). The availability of multichannel intraluminal impedance and pH monitoring (MII-pH) seems to show better performances in diagnosing extraesophageal manifestations of GERD thanks to its ability to evaluate acid and nonacid refluxes other than their proximal extension (24-27). However, the poor sensitivity and specificity of all currently available diagnostic tests for LPR has been highlighted by several review articles (2, 28, 29). In a

The diagnosis of laryngopharyngeal reflux is difficult and complex: laryngoscopy, impedence and pH monitoring may help, but sometime the diagnosis remains controversial.

population of patients with laryngoscopic findings of LPR, our group showed that MII-pH confirmed GERD diagnosis in less than 40% of patients, (11) thus highlighting the critical issue of nonspecific symptoms and laryngoscopic findings of LPR (30). Moreover, Ribolsi et al. showed that baseline impedance value, obtained recording the value of basal impedance during nighttime, it is possible to increase the diagnostic efficacy of MII-pH analysis in patients with chronic caught (31). Recently, baseline impedance value resulted able to improve diagnostic power of MII-pH monitoring (32-35).

New promising diagnostic techniques have been developed for extraesophageal reflux syndromes, in particular, an immunologic pepsin assay (PeptestTM), which has been shown to be a rapid, sensitive, and specific tool (36, 37), and a new pH pharyngeal catheter (manufactured by Restech, San Diego, CA, USA) that recent study documented as highly sensitive and minimally invasive device for the detection of liquid or vapors of acid reflux in the posterior oropharynx (38). However, limited data on their diagnostic accuracy and potential clinical application are available.

Management of laryngeal symptoms of reflux disease

The primary aim in treatment of LPRD is focused to obtain the best control both acid and non-acid reflux events. Given the poor sensitivity and specificity of currently available diagnostic modalities in LPR (Table 1), most treatment algorithms recommend initial empiric treatment with acid suppressing medications. However, recent meta-analyses have provided conflicting conclusions with respect to the utility of PPI therapy (14, 15), viable treatment strategies should include a combination of lifestyle modifications, medications, and perhaps even consideration of surgical intervention in a select subgroup of patients who have refractory symptoms.

Lifestyle modifications

A correct approach to GERD-related symptoms need to consider specific lifestyle modification other than a PPI treatment. Diet and lifestyle modifications are effective interventions for GERD, despite the fact that few robust data have been published (39, 40).

A reduction in body weight especially in overweight and obese patients is always recommended.

Some modifications may be suggested in patients with suspected GERD and these includes, first of all, a reduction in body weight especially in overweight and obese patients. This section also considered the potential effect of specific foods, alcohol and tobacco consumption and sleep position in preventing GERD-related symptoms.

Obesity

The incidence of obesity in Western countries has increased dramatically (41), and this has occurred in concordance with an increase in the number of pa-

Table 1 - Advantages and disadvantages of diagnostic methods for laryngopharyngeal reflux.

Method	PRO	CONTRA
Endoscopy	• Direct view of mucosa	• High cost • Low sensibility and specificity
Laryngoscopy	• Less Invasive than EGD • Direct view of larynx	• No specific signs for reflux injury • Variability inter-operator
pH monitoring	• Ambulatory • Prolonged monitoring • Easy to perform	• Low specificity • No pH predictors of treatment response • Need a catheter, uncomfortable
Impedence and pH monitoring	• Ambulatory • Prolonged monitoring • Easy to perform • Differentiates acid reflux to non-acid reflux	• Real specificity is unknown • Unknown clinical relevance when abnormal on PPI therapy • Need a catheter, uncomfortable
ResTech Dx-pH	• Faster detection rate and faster time to equilibrium pH than traditional pH catheters	• Unknown clinical relevance • Need more controlled outcome study
Pepsin test	• More comfortable • Fast and easy detection of salivary pepsin • Good specificity and sensibility	• Few controlled outcome studies

Reflux symptoms are exacerbated by weight gain.

tients suffering from GERD (42). Multiple epidemiological studies clearly demonstrate an association between obesity and GERD and physiologic investigations support a biologically plausible relationship between obesity and GERD (43). The effect of BMI on GERD occurrence seems to be independent of total caloric intake, dietary intake of fiber, fruits and vegetables, or other macro or micronutrients (43). Obesity is supposed to modify esophagogastric junction (EGJ) morphology and function. Indeed, obesity generates a mechanical disruption of EGJ by promoting an axial separation between the lower esophageal sphincter (LES) and the extrinsic crural diaphragm (44). Tolone et al. showed a very high risk of disruption of EGJ morphology in a cohort of obese patients before undergoing bariatric surgery evaluated with high resolution manometry (45). Moreover, pathophysiological data obtained with impedance and pH analysis showed that patients with overweight and obesity had abnormal esophageal acid exposure time and number of reflux events (46).

Clinical data showed that reflux related symptoms have been shown to be exacerbated or improved over time concomitant with weight gain or loss, respectively (47). The HUNT study showed that, among individuals with GERD-related symptoms, a reduction higher than 3.5 units in BMI is related to a reduction or cessation in weekly antireflux medication use (48). In line with this results, de Bortoli et al. showed that a voluptuary and controlled weight loss was associated with a reduction in symptom perception and in dosage of PPI treatment (49). Moreover, few data are available to determine whether weight loss is able to improve GERD-related symptoms such as LPR.

Recently bariatric surgery has become an increasingly popular option, particularly in patients with concomitant diabetes or BMI higher than 40.

Data regarding bariatric surgery in controlling reflux related symptom is quite controversial.

The Roux-en-Y gastric bypass is considered to be the best option to treat obese patients with reflux (50). This operation does not disrupt natural anti-reflux mechanisms and has the added benefit of decreasing the number of acid-secreting parietal cells (51). Consequently, Roux-en-Y gastric bypass leads to amelioration of reflux symptoms in obese patients, in addition to sizable and durable weight loss (52, 53). Further studies are needed to evaluate treatment of laryngeal reflux symptoms in obese patients.

Foods and eating habits

Although few data are available on this matter, in clinical practice different foods are indicated to influence the occurrence of refluxes and, generally, patients are advised against taking food late in the evening (15). High-fat foods and chocolate are empirically indicated as foods able to reduce LES pressure or to prolong gastric emptying; however, there have been no cessation trials evaluating the impact on GERD outcomes (54, 55). A strict low acid diet can be beneficial to patients with PPI-resistant LPR. A low acid diet, eliminating food and beverages at pH less than 5 for a minimum of two weeks, was used in patients with LPR and symptoms in 95% of patients were found to be improved based on reflux symptom index (RSI) and the reflux finding score (RFS) (56). Interestingly, adherence to the mediterranean diet, which advocates for the consumption of healthier fats such as those found in fish and olive oil, has been shown to decrease the risk of GERD (57).

Heartburn may be exacerbated by spicy foods attributable to direct irritation of already inflamed lower esophageal mucosa. Nebel et al. (58) reported spicy foods as the cause of heartburn in 88% out of patients. Orange juice has been implicated in GERD symptoms even if orange juice infusion did not change LES pressure (59). In a cross-sectional study in patients followed at Veterans Administration healthcare facilities, high dietary fat intake was associated with an increased risk of GERD and erosive esophagitis (60). However, several other studies reported conflicting data showing that a high-fat diet had no effect on transient LES relaxation or esophageal acid exposure (61-64). Although it is unclear whether caloric density contributes to esophageal symptoms and acid exposure, a recent randomized study including a small group of patients found that esophageal acid exposure was higher with ingestion of a high calorie diet (1000 kcal *versus* 500 kcal), and reflux symptoms were affected by the fat content but not density (65). Carbonated beverages have been associated with promoting GERD symptoms by decreasing LES pressure and were found to predict GERD symptoms in a multivariate analysis (66).

A Norwegian case-control study reported a negative association between GERD and coffee (odds ratio [OR] 0.5; 95% confidence interval [CI] 0.4-0.6) among subjects who drank 4-7 cups per day compared with those who did not drink coffee (67). In the same study, consumption of dietary fibers was found to be a protective factor (67). In a large cross-sectional population-based study, consuming bread and fibers at least two meals per day caused a 50% reduction in reflux symptoms (68). Likewise, in another cross-sectional study, high fiber intake correlated with a reduced risk of GERD symptoms (60). The mechanism through which fiber is associated with a decreased risk is unknown, however increased gastric empting could be a reasonable hypothesis. On the other hand, an individualized approach in which patients maintain a food diary to track and eliminate specific offending agents from their diet should be implemented.

Voluptuary habits: tobacco and alcohol consumption

Few data are available for voluptuary habits such as cigarettes smoking and alcohol consumption. Smokers have an increased incidence of reflux symptoms compared with nonsmokers (69, 70). Nilsson et al. (67) revealed, in a multivariate analysis, that among individuals who had smoked daily for more than 20 years, the risk of reflux was significantly increased by 70%, compared with those who had smoked daily for less than a year (OR 1.7; 95% CI 1.5-1.9). A relation has been considered between smoking cigarettes and

a prolonged acid exposure, a decrease in LES pressure, and diminished salivation, which decreases the rate of esophageal acid clearance (71). Smit et al. examined 15 smokers with 24-hour double-probe pH monitoring and found that pH was < 4 for a greater percentage of time during smoking periods in the distal and proximal esophagus as compared to smoke-free periods (72). In the HUNT study, quitting or reducing smoking resulted in an almost two-fold improvement in severe GERD symptoms, as compared with those who continued to smoke (48).

Alcoholic beverages are considered able to precipitate heartburn perception (73). Alcohol may increase gastric acid exposure by stimulating gastrin production, lowering LES pressure, increasing spontaneous LES relaxations, and impairing esophageal motility and gastric emptying (74). Even if few data are available, there are no differences in increasing risk between large amounts of high-alcohol beverages such as whiskey and vodka (75, 76), and even moderate amounts of beer or red and white wine (73). However, when compared with red wine, white wine caused more esophageal acid exposure and a greater decrease in LES pressure (77).

Nilsson et al. (67) did not find alcohol to be a risk factor for triggering reflux symptoms in two consecutive Norwegian public health surveys. In a literature review of publications regarding lifestyle modification and GERD, Kaltenbach et al. (40) concluded that alcohol cessation was not associated with a rise in esophageal pH or improvement in reflux symptoms. More studies are needed in LPR patients who specifically have worsening of their symptoms after alcohol consumption.

Sleep position

There are different indications that body position during the sleeping period is related to reflux of gastric content in the esophagus. The sleep period alters physiologic mechanisms able to protect against reflux events. The mechanisms that seems depressed during sleep include the heartburn perception, the frequency of swallowing and the suppression of salivary secretion (78). Some investigations have shown that esophageal acid clearance is significantly prolonged during sleep compared with the waking state; this is true even when sleeping subjects are compared with awake subjects in the supine position (79). Head-of-the-bed elevation can be achieved by putting either 6-8 inch blocks under the bed legs at the head of the bed. In a randomized controlled trial, Harvey et al. (80) showed that raising the head of the bed alone or in combination with ranitidine therapy improved both symptoms as well as endoscopic findings in patients with moderately/severe esophagitis. In patients with LPR, Hoppo et al. (81) supposed that upright body position may effectively shorten the intra-gastric LES, causing enhanced reflux of air and gastric contents. This study proposed that in the upright position, air in the stomach moves upward and leads to LES relaxation by affecting the stretch receptors through gastric wall tension and consequently leads to reflux of aerosolized gastric contents into the esophagus and larynx (81).

By means of esophageal manometry, 24 h pH monitoring, and barium studies, Shay et al. (82) showed, in a group of patients with GERD-related symptoms, that in the right lateral decubitus position, the gastroesophageal junction is submerged below liquid gastric contents, which results in an eightfold increase in acid exposure as compared to the left lateral decubitus position (82). Therefore, patients with GERD-related symptom as well as with LPRD should be advised to sleep in the left lateral decubitus position or to elevate head of bed to decrease acid exposure.

Pharmacological treatment

Considering the poor sensitivity and specificity of all currently available diagnostic tests, an empiric trial of therapy represents the first step to confirm LPRD and to treat it accordingly. However, there is no accepted treatment protocol for most patients with LPRD. Since their introduction in the 1980s, PPIs have demonstrated the best suppression of gastric acid secretion, clearly showing a distinct advantage (either for healing and symptom relief) over H2 receptor antagonists (83). Thus, H2 receptor antagonists have restricted their role mainly for patients who suffer from nocturnal acid breakthrough despite twice-daily PPI therapy (84), or for long-term management of reflux symptoms on an 'as needed' basis (85). Prokinetic agents, although scarcely evaluated, are usually considered unhelpful in LPRD (15).

Proton pump inhibitors

PPI therapy is considered to be the mainstay of care in patients with GERD (86); however, its efficacy for the treatment of LPRD remains doubtful. In clinical practice, consistently with the assumption that the upper aero-digestive tract is more sensitive to acid refluxes than the esophagus, it is believed that patients with reflux-related laryngitis require higher doses and a longer trial of PPIs to achieve an improvement of laryngeal symptoms than those with typical GERD symptoms (87-91). On the other hand, placebo-controlled trials have failed to demonstrate any therapeutic benefit of PPIs (42, 92-94). In 2006, a prospective multicenter randomized study, with 145 patients having symptoms and endoscopic signs of LPR, did not show any benefit in patients treated with esomeprazole 40 mg twice daily for 4 months *versus* placebo (95). In addition, a Cochrane systematic review of 302 studies did not find any high-quality trials meeting the inclusion criteria to assess the effectiveness of anti-reflux therapy for hoarseness (96).

A minority of patients with LPR responds to PPI therapy, but most patients don't show any symptomatic improvement, particularly with regard to extraoesophageal symptoms.

A systematic review and a meta-analysis of randomized controlled trials failed to demonstrate superiority of PPIs over placebo for the treatment of suspected LPR (97, 98). Conversely, more recent studies have

demonstrated effectiveness in treating reflux symptoms and improving laryngeal inflammation.
Reichel et al. (99) reported a randomized, double-blind, placebo-controlled trial with esomeprazole 20 mg twice daily for 3 months in patients with symptoms and endoscopic signs of LPR, which found significant improvement in both symptoms and laryngeal examination. Likewise, Lam et al. (100) performed a prospective, randomized, double-blind, placebo-controlled study with rabeprazole 20 mg twice daily for 3 months in patients with symptoms and endoscopic signs of LPR, resulting in a significant improvement of symptoms, but not laryngeal findings. However, Vaezi (101) argued that the real significant improvement was for heartburn symptoms and not for chronic throat symptoms. In line with this sentence, it is important to highlight that PPI therapy in LPR and twice daily dosing are both unapproved indications for these agents but one that is recommended by both gastroenterologist and ear-nose-throat experts and guidelines (28, 89, 102). Treating suspected patients initially with twice daily therapy for no more than 2 months is a reasonable initial approach. If patients do not respond symptomatically with this approach it is likely that their symptoms are not reflux related unless they complain of regurgitation, which is a volume phenomenon that PPIs may not be able to control.
However, in patients who do respond to a 2-month course of therapy, tapering of the dose to once daily and discontinuing the evening dose first is a reasonable approach. The lowest acid suppression controlling patients symptoms should be utilized for many reasons including cost, avoiding short term (headache, abdominal pain, diarrhea) as well as potential long-term (osteoporosis, anemia, hip fractures) side effects, and proposed clopidogrel interactions (91, 103, 104).

Raft-forming gel preparation (alginate)

Traditional antiacids are frequently used as add-on therapy in order to neutralize gastric acidity and to help control heartburn in GERD patients (105-107). They are polysaccharides found in algae and convert into a gel form when they combine with cations. In particular, they form a physical barrier against gastric acid, bile salts, and pepsin, and have the advantage of being a non-systemic medication, indicated for pregnant. In a prospective, randomized controlled study, liquid alginate preparations (taken four times daily) have been shown to be effective in treatment of LPR symptoms and signs (108). Of note, considering that pharyngeal and laryngeal cancer might represent LPR complications, a statistically significant reduction in squamous cell carcinoma volume was observed in hamsters that received alginate prior to known carcinogen [7,12-dimethylbenzanthracene (DMBA)] and human pepsin application, compared with hamsters painted with DMBA and human pepsin alone. Thus, alginate suspension provided protection from pepsin-enhanced tumor growth (15). Alginates should be given after each meal and last thing at night, and nothing should be taken by mouth after the nocturnal dose (15).

In a single prospective, randomized controlled study, liquid alginate preparations have been shown to be effective in treatment of LPR symptoms and signs.

Surgical therapy

Laparoscopic antireflux surgery (LARS) is a well-established and highly efficacious treatment for GERD and has been shown to provide durable relief from the typical reflux symptoms (109). In particular, the surgical therapy is helpful in allowing the majority of patients suffering from GERD to discontinue acid suppression therapy, to achieve resolution of associated esophagitis, and to arrest or perhaps even reverse the metaplasia/dysplasia induced by frequent exposure of the esophageal mucosa to gastric contents (110-112). Few controversial data are available about surgical outcome of LPRD. A clinical prospective study in patients with LPRD selected for surgical treatment, in which the symptoms and signs had responded to anti-reflux medication, the laparoscopic fundoplication was found to be an effective and safe treatment of LPRD (113). Moreover, in patients with objective evidence of GERD, LARS was effective in relieving LPR symptoms (114, 115). On the other hand, LARS has shown disappointing results in controlling LPR-related symptoms in patients unresponsive to aggressive PPI therapy (116). Likewise, prior studies demonstrated a poor surgical outcome for the resolution of laryngeal symptoms especially in PPI non-responders (117, 118). It is necessary for the surgeon to perform a detailed workup including esophagogastroduodenoscopy, esophageal manometry, gastric emptying test, MII-pH or pH-metry, and upper gastrointestinal radiography for all patients scheduled for LARS, primarily to exclude malignancy and motility problems such as achalasia and gastroparesis and then to detect a cause-effect relation between pathological acid exposure time and laryngeal symptoms/findings (119). The patients who are selected for LARS must be informed that laparoscopic fundoplication may correct the underlying mechanical defect but they should be warned that the response of their laryngeal symptoms to surgery would still be uncertain (117). When compared to PPI therapy, surgical fundoplication in GERD resulted in equal 5-year remission rates (92 and 85%, respectively with no statistical significance) in a recent study (120). Follow up of this trial showed that baseline gastric or esophageal pH was not a predictive parameter on patient outcome (121). The LARS approach could be more strongly suggested if patients showed a complete relief of laryngeal symptoms during PPI therapy or if 24-h pathophysiological studies demonstrated that nonacid reflux events are predominant. Moreover, the surgeon must carefully select patients before suggesting LARS and a Regional Referral Center special-

Laparoscopic fundoplication has similar efficacy, less invasiveness, less postoperative discomfort, and a shorter recovery time as compared to the open surgery technique.

ized in esophageal surgery is recommended to reduce postoperative complications. In this matter, patients should be warned of possible postoperative dysphagia, bloating, flatulence, diarrhea, and recurrence of the symptoms (122). Referring patients with LPR for fundoplication is much more challenging than treating those typical GERD. An earlier study using laparoscopic Hill repair in 145 patients found a reduction in sore throat from 43 to 8%, cough from 41 to 8% and voice loss decrease from 25 to 11% (123). Another study evaluated 40 patients who underwent laparoscopic Nissen fundoplication for complaints of reflux laryngitis. After 3 months, 79.3% of patients had decreased inflammation noted on otorhinolaryngeal exam, and 41.4% of patients described improvement in voice quality. After 12 months, these figures were 92.3 and 38.5%, respectively. After a median follow-up of 42 months, 62.5% of patients reported either no cough or mild cough or hoarseness (124). Weber et al. (125) evaluated 25 professional voice users with LPR refractory to medical management showed that laparoscopic Nissen fundoplication reduced total acid levels on pH monitoring, improved symptom indices and even decreased or eliminated the need for post-operative PPI for most patients (125). Swoger et al. (116) studied patients with suspected LPR who continued to have laryngeal symptoms despite four months of aggressive PPI therapy. Of the 10 patients who underwent Nissen fundoplication, only one patient reported improvement of laryngeal symptoms at one year. To further elucidate which patient subgroup among those with extraesophageal symptoms would benefit from Nissen fundoplication, Francis et al. (126) performed a retrospective cohort study and found that patients with heartburn with or without regurgitation and esophageal pH < 4 over more than 12% of a 24-hour period were predictive of post-fundoplication resolution of the presenting extraesophageal reflux symptom. To date, the clinical guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommend antireflux surgery for patients who: (1) have failed or are unable to tolerate medications; (2) have significant extraesophageal manifestation such as aspiration, asthma, or cough; (3) have the complication of GERD-like peptic stricture.

The role of surgical fundoplication in treatment of GERD is well established. Fundoplication is now more commonly performed laparoscopically, given that laparoscopic fundoplication has similar efficacy, is less invasive, leads to less postoperative discomfort, and has a shorter recovery time as compared to the open technique (127). There are important evaluations to do before patients undergo anti-reflux surgery: EGDS, esophageal manometry, 24-hour pH monitoring, and chest and upper gastrointestinal radiography to rule out motility problems, such as achalasia or gastroparesis, and malignancy (127). In patients with typical GERD symptoms, the first indication for antireflux surgery is continued reflux or regurgitation with evidence of physiological mechanical barrier disruption (hiatal hernia). Since the diaphragm cruces act as an extrinsic sphincter on the LES, the presence of a hiatal hernia can disrupt the LES and potentially allow persistent refluxate to pass upstream through LES despite maximal PPI therapy. Another indication for fundoplication is an inability to tolerate or unwillingness to take acid-suppressive medications. Hence, surgical fundoplication may be useful in select patients with LPR who continue to have regurgitation despite PPI therapy; have moderate to severe reflux measured by pH monitoring off therapy; and who might have a mechanical defect such as a moderate sized hiatal hernia (greater than 4 cm). Otherwise, surgery is not recommended in patients who report worsening symptoms but who have only minimal reflux by objective testing. Patients should also be adviced that surgical intervention can lead to unintended side effects such as postoperative dysphagia, bloating, and dumping syndrome causing persistent diarrhea. Moreover, surgery sometimes cannot prevent symptom recurrence.

Conclusions

This review analyzed the role of GERD in LPRD, while many patients are diagnosed with LPR, not all have the disease. This is predominantly due to poor sensitivity of diagnostic testing and poor specificity of symptoms. These patients are often first treated with aggressive acid suppressive therapy. In many, this treatment is inappropriately continued despite lack of response leading to unnecessary cost as well as potential drug side effects.

We want to underline two important clinical reminders: 1) all patients should be tapered from empirically initiated acid-suppressive therapy. This includes those who respond to such therapy in order to determine the minimum dose of acid suppression that will keep the patient asymptomatic; 2) surgical fundoplication should be considered only in those who respond to acid suppression and cannot or will not take such therapy or in those whose LPR symptoms are accompanied by typical symptoms of heartburn, regurgitation, and significant reflux by pH (or MII-pH) monitoring off PPI therapy with an abnormal acid esophageal exposure time. New and up and coming parameters as MNBI and PSPW index seems promising and able to improve diagnosis of GERD in LPRD patients.

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