Osteopathic Family Physician (2011) 3, 58-65

ELSEVIER

acofp Osteopathic Family Physician

Clinical management of gastroesophageal reflux disease

Renata Jarosz, DO,[a] Thomas G. Zimmerman, DO, FACOFP,[b] Daniel Van Arsdale, DO[c]

From [a]Stanford Hospital Physical Medicine and Rehabilitation Residency Program, Redwood City, CA, [b]South Nassau Family Medicine, Oceanside, NY, and [c]Southampton Hospital, Southampton, NY.

KEYWORDS:
Gastroesophageal;
Reflux;
Disease;
GERD;
Current;
Treatment;
Diagnosis;
Management;
Osteopathic;
Manipulative;
Treatment;
OMT;
Barrett;
Medical;
Medications

Gastroesophageal reflux disease (GERD) is a common problem that occurs in both adult and pediatric populations and can significantly degrade patients' quality of life and lead to life-threatening complications. A prudent course of management in a patient with classic GERD symptoms would be to empirically prescribe lifestyle modifications and a proton pump inhibitor (PPI) for six to eight weeks. Osteopathic manipulative treatment may also be a useful adjunct. If the patient is unable to afford a PPI, a histamine type-2 receptor antagonist may be substituted (although they are much less effective). If resolution of symptoms occurs, the therapeutic response can confirm the diagnosis of uncomplicated GERD. If the patient has recurrent or intractable symptoms, the next step would be to order pH monitoring, manometry, or endoscopic evaluation of the esophagus and stomach (esophagogastroduodenoscopy [EGD]). If there are any atypical symptoms such as persistent cough, asthma, melena, sore throat, or hoarse voice, EGD should be ordered immediately. Patients with chronic esophagitis or extra-esophageal symptoms who have failed (or refused) medical management should consider fundoplication.

Gastroesophageal reflux disease (GERD) is a common problem that occurs in both adult and pediatric populations in the United States (US). The economic impact of GERD is enormous; typical GERD therapy costs approximate $10 billion per annum in the (US).[1] GERD is referred to as "heartburn" because the most common symptom is a substernal burning discomfort.[2] GERD refers to the retrograde passage of gastric contents into the esophagus. It is believed that transient lower esophageal sphincter relaxations are a major cause for reflux. Untreated GERD can lead to dysplasia of the esophageal mucosa (known as Barrett's esophagus [BE][3]) and subsequent esophageal adenocarcinoma. Because the rate of adenocarcinoma has increased dramatically over the last 20 to 30 years, [4] it is extremely important for physicians to properly evaluate and manage GERD. Table 1 outlines some key points of information for readers to consider.

Corresponding author: Thomas G. Zimmerman, DO, FACOFP, South Nassau Family Medicine, 196 Merrick Road, Oceanside, NY 11572-1420.
E-mail address: tzimmerman@snch.org.

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doi:10.1016/j.osfp.2010.12.003

Epidemiology

Although GERD has been classically thought of as primarily a disease of the Western cultures, the number of cases has grown in the Eastern countries with the spread of the Western diet and lifestyle. Prevalence of heartburn is 8% in Italy, 10% in Japan, 17% in Canada, and 20 to 25% in the (US).[5] More than 60 million adult Americans suffer from heartburn at least once a month and more than 25 million experience heartburn daily.[6] A recent study in the US revealed that nearly 35% of all subjects experienced GERD symptoms, with the highest rates (50%) present in Hispanic populations.[7] For patients with GERD symptoms, 40 to

Table 1 Key points for GERD

- Common in both adults and children; accounts for $10 billion in medical costs per year in the US
- Usually presents as heartburn, but also as a cough, dysphagia, or hoarse voice
- Can significantly affect patients' quality of life, as well as lead to serious complications such as esophageal erosions, dysplasia, and cancer
- Weight loss—progressive reduction in weight may lower abdominal pressure, which in turn leads to decrease in esophageal reflux
- Although an empiric trial of proton-pump inhibitor therapy can be used in many patients, endoscopic examination is suggested in patients with recurrent or intractable symptoms

60% or more have reflux esophagitis. GERD appears to be more prevalent in pregnant women[8] and a higher complication rate exists among the elderly.[9] It is also common in pediatric populations. Complications of GERD are more frequent in white males and with increasing age. The prevalence of heartburn increases dramatically after the age of 40 years. Obesity can also increase the likelihood of GERD by 300% or more.[1]

Pathophysiology

Most patients with GERD actually have normal baseline lower esophageal sphincter (LES) tone. The most common mechanism for acid reflux is *transient* relaxation of the LES (~90% of reflux episodes in normal subjects and 75% of episodes in patients with symptomatic GERD).[10] Other mechanisms include breaching the LES as a result of increased intra-abdominal pressure (strain-induced reflux) and a baseline low LES pressure. The latter two mechanisms increase in frequency with greater reflux severity. Other factors include delayed gastric emptying (cofactor in 20% of GERD patients), medication use (particularly calcium-channel blockers), hiatal hernia (increased strain-induced reflux and poor acid clearance from hernia sac), and poor esophageal acid clearance (esophageal dysmotility, scleroderma, decreased salivary production).[11]

Clinical presentation

Patients typically complain of a burning sensation in the chest, vomiting, acidic taste in the mouth, and regurgitation. Often, heartburn may wake patients at night. Some atypical symptoms include anginalike chest pain, dysphagia, hoarseness, and chronic cough. Many times, children with "silent" GERD may present with chronic cough and asthma symptoms as opposed to actual heartburn.[12]

GERD may mimic peptic ulcer disease, infectious and toxic esophagitis, dyspepsia, chronic gallbladder disease, esophageal motility disorders, chronic pancreatitis, and irritable bowel syndrome (IBS). The differential diagnosis should always include angina, especially in patients with known coronary artery disease or its risk factors, as well as diabetes mellitus.[1]

With the availability of H2 receptor blockers and, more recently, proton pump inhibitors (PPIs), it is ever more important for the astute clinician to ask all patients about the occurrence of reflux symptoms. Patients self-medicating with over-the-counter (OTC) PPIs are likely to be largely symptom-free and may not admit to symptoms unless directly questioned; this is of great concern if these patients go undiagnosed and are never properly evaluated, as discussed next.

Diagnostic strategies

History and physical examination

In general, patients with intermittent, typical symptoms do not require any diagnostic evaluation and may be treated empirically.[13] Exceptions include patients with alarm symptoms (Table 2) such as weight loss, bleeding, anemia, odynophagia, dysphagia, or symptoms that persist for more than six weeks despite appropriate treatment.[14]

A comprehensive physical examination should be performed. Epigastric tenderness may suggest peptic ulcer disease, gastritis, or other disease processes more than GERD. A digital rectal examination and fecal occult blood test should be done to rule out gastrointestinal (GI) bleeding, and an electrocardiogram should be done to identify any cardiac disease. One can also consider obtaining a complete blood count to identify any chronic blood loss.[1] Microcytic anemia accompanied with iron deficiency (especially in men and postmenopausal or post-hysterectomy women) should undergo both upper and lower endoscopic examination to search for any hemorrhagic ulcers, BE, or GI malignancies.[15]

Table 2 Warning signs of complicated GERD

- Dysphagia
- Odynophagia
- Anemia (especially iron deficiency)
- Bleeding (upper or lower GI)
- Weight loss
- Early satiety

Adapted from reference 14.

Empiric trial of therapy

Resolution of symptoms after a 14-day trial of PPIs has been suggested to be an accurate method of diagnosing GERD.[13] One study by Hillman using decision analysis demonstrated that empiric omeprazole therapy could be expected on average to be $1800 less costly than that of ranitidine.[16] Because the cost of omeprazole has fallen significantly since this study was published in 1992, one can extrapolate even greater overall savings today. Most patients can be diagnosed clinically with GERD by combining history and physical exam findings with response to PPIs.

Upper GI series

An upper GI (UGI) or barium swallow is an radiographic examination of the esophagus and stomach. This imaging study is helpful to ascertain any anatomical disorders or complications of GERD.[17] A patient who has fasted overnight is given a barium "shake" to drink, which coats the digestive tract so it becomes more visible on the film. Movement of barium is observed while the patient is in different positions (Fig. 1). Barium swallowing can detect esophageal strictures and is also a reliable test for patients with dysphagia with an increase in sensitivity compared to esophagogastroduodenoscopy (EGD). Barium swallowing, however, is not sensitive enough to detect mucosal lesions such as esophagitis, and it often misses actual reflux as well.[18,19]

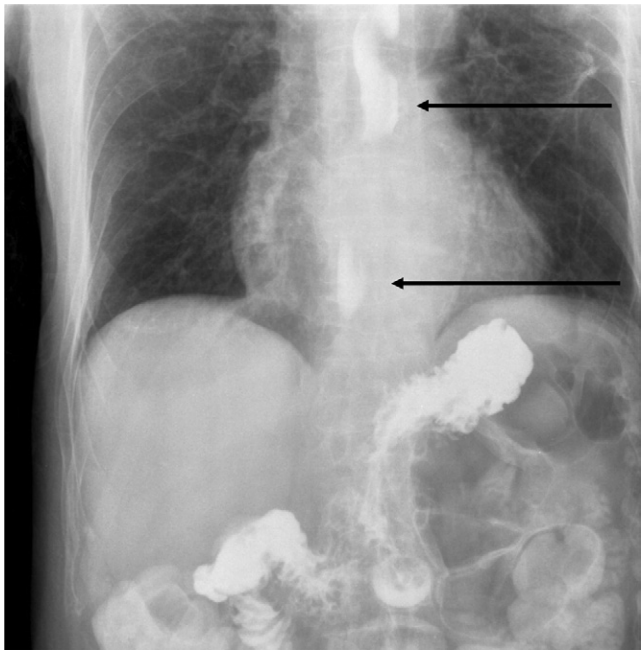

Figure 1 Upper GI series. X-ray of the abdomen and chest in a patient with a gastrostomy. Radiocontrast was injected into the stomach and quickly seen migrating upward through the entire esophagus (*arrows*). The patient had severe reflux esophagitis (Los Angeles grade D). (Figure courtesy Steven Fruitsmaak at http://en.wikipedia.org/wiki/File:Gastroesophageal_reflux_barium_X-ray.jpg).

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy is the gold standard for diagnosis of GERD and its possible complications. It consists of an examination of the lining of the esophagus, stomach, and upper duodenum with a small camera (flexible endoscope) inserted down the throat during conscious sedation. Studies suggest that empiric treatment of GERD with PPIs is more cost-effective than endoscopy, but EGD is much more sensitive at diagnosing mucosal injury (esophagitis) and/or dysplasia (BE).[20] EGD should be reserved for patients with long-lasting heartburn, dysphagia, or signs of GI bleeding, especially after a specific trial of acid suppression therapy. It should be noted, however, that a recent course of a PPI will often make the erosive changes associated with significant GERD harder to visualize on EGD.[21]

Acidity/impedance pH monitoring

Twenty-four-hour pH monitoring has been used since the 1970s to help document the presence of gastric juices in the esophagus.[21] Testing for the presence of gastric juices in the esophagus can be particularly useful in patients with symptoms of GERD but negative EGD findings.[22] Traditionally, a wired antimony electrode is inserted transnasally into the esophagus and positioned about 5 cm above the superior margin of the lower esophageal sphincter.[18] The total percentage time of esophageal pH below 4.0 is considered to be the most useful outcome measure.[1,23] There is also a wireless Bravo (Medtronic, Inc., Minneapolis, MN) pH-monitoring system that has been recently developed that allows 48-hour pH monitoring without using the transnasal catheter that some patients find intolerable.[24] Figure 2 shows the capsule and a sample report. This system is preferred for patients who cannot tolerate the catheter, and studies suggest that the data it provides are comparable with the wired electrode systems.[23] Unfortunately, many GERD patients will have normal pH studies because the refluxate causing the symptoms may be of neutral or slightly alkaline pH (especially patients taking PPIs). These findings also help explain why antacids, which can clearly neutralize the stomach's acidic contents, are often ineffective in chronic GERD patients.[23] Over the last 10 years, a new technique called ambulatory esophageal *impedance–pH monitoring* has been developed that can detect all types of gastroesophageal reflux with higher sensitivity and specificity.[25]

Esophageal manometry

Esophageal manometry is most useful in the evaluation of patients with dysphagia or odynophagia. Manometry assesses peristalsis and contractile pressures in the body of

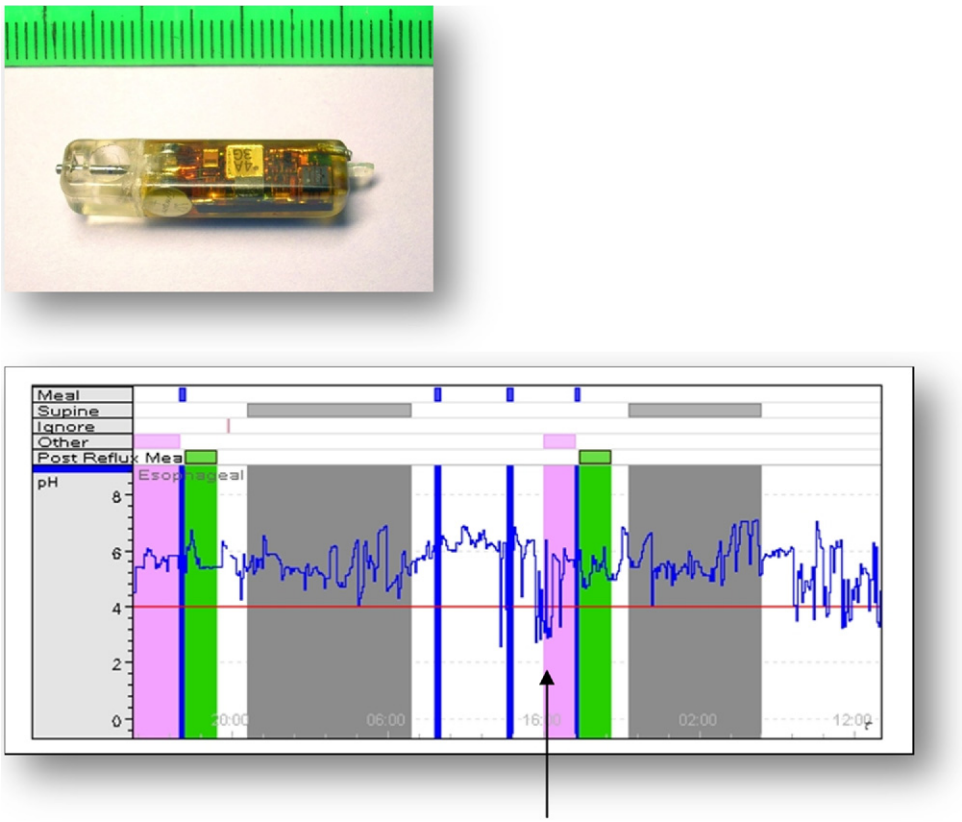

Figure 2 Bravo wireless pH monitoring and tracing. Top figure, Bravo pH wireless capsule. Bottom figure, Sample Bravo pH monitoring tracing. Periods of sleep are indicated by gray bars; this patient had significant acid reflux at 1600 h (*arrow*).

the esophagus, in addition to measuring resting tone and relaxation of both the lower and upper esophageal sphincters. Unfortunately, it is not as useful for the diagnosis of GERD because most subjects have normal findings. Its main purpose is for patients with dysphagia or achalasia, and in preoperative evaluation before antireflux surgery.[26]

Complications

GERD is a common chronic and relapsing condition that can result in serious complications for affected individuals. It is known that the productivity, quality of life, and overall well-being of individuals with GERD is compromised because of heartburn, the hallmark of acid regurgitation. Many patients rate their quality of life to be lower than that reported by patients with untreated angina pectoris or chronic heart failure. Nocturnal episodes of acid reflux can severely affect a patient's quality of life, resulting in ongoing daytime somnolence and irritability.[27]

A significant number of patients (especially pediatric patients[12]) may present with purely extra-esophageal symptoms such as hoarse voice,[28] cough, and wheezing. These patients may be diagnosed primarily with asthma, when indeed the precipitating factor is GERD.[29] Studies have shown significant improvement in "asthma" in response to PPI treatment.[30]

Chronic, repeated exposure of the esophagus to acidic refluxates can lead to the development of esophagitis, an inflammation of esophageal mucosa, whose characteristics are hyperemia, presence of inflammatory cells, and basal zone hyperplasia. When endoscopy reveals actual mucosal damage such as ulcerations, friability, and bleeding, the diagnosis of erosive esophagitis is made.[11] Chronic erosive esophagitis can cause the normal distal squamous epithelium to transform into a dysplastic columnar epithelium known as Barrett's esophagus. BE can be recognized as a red mucosa located between the smooth, pale-pink esophageal squamous and the light-brown gastric mucosa. Its existence may be characterized as tongues or patches extending up from the gastroesophageal junction. Patients with BE (especially segments longer than 2-3 cm) should be monitored closely with serial EGDs to watch for the development of adenocarcinoma (in which the rate of development is 30-125 times the risk as that of the general population).[11]

Treatment

The main objectives of GERD treatment are to reduce or eliminate symptoms, improve quality of life, and reduce or prevent complications. It is extremely important to have continued follow-up with these patients to ensure that they

Table 3 Lifestyle modifications for GERD

- Head elevation—increasing bed head height by 6 inches may lower abdominal pressure as well as distal esophageal acid exposure
- Avoid foods that may reduce LES tone—chocolate, peppermint, spicy and acidic foods (pizza, tomatoes), cruciferous vegetables (cabbage, onions, cauliflower, Brussels sprouts, broccoli) and fatty foods
- Avoid eating or drinking less than 3-4 hours before bedtime
- More frequent, but smaller meals—may decrease acid production.
- Weight loss—progressive reduction in weight may lower abdominal pressure, which in turn leads to decrease in esophageal reflux
- Smoking cessation and minimal caffeine/alcohol consumption—all may lower LES pressure, resulting in incompetence of the LES
- Avoid medication that decreases LES pressure such as muscle relaxants
- Avoid tight clothing around the waist—tight clothing tends to increase abdominal pressure and promote gastroesophageal reflux

Adapted from reference 36.

are appropriately treated and, if necessary, re-evaluated over time.[31]

Lifestyle modifications

In our opinion, the foundation of treatment for all patients with GERD should be comprehensive lifestyle modifications. Table 3 shows the measures that have been traditionally suggested. Meta-analysis of recommended lifestyle modifications has found that the measures directly related to the physical reflux of gastric contents (raising the head of the bed, weight loss) were effective and other more indirect measures (dietary restrictions, tobacco and alcohol avoidance) were statistically ineffective.[32] However, because the reporting of GERD symptoms is itself very subjective, it would still be prudent to advocate all of these lifestyle modifications. In our clinical experience, we have encountered many patients who were able to subjectively decrease the frequency and severity of GERD symptoms with these changes.

Medical treatments

Over-the-counter antacids such as calcium carbonate, sodium bicarbonate, magnesium hydroxide, and aluminum hydroxide are used by many patients with varying, transient effectiveness. Alginic acid is an antirefluxant that, when combined with saliva, produces a foam thought to hinder the passage of acid from the stomach into the esophagus. Because of their fast onset of action, these agents are best used for occasional symptoms. However, their therapeutic effects usually last only 30 to 60 minutes and are usually followed by a reflex increase in acid production by the stomach as they are cleared.[33]

Histamine type-2 receptors antagonists (H2Ras), are another class of agents that can serve as an appropriate, initial patient-directed therapy for mild to moderate GERD.[34] All of the acid reducers in this class are about equally effective. The OTC dose of H2RAs is uniformly one half of the standard lowest original prescription dose for each compound. In general, most people with mild to moderate GERD symptoms who take acid reducers find improvement in their symptoms. Acid blockers have been used since the 1960s and are considered very safe; caution should be used, however, particularly with cimetidine, because of drug interactions associated with its inhibition of the cytochrome P450 system. A major weakness of the H2RAs as a class is the development of tachyphylaxis; after 30 days of use, their efficacy can decrease significantly. Table 4 lists the more commonly used H2RAs.[1]

Proton pump inhibitors have emerged as the treatment of choice for GERD because of their superior, continued therapeutic relief of symptoms.[35] Based on several randomized, controlled trials, PPIs proved to be more effective than both H2RAs and placebo in controlling symptoms and in actual healing from erosive esophagitis over a four- to eight-week period. PPIs also are not associated with tachyphylaxis as are H2RAs.[36] Although PPIs are, on average, initially much more expensive than antacids or H2RAs, their effectiveness at reducing complications has been well documented. Table 5 lists PPIs currently available in the US.[37]

Prokinetic agents such as metoclopramide have been periodically discussed in the literature as being able to increase LES tone and increase gastric emptying to reduce the occurrence of acid reflux. However, its use is limited because of undesirable central nervous system side effects such as restlessness and tremors.[38]

Table 4 Histamine type-2 receptor blockers

Drug name	Typical Rx dosage	Lowest monthly cost (generic)
Cimetidine (Tagamet*)	400-800 mg twice daily	$32
Ranitidine (Zantac*)	150 mg twice daily	$24
Nizatidine (Axid*)	150 mg twice daily	$52
Famotidine (Pepcid†)	20-40 mg twice daily	$ 8

Adapted from reference 336; prices estimated from drugstore.com.
*GlaxoSmithKline, London, UK.
†Johnson & Johnson–Merck Consumer Pharmaceuticals, Fort Washington, PA.

Table 5 Proton pump inhibitors

Drug name	Typical Rx dosage	Lowest monthly cost
omeprazole (Prilosec*)	20 mg QD to 40 mg BID	$ 18
lansoprazole (Prevacid†)	30 mg QD/BID	$100
pantoprazole (Protonix‡)	40 mg QD/BID	$110
rabeprazole (Aciphex§)	20 mg QD/BID	$219
esomeprazole (Nexium¶)	20 mg QD to 40 mg BID	$190
Omeprazole + sodium bicarbonate (Zegerid‖)	20-40 mg (omeprazole) QD	$ 24

Adapted from reference 36; prices estimated from drugstore.com.
*Procter & Gamble Co., Mason, OH.
†Novartis Intl AG, Basel, Switzerland.
‡Wyeth Pharmaceuticals, Madison, NJ.
§Eisai Co., Ltd., Tokyo, Japan.
¶AstraZeneca, plc., London, UK.
‖Santarus, Inc., San Diego, CA.

Surgery

Surgical procedures are indicated for patients whose GERD symptoms are severe and/or nonresponsive medical treatments, including chronic esophagitis, BE, and pulmonary or laryngeal pathology secondary to recurrent reflux. Esophageal manometry must be done as part of the presurgical evaluation to document the absence of any motility problems.[1] The most common procedure performed is called *fundoplication*, of which there are two types: Nissen and Toupet. In these procedures, a new "valve" is constructed as the upper portion of the stomach (fundus) is wrapped around the lower end of the esophagus and fixed (plication). The wrap in the Nissen procedure is a full 360 degrees, whereas in the Toupet, it is 270 degrees. The wrap supports the LES muscle to help reduce transient LES relaxation and the subsequent flow of peptic juices from the stomach into the esophagus.[39] Figure 3 illustrates the Nissen procedure.

The success rate for the laparoscopic procedure is 90 to 95% for patients who have the typical symptoms of GERD, such as heartburn, regurgitation, or belching. For patients with less typical symptoms, including hoarseness and chronic cough, the surgery is about 70 to 80% effective at relieving their symptoms. Although rare, the following complications and side effects may occur: injury to the esophagus, stomach, or spleen; bleeding, negligible symptom improvement; difficulty swallowing after surgery; loss of the ability to belch or vomit; and stomach bloating.[1] The laparoscopic Nissen fundoplication offers less morbidity and mortality and shorter hospital stays (1-2 days) than the open procedure (4-7 days) with at least the same short-term outcome as the open procedure and better results compared with medical therapy.[40] The mortality rate of the laparoscopic Nissen fundoplication is 0.2%.[1]

Osteopathic manipulative treatment

Because the etiologies of GERD are multifactorial (physical reflux of acid, excess acid production, etc.), it is logical that there are various ways to treat it using osteopathic manipulative treatment (OMT). Although there has been a paucity of research on the effects of OMT on GERD, there are some studies demonstrating the clinical effectiveness of other types of manual manipulation.[41] Although many GERD patients may still need concomitant medical treatment, OMT may well be able to reduce overall requirement for medicine, reduce health care costs, and improve patients' quality of life. There are many anecdotal reports of the effectiveness of OMT on GERD, some dating back more than 100 years.[42]

As a chronic condition, the gross musculoskeletal findings may reveal evidence of chronic change. The skin may

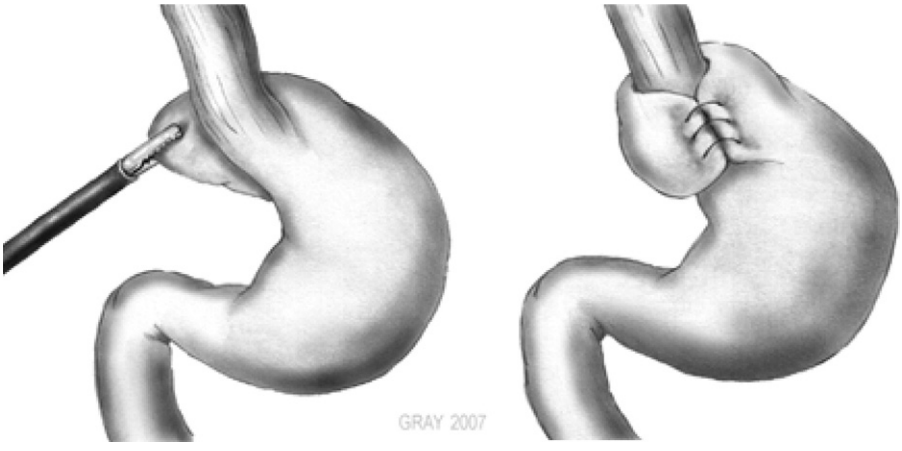

Figure 3 Nissen fundoplication. In the Nissen fundoplication, the gastric fundus is wrapped (plicated) around the distal esophagus to increase resting LES and thus reduce the incidence of GERD.[1] (*Public domain image courtesy James Gray, MD).*

feel cool or dry. The underlying musculature may be contractured and feel ropey. There will be a noticeable limitation of motion and tenderness over the transverse and spinous process of the involved vertebral segments. According to Kuchera, the sympathetic innervations of the upper GI tract are located at the T5-T11 vertebrae. Thus, patients with GERD are most likely to have facilitated segments and somatic dysfunctions in these areas.[43] It is well documented that stimulation of the autonomic nervous system (which can occur with somatic dysfunction) can result in decreased motility of the stomach,[44] which can exacerbate reflux into the esophagus. A common manipulative technique to normalize the sympathetic tone is rib raising[45] to the T5-T9 appropriate rib segments for the esophagus and stomach.

An important factor that contributes to the competence of the gastroesophageal junction and LES is the action of the diaphragm. Thus, a pertinent aspect of manipulative treatment of the upper GI system is ensuring that the diaphragm is properly domed, whereby both sides are working symmetrically during respiration.[46]

Stimulation of the vagus nerve activates and increases peristaltic action and secretion in the stomach glands. To reduce vagal activity to the stomach and esophagus, and relieve fascial tensions around the ganglion nodosum, the occipito-atlantal and atlanto-axial joints, and the suboccipital area can be treated with muscle energy[47] and myofascial release techniques.[48]

Future directions

One promising therapeutic agent called lesogaberan is being studied by several researchers. It is a novel γ-aminobutyric acid type-B receptor agonist that acts to inhibit transient lower esophageal sphincter relaxation and reduced symptomatic episodes by 35% when used in conjunction with PPI treatment.[49] Of course, further trials will be required to demonstrate this drug's efficacy and safety profile.

Many endoscopic procedures involving plication and ablation have been developed over the past few years, with the promise of equivalent efficacy and decreased morbidity compared with laparoscopic or open procedures. Unfortunately, more research on the benefits vs risks of these procedures is needed before they can be approved for widespread use.[50,51]

Summary

Improvement in the quality of life of patients with GERD starts with the proper diagnosis and understanding the changes that occur secondary to GERD. The astute physician must then implement rational interventions to alleviate the patient's symptoms, prevent complications, and improve quality of life.

There has been considerable debate on whether medical or surgical treatment of GERD is most effective.[52] What is clear, however, is that the final decision on which modality is used must be based on each patient's individual circumstances and needs.

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