

Gastroesophageal Reflux Disease (GERD): A Review of Conventional and Alternative Treatments

Lyn Patrick, ND

Abstract

Gastroesophageal reflux disorder (GERD), a common disorder in the Western world, can lead to complications that include esophageal stricture and esophageal adenocarcinoma. Multiple challenges are associated with GERD treatment. First, lack of symptoms does not correlate with the absence of or the healing of esophageal lesions. Second, proton pump inhibitors, the current standard of care for GERD, are ineffective for the majority of GERD patients who have non-erosive disease. This article discusses these challenges, investigates the mechanisms of damage in GERD, and explores the existing data on unconventional forms of treatment, including melatonin, acupuncture, botanicals, and dietary interventions.

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Introduction

GERD is defined as a “condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.”¹ Heartburn, estimated to occur daily in seven percent of the U.S. population, is the most common symptom of GERD.² Between 20 and 40 percent of those experiencing common heartburn are predicted to actually have a diagnosis of GERD. In addition to heartburn, regurgitation and difficulty swallowing are common GERD symptoms. GERD also includes subcategories of diagnosis: non-erosive esophageal reflux disease (NERD) and the additional pathologies that result as GERD progresses, including esophageal ulcer, esophageal stricture, Barrett’s esophagus, and Barrett’s carcinoma (esophageal adenocarcinoma).¹

In the United States, GERD is the most common diagnosis of all presenting gastrointestinal (GI)-related complaints and accounts for about four percent of all visits in family practice.³ An estimated 14-20 percent of all U.S. adults have some

degree of gastroesophageal reflux.³ Although symptoms are only considered clinically significant if they occur at least twice weekly, in Europe and North America an estimated 10-30 percent of the population complains of symptoms related to GERD at least once weekly.^{1,4} Evidence for the prevalence of GERD symptoms also comes indirectly from the use of proton pump inhibitors (PPIs), a first-line therapy for GERD. Americans spend in excess of 10 billion dollars yearly on PPIs, while two PPIs were reported as being among the top five selling pharmaceuticals in a 2006 study.⁵ Despite the use of PPIs, the incidence of esophageal adenocarcinoma, a complication of erosive esophagitis, has been increasing significantly in the past 20 years, with an estimated increase of 200-600 percent.⁶

GERD-Associated Symptoms

While heartburn, regurgitation, and difficulty swallowing are the most common GERD-related complaints, GERD can manifest a variety of other symptoms. This recognition has led to a broader definition of GERD-related symptomology, which can include laryngitis, cough, asthma, and dental erosions, for example.¹

Regurgitation or aspiration of gastric juice in GERD can cause chronic cough, dental erosion, recurrent pneumonitis, or idiopathic pulmonary fibrosis. In one cohort of patients with idiopathic pulmonary fibrosis, 67 percent were later diagnosed with GERD.⁷ GERD can also manifest as chronic sinusitis, posterior laryngitis, nocturnal choking, chronic hoarseness, otitis media, idiopathic pulmonary fibrosis, and asthma.⁸ Epidemiological evidence suggests that 34-89 percent of asthmatics have GERD (irrespective of the use of bronchodilators).⁹

Lyn Patrick, ND – 1984 graduate of Bastyr University; consulting practice in chronic hepatitis C; Board Consultant for the American College for the Advancement of Medicine and on the faculty of ACAM Environmental Medicine and Metal Toxicology courses and lectures internationally on chronic hepatitis C, and Environmental Medicine; Contributing Editor for *Alternative Medicine Review*. Email: lpatrick@frontier.net

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GERD is a common cause of unexplained sleep disturbance. It can also manifest as angina-like pain radiating to the back, neck, jaw, or arms, hypersalivation, globus sensation (perception of a constant lump in the throat), nausea, or dysphagia.⁸

Eosinophilic esophagitis, often diagnosed in GERD, may be a separate entity or may arise as a feature of GERD. As a separate entity, it is related to a histological finding of high eosinophil counts (>15 eosinophils per high-powered field) and eosinophil degranulation on biopsy and is more commonly found in younger patients without hiatal hernia. Symptoms include dysphagia, chest pain, and food impaction.¹⁰ Eosinophilic esophagitis responds to elemental diets and elimination of food allergens.¹¹

Conditions Associated with GERD

Hiatal Hernia

Hiatal hernia is associated with an increased risk for GERD. Estimates suggest that 75 percent of those with esophagitis have a hiatal hernia, while the incidence of hiatal hernia increases to 90 percent in persons with Barrett's esophagus. Hiatal hernia can produce a separation of the lower esophageal sphincter (LES) from the crural diaphragm, causing a weakening of the gastroesophageal barrier. The result is a degree of functional incompetence at this barrier. This has been demonstrated in hiatal hernia patients with GERD.¹²

Obesity and Metabolic Syndrome

Obesity in general, and abdominal obesity specifically, is associated with an increased risk for GERD. In a meta-analysis, being categorized as overweight (BMI >25-30 kg/m²) or obese (BMI >30 kg/m²) was associated with GERD symptoms, erosive esophagitis, and esophageal carcinoma.¹³ There is also a relationship between visceral adiposity and GERD. Presumably the increased visceral fat leads to increased intra-abdominal and intragastric pressure, resulting in a predisposition for hiatal hernia.¹⁴ Obese individuals reportedly have an increased number of transient lower esophageal sphincter relaxation (TLESR) episodes secondary to gastric distention.¹⁵

Metabolic syndrome is a risk factor for GERD and its progression. Subjects with hypercholesterolemia, hyperuricemia, enlarged waist circumference, hypertension, low HDL-cholesterol level, hypertriglyceridemia, and a diagnosis of metabolic syndrome were more likely to progress from a

nonerosive esophagitis to erosive disease and less likely to regress from erosive to nonerosive states.¹⁶

Diagnosis

The diagnostic guidelines for GERD depend on whether the symptoms are complicated or uncomplicated. An uncomplicated presentation (heartburn, regurgitation, or both, often occurring after meals and aggravated by lying down or bending over, with relief obtained from antacids) is treated empirically with single daily-dose PPI.¹⁷ If no relief is obtained, the dosage is doubled. Lack of response to a PPI necessitates further diagnostic workup (upper GI endoscopy, esophageal biopsy, ambulatory esophageal pH monitoring, impedance monitoring, and esophageal Bilitest for bile detection). Current U.S. treatment guidelines recommend treatment without invasive diagnostic testing unless dysphagia, weight loss, gastrointestinal blood loss, or anemia is present. Details are provided in the treatment guidelines of the American College of Gastroenterology.¹⁷

Endoscopy is used to identify Barrett's esophagus and esophagitis in patients with long-term symptoms or alarm symptoms. A negative endoscopy does not rule out GERD; in fact, the majority of GERD patients have negative endoscopic findings. There is a non-linear, and at times paradoxical, relationship between the severity of symptoms and the severity of endoscopic findings. It is possible to have severe symptoms of GERD with negative endoscopic findings, while it is also possible to have no GERD symptoms and positive endoscopic findings. Therefore, the absence of symptoms does not indicate the absence of pathology. In one study of 1,000 northern Europeans, only 40 percent of patients with Barrett's esophagus and only 30 percent with GERD esophagitis were symptomatic.¹⁸ Barrett's esophagus (which occurs in only 0.25-3.9 percent of all cases of GERD but in 6-12 percent of all GERD patients referred for endoscopy), hemorrhagic esophageal stricture, and esophageal adenocarcinoma are also often asymptomatic.¹⁹

Self-assessment questionnaires can mimic the diagnostic accuracy of gastroenterology practices. For example, the GERDQ is a self-assessment questionnaire that was shown to have 65-percent sensitivity and 71-percent specificity in a sample of 300 patients, similar to the diagnostic accuracy achieved by gastroenterologists.²⁰ The questionnaire (Table 1) is a six-question, easy-to-score list that assesses frequency of symptoms during the previous week. A symptom score of 8 or higher

indicates a high likelihood of the presence of GERD. This questionnaire was also determined to be a predictor of response to PPI. Individuals who had no single question receiving a score of more than 1 were most likely to have a positive response to treatment.²⁰

Abnormal Physiology Involved in GERD

Some reflux is normal. Reflux is diluted with saliva and the esophagus clears the diluted refluxed acid with peristaltic action. Having a properly functioning LES with normal pressure and a normal number of episodes of transient relaxation (in the absence of swallowing) is also part of the physiological mechanism that protects against damage from stomach acid reflux. For the LES to perform this function properly, the gastroesophageal junction must be positioned in the abdomen so the diaphragmatic crura can assist the LES, in essence functioning as an external sphincter. The common defects in the pathogenesis of GERD are delayed gastric emptying, reduced pressure in the LES, increase in transient LES relaxations, ineffective clearance of reflux from the esophagus, and impaired esophageal mucosal defense.²¹

Refluxate: The Damaging Effect of Acid, Pepsin, Bile, and Pancreatic Secretions

Most reflux events do not produce symptoms of GERD. In a study of a combined total of 1,807 reflux episodes in GERD patients, only 203 episodes produced symptoms.²² In this study, reflux occurred routinely and was involved in the mechanism of belching. The symptom-producing reflux events of GERD patients in the study were related to lower pH, longer acid clearance time, and higher total acid exposure. Reflux with higher pH (4-7) produced symptoms only 15 percent of the time.²²

Bile acid and pancreatic secretions (termed duodeno-gastric-esophageal reflux or DGER) are also commonly found in the refluxate of GERD patients. Both are related to an increased risk of esophageal damage and the presence of DGER is associated with heartburn. One study of 65 patients with reflux who were non-responsive to PPI found that, while only 37 percent had acid reflux, 64 percent had DGER. The most severe esophagitis occurred in the 26 percent with both acid- and bile-based reflux.²³ Another study of the effect of DGER in GERD patients with active reflux found that 51 percent had DGER present in refluxate. Symptoms of reflux were related to higher levels of DGER and higher levels of DGER

Table 1. GERDQ Symptoms are Scored for the Previous Seven Days

Question	Frequency score (points) for symptom			
	0 days	1 day	2-3 days	4-7 days
How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
How often did you have pain in the center of your stomach?	3	2	1	0
How often did you have nausea?	3	2	1	0
How often did you have difficulty getting a good nights sleep because of heartburn and/or regurgitation	0	1	2	3
How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take (such as Tums, Rolaids or Maalox)?	0	1	2	3

Adapted from: Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009;30:1030-1038.

increased risk for the severity of esophageal damage and Barrett's esophagus.²⁴

In vitro studies show bile acids alone, in a low pH environment, can induce oxidative damage in a model of Barrett's esophagus and that oxidative damage can lead to esophageal inflammation.²⁵ Although the use of PPI therapy has been shown to reduce DGER, this effect is not consistent or predictable. The use of promotility agents (e.g., baclofen 20 mg) has been shown to reduce symptoms in patients with DGER who were not responsive to PPI, suggesting that motility problems in these patients might be the source of DGER.²³

Lower Esophageal Sphincter Relaxation

The majority of cases of GERD involve resting LES pressures that are within the normal range.^{21,26} Reflux occurs instead during TLESR, which is part of the normal function of the LES. This relaxation is not related to swallowing or peristaltic action, but is responsible for the occurrence of belching in normal stomach function. In GERD, the relaxation of this sphincter is directly related to reflux episodes. Gastric distention is believed to be the trigger for reflux during transient relaxation and may be the reason that postprandial reflux, triggered by stretch receptors in the stomach, is more common than at any other time.²¹

Another cause of TLESR involves colonic fermentation of carbohydrate. Between two and 20 percent of all ingested carbohydrate is metabolized into short-chain fatty acids by intestinal flora in the colon.²⁷ Lactose is known to be one of the most poorly absorbed disaccharides. When healthy human subjects were given colonic infusions of 30 g of lactose along with short-chain fatty acids (SCFA), the numbers of TLESR and acid reflux episodes that followed were significantly elevated. The SCFA infusions also lowered LES pressure and increased the number of reflux episodes more significantly than lactose itself.²⁸ The amount of lactose used in this study was a relatively large dose (30 g lactose is equivalent to 1 liter of cow's milk or 2.5 cups of ice cream). The dose was chosen in an attempt to duplicate what might occur if lactose was given to a lactose-intolerant individual. This amount of lactose would lead to 135 mmol of SCFA, the amount infused in the study. This research agrees with other studies where lactose and SCFA administration has resulted in delayed gastric emptying and gastric distention.^{29,30}

Esophageal Involvement

Esophageal erosion is a result of both the time that esophageal tissue is exposed to stomach contents and the sensitivity of the esophageal tissue to those fluids. Reflux of the stomach contents occurs as part of normal physiology. Normal mechanisms for removing and diluting refluxed stomach contents include esophageal peristalsis to eliminate the reflux and salivary bicarbonate to neutralize it.³¹ Although it is known the ability of the esophagus to clear reflux contents is delayed in GERD, it is not clear which comes first – esophageal injury or slowed peristalsis.³²

Gastric Emptying

Delayed gastric emptying is a risk factor for GERD. In studies of gastric emptying rates, approximately 10-40 percent of GERD patients demonstrate delayed gastric emptying.³³ The relationship between delayed emptying times and esophageal acid exposure is complex; delayed gastric emptying results in less acidic refluxate, but does not increase the number of reflux events.³³ Slower gastric emptying does, however, induce gastric distension and results in a greater volume of refluxate. This may be why GERD patients with both gastric and esophageal motility problems tend to have increased damage. Studies, however, have failed to find a direct connection between delayed gastric emptying and esophageal acid exposure.³⁴

GERD and Acidity

The mechanisms that allow episodes of reflux to be felt by patients are complex. They include the time the reflux remains in the esophagus, the volume of reflux, the ability of the esophagus to neutralize the reflux with bicarbonate from saliva, and the acidity of the reflux fluid.^{22,35} A consensus definition of differing levels of acidity in reflux contents has been established: "Acid reflux" (pH < 4), "weakly acid reflux" (pH 4-7), and "weakly alkaline reflux" (pH ≥ 7).³⁶ It is estimated that in GERD patients not taking PPIs, approximately 50 percent of all reflux episodes have a weakly acidic pH above 4.³⁷

In a study evaluating the acidity of reflux and its symptom-provoking effects, both weakly acidic and acid reflux were able to generate symptoms of heartburn.³⁵ In patients with GERD who do not respond to PPIs, weakly acidic reflux may be responsible for 30-40 percent of symptoms.³⁸ In one group, a strong positive association between symptoms and weakly acidic reflux was found in 37 percent of 168 patients who did not respond to PPI therapy, but were still on medication.³⁹ In another

study of 200 patients who were PPI non-responders, 50 percent had weakly acidic reflux and the other 50 percent had weakly acidic reflux mixed with acidic reflux.⁴⁰ One proposed theory to explain why weakly acidic reflux can cause esophageal damage is that the gas in weakly acidic reflux may cause distension of the proximal esophagus, leading to dilation of the intercellular spaces (DIS), a known mechanism in esophagitis that increases mucosal permeability and heartburn. Increased esophageal DIS leading to heartburn has been shown to occur in persons who are exposed to weakly acidic bile-containing solutions.⁴¹

Non-erosive Reflux Disease: The Paradox

In a European study, 66 percent of those reporting symptoms had no evidence of erosive esophagitis – classified as non-erosive reflux disease (NERD).¹⁹ NERD accounts for 50-85 percent of all GERD diagnoses.⁴² NERD is referred to as functional heartburn, defined as “retrosternal burning in the absence of pathological gastro-esophageal reflux, pathology-based motility disorders or structural explanations.” Because only 50 percent of NERD diagnoses respond to PPI therapy, research is expanding to understand the complex etiology of NERD.⁴³

NERD is difficult to assess. Negative endoscopic findings of NERD patients do not generally correlate with symptom severity.⁴⁴ In other words, a NERD patient may have a negative endoscopy and severe symptoms of heartburn, theoretically explained by esophageal hypersensitivity. This hypersensitivity is believed to result from lowered mucosal immunity and inflammation, allowing refluxate effective access to intercellular spaces, causing DIS and resulting in symptoms of esophageal pain or heartburn. Psychological stress has also been shown to result in increased perception of esophageal pain in NERD.⁴⁵

NERD patients are less likely to have abnormal esophageal exposure to gastric contents (acid, pepsin, and bile) and lower nighttime esophageal acid exposure than those with erosive esophagitis.⁴⁶ Although NERD patients have decreased peristalsis, it is less severe than those with erosive esophagitis. NERD patients also have only mildly reduced LES pressure.⁴⁷ Hiatal hernia, a major risk factor for reflux esophagitis, only occurs in 29 percent of NERD diagnoses compared to 71 percent of those with erosive esophagitis.⁴⁸

Regardless of the presence or absence of symptoms, NERD does not generally appear to progress to erosive esophagitis. The largest population-based

study of 12,374 GERD patients, taken from a pool of patients seen from 1977 to 2001, found that only 4.4 percent progressed from NERD to esophageal lesions within a five-year period.⁴⁹ As many as 25 percent of NERD patients also appear to have esophagitis that resolves and reoccurs, according to an investigation of two-year follow-ups.⁵⁰

Treatment of GERD: Lifestyle Interventions

Avoidance of tobacco, alcohol, chocolate, and citrus juice is typically recommended for GERD treatment.⁵¹ While published GERD trials provide evidence that smoking, alcohol, carbonated beverages, coffee, and chocolate ingestion lead to decreased LES pressures, there is disagreement regarding whether dietary and lifestyle changes can result in actual clinical improvement in GERD. A review of the literature included 2,039 studies on lifestyle factors, including weight loss, timing of meals, elevation of head during sleep, and avoidance of alcohol, smoking, coffee, citrus, and chocolate. Of the 100 relevant studies, no evidence was found for the efficacy of dietary measures or smoking or alcohol cessation in improving symptomatology, LES pressure, or esophageal pH profiles. The only efficacious factors were elevation of the head of the bed and lifestyle interventions that led to weight loss (mean loss of 12.4 kg in 13 weeks).⁵¹

Although spearmint intake has been shown to lower LES tone in one double-blind randomized controlled trial of GERD patients, it was not shown to worsen GERD symptoms.⁵²

The Geneva Workshop Report, a consensus group of 35 gastroenterologists from 16 countries, agreed that most reflux is postprandial and avoidance of any foods and beverages that provoke reflux is therapeutic.⁵³ This group also agreed, contrary to the meta-analysis cited above, that nocturnal reflux is only a problem in a small subgroup of patients, that only these individuals benefit from bed head elevation, and that it is not effective as a first line of treatment in most patients.⁵³

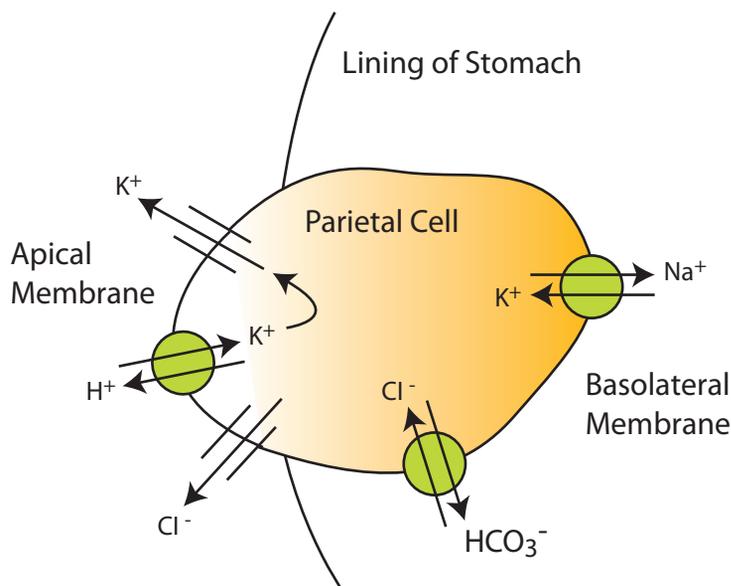
Medications Used to Treat GERD Antacids

Over-the-counter (OTC) antacids offer rapid, short-term relief from GERD symptoms. In one study that included 1,009 GERD patients, antacids were commonly used to treat break-through symptoms not effectively treated by standard PPI medication. While offering symptomatic relief, antacids have not been shown to contribute to the healing of erosive esophagitis.⁵⁴

Histamine H2-receptor Antagonists

Histamine H2-receptor antagonists (ranitidine, famotidine, cimetidine, nizatidine), like antacids, provide temporary relief, albeit with a slower onset of action than antacids. Long-term use of these medications for GERD is not recommended because the body develops tolerance within 1-2 weeks, and they are not as effective as PPIs for healing erosive esophagitis.⁵⁵

Figure 1. Gastric Acid Secretion Occurs via Hydrogen/Potassium ATPase



Adapted from: Vesper BJ, Altman KW, Elseth KM, et al. Esophageal Reflux Disease (GERD): Is there more to the story? *Chem Med Chem* 2008;3:552-559.

Prokinetics

Prokinetic medications (cisapride, metoclopramide) activate serotonergic or dopaminergic receptors to increase esophageal and gastric peristalsis, which addresses the delayed esophageal clearance seen in GERD patients.³² Prokinetic medication results in approximately 70-percent acid suppression in the gut, but the symptom relief is both slow in onset and short-term (4-8 hours).⁵⁶ These medications have not been shown to be effective in healing high-grade esophagitis. The side effect profile of prokinetics, which includes tremor, tardive dyskinesia, fatigue, and increased risk for cardiac events, limits their use for GERD.⁵⁴

Proton Pump Inhibitors

PPIs (pantoprazole, lansoprazole, esomeprazole, omeprazole, rabeprazole) are the standard of care for the treatment of GERD. The number of yearly prescriptions for PPIs has doubled in the last 10 years.⁵ Currently, 21 percent of all PPI prescriptions in the Netherlands are written specifically for gastro-protection of patients on non-steroidal anti-inflammatory drugs or aspirin. The mechanism of action of PPIs involves blocking the gastric acid pump of the parietal cells in the stomach. This pump, commonly known as hydrogen/potassium ATPase (H⁺/K⁺-ATPase) is the last step necessary for the release of hydrochloric acid from the parietal cell into the stomach lumen (Figure 1).⁵⁶ PPIs provide faster relief than prokinetics or H2-blocking agents and have good evidence for long-term healing of esophageal erosion (including Barrett's esophagus). Side effect profile includes nausea, diarrhea, headache, insomnia, and anaphylaxis.⁵⁴

Concerns associated with PPI use for GERD include failure to respond, rebound gastritis, atrophic gastritis, *Helicobacter pylori* or *Clostridium difficile* infection, and other drug-induced side effects.

A recent article assessing the need for management of PPI failure states, "The failure of PPI to resolve GERD symptoms has become the most commonly seen patient scenario in gastroenterology practices."⁵⁷ A meta-analysis of GERD patients on a once daily dosage of a PPI reported that 25-40 percent of these patients continued to have symptoms.⁵⁸ While the standard of care with PPI involves doubling the dose if an initial single dose is ineffective, only 20-25 percent of patients who fail initial treatment respond to doubling the dose.⁵⁹ The majority of non-responders most likely have NERD.⁵⁶ Reasons for the lack of clinical response to PPI in persons with NERD include weakly acidic reflux, delayed motility, reflux that contains bile, and increased esophageal pain sensitivity.¹⁴ Regardless of the reason, PPI therapy appears to be only partially effective for addressing the underlying issues in NERD patients.

Evidence indicates that when patients discontinue PPIs after long-term treatment, they eventually relapse.⁶⁰ PPIs can induce parietal cell proliferation, which leads to a state of hyperacidity after discontinuation. This rebound hyperacidity can create a dependence on continued PPI use, an issue that has become a concern among researchers and clinicians. A study reported that 33 percent of

patients given PPIs, supposedly for short-term use, renew the prescription.⁶¹ On interview, primary care clinicians viewed reduction or withdrawal of long-term PPI medication as difficult.⁶² A recent review of the long-term use of PPIs states, “Profound acid suppressive therapy leads to hypergastrinaemia in nearly all patients.”⁶³ Serum gastrin levels (clinically used to evaluate parietal cell hyperplasia and to predict the rebound acidity that occurs with long-term use of PPI) are commonly increased to four times the upper limit of normal while on PPI medication. In some patients, levels can be elevated to 40 times the upper limit of normal (4,000 ng/L). These elevated levels normalize very slowly after PPI withdrawal.⁶³

In 120 healthy volunteers, rebound acid hypersecretion occurred after as little as eight weeks of PPI treatment. Forty-four percent of those in the study who were on a PPI for eight weeks experienced acid-related symptoms 9-12 weeks after discontinuing the PPI. The authors of this study suggested that patients taper off PPIs more gradually than is commonly suggested, due to the observation that symptoms lasted up to four weeks post-discontinuation.⁶⁴ Two additional studies report increased acid production can continue more than eight weeks post PPI discontinuation,^{65,66} lending credence to the concerns about rebound hyperacidity and the need to taper off slowly.

Persons who experience rebound acidity as a result of PPI withdrawal are more likely to be infected with *H. pylori* and to develop atrophic gastritis.⁶⁷ Atrophic gastritis has been seen in 30 percent of patients infected with *H. pylori* on long-term PPI therapy.^{68,69} Findings of an increased incidence of atrophic gastritis in GERD patients on long-term PPI therapy have been confirmed in multiple studies.^{70,71} One 12-month study of PPI therapy did not find increased atrophic gastritis, although they did report increased levels of inflammation in the corpus of the stomach.⁷² Other studies report that, although *H. pylori* infection increases the risk for atrophic gastritis in GERD, it might be protective for severe reflux esophagitis, Barrett’s esophagus, and esophageal adenocarcinoma.⁷³ Erosive reflux esophagitis occurs significantly more often in the absence of *H. pylori* infection.⁷⁴ The “protective effect” of *H. pylori* is apparent in the most virulent strain (cagA+). The risk of developing Barrett’s esophagus with dysplasia or adenocarcinoma is decreased two-fold in individuals infected with the cagA+ strain when compared with *H. pylori*-negative esophagitis

patients.⁷⁵ This protective effect of *H. pylori* is presumably due to *H. pylori*-induced atrophy of the parietal cells. The atrophied cells produce less acid which reduces the acid load on the esophagus. This hypochlorhydric effect is lost when *H. pylori* is successfully treated.^{74,75} Further evidence in support of this protective relationship has been shown when treatment of *H. pylori* has promoted the development of esophagitis in both patients with GERD and otherwise healthy patients.^{76,77}

Concern has been raised about the risk for nosocomial and outpatient *Clostridium difficile* infection in long-term PPI users. Studies have found a dosage-related risk for PPI users as well as increased risk for reinfection.⁷⁸ In one prospective study of inpatient *C. difficile* cases, 64 percent of patients were on a PPI when the infection developed. The authors could find no valid indication for PPI therapy in 63 percent of the cases.⁷⁹

PPI use is also linked to a significant increased risk for hospital-acquired pneumonia⁸⁰ and a doubling of risk for reinfection with community-acquired pneumonia.⁸¹

There is also a modest increased risk for fractures of the hip, spine, and lower arm, and increased risk for the number of total fractures in menopausal women on a PPI.⁸²

Surgical Intervention for GERD

The primary surgical intervention for the treatment of GERD is laparoscopic fundoplication, a procedure where the fundus of the stomach is wrapped around the esophagus to create a new cardiac valve-equivalent at the gastroesophageal junction. It is often recommended for patients who have diagnosed erosive GERD, Barrett’s esophagus, or cardiac conduction defects, for postmenopausal women with osteoporosis, patients who have poor compliance with medication, and for those with serious respiratory or oral manifestations of GERD. An examination of the data available on the comparison of medication to surgical intervention by the Agency for Healthcare Research and Quality revealed that 10-65 percent of patients undergoing surgical intervention still require medication. The analysis also found that PPIs appear to be as effective as surgery for improving symptoms and decreasing esophageal acid exposure.⁸³

Alternative Treatments for GERD Low-Carbohydrate Diet

Although there have been no large scale trials of GERD and low-carbohydrate diets, a case series⁸⁴ and two small trials^{85,86} provide evidence that

Table 2. Acupuncture versus Omeprazole: Points Used in the Study

Per 6	Neiguan
St 36	Zusanli
CV 12	Zhangwan
CV 17	Shanzhong
Liv 3	Taichong
Sp 9	Yinlingquan

low-carbohydrate diets may be related to symptom improvement. In the first small case series, five individuals followed the standard Atkins diet, which restricts carbohydrates to 20 g daily, while allowing unlimited access to protein and fat. According to patient self-reports, all five patients had a remission of GERD symptoms within one day to two weeks from the time they started the diet, and symptoms reoccurred when it was discontinued. Three of the five individuals restricted caffeine or coffee, and alcohol was not eliminated in all cases. Because dietary change in these cases included

reduction or elimination of caffeine in three cases or elimination of other potentially bothersome foods (e.g., tomato sauce, fruit juices), it is not clear whether reduction of dietary carbohydrate was the only factor involved in the elimination of GERD symptoms.⁸⁴

In an older, non-randomized, crossover study, 41 participants with diagnosed severe dyspepsia were placed on either a low-carbohydrate diet or a “gastric diet” (defined as a low-fat diet that eliminated caffeine and alcohol) for three months, then crossed over to the alternate, low-carbohydrate diet. Sixty-eight percent of the participants had improvement on the low-carbohydrate diet compared to the “gastric diet,” 27 percent did not notice any difference between diets, and five percent had a worsening of symptoms on the low-carbohydrate diet.⁸⁵

A recent study assessed eight obese individuals with GERD on a diet that, like the Atkins diet, was restricted to 20 g carbohydrate daily. Participants underwent esophageal pH monitoring and completed the GERD Symptom Assessment Scale-Distress Subscale (GSAS-ds) pre-initiation of the diet and six days later. The authors concluded that after six days on the diet, the symptom scale improved and esophageal acid exposure dropped significantly.⁸⁶

Acupuncture

Standard of care in patients who do not respond to a single dose (20 mg once daily) of a PPI is to double the dose (20 mg bid). A recent U.S. trial looked at the efficacy of acupuncture versus doubling the PPI dose in patients who failed single-dose PPI treatment. Thirty patients with endoscopy-diagnosed NERD were randomized to receive their original PPI dose (omeprazole 20 mg once daily) plus acupuncture, or a double PPI dose (omeprazole 20 mg twice daily). Acupuncture treatment consisted of five points (Table 2) and was administered in 10 sessions over a four-week period. The acupuncture point Spleen 9 was either included or omitted based on a traditional Chinese medicine (TCM) evaluation conducted by the practitioner. At week 4, symptom assessments from both groups were compared to pretrial symptom ratings. Improvement in the symptom survey of those in the double-dose PPI group was only statistically improved for the symptom of daytime heartburn (Table 3). All symptoms in the acupuncture plus single dose PPI group improved significantly (Table 4).⁸⁷ The authors concluded that suppression of gastric acid secretion alone is an unlikely reason the acupuncture group improved significantly; more

Table 3. Symptom Ratings after Four Weeks of Double-dose Omeprazole Compared to Baseline

Symptom value	Baseline	4 weeks	P-value
Daytime heartburn	12.867 ± 1.816	16.400 ± 1.632	0.030
Night-time heartburn	12.800 ± 1.694	15.667 ± 1.305	0.065
Acid regurgitation	8.993 ± 2.226	7.400 ± 1.712	0.299
Dysphagia	6.333 ± 2.267	7.200 ± 1.996	0.495
Chest pain	6.000 ± 1.813	5.800 ± 1.529	0.920

Adapted from: Dickman R, Schiff E, Holland A, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. *Aliment Pharmacol Ther* 2007;26:1333-1344.

Table 4. Symptom Ratings after Four Weeks of Acupuncture Plus Single-dose Omeprazole Compared to Baseline

Symptom value	Baseline	4 weeks	P-value
Daytime heartburn	18.333 ± 1.816	3.267 ± 1.632	<0.001
Night-time heartburn	18.067 ± 1.694	3.600 ± 1.305	<0.001
Acid regurgitation	14.867 ± 2.226	3.733 ± 1.712	<0.001
Dysphagia	6.600 ± 2.267	2.933 ± 1.996	0.007
Chest pain	7.200 ± 1.813	1.267 ± 1.529	0.006

Adapted from: Dickman R, Schiff E, Holland A, et al. Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn. *Aliment Pharmacol Ther* 2007;26:1333-1344.

probable mechanisms involved increased gastric and esophageal motility and decreased pain perception.⁸⁷

Studies suggest other potential mechanisms associated with symptom improvement with acupuncture treatment. Acupuncture increases gastric peristalsis and accelerates gastric emptying in patients with dyspepsia.^{88,89} Perhaps more importantly, acupuncture improves esophageal peristalsis, limits lower esophageal sphincter relaxation, and reduces esophageal pain perception.^{90,91}

Melatonin

Up to 500 times more melatonin is synthesized in the mammalian intestinal tract than in the pineal gland.⁹² Although production is highest in the stomach, small intestine, and distal colon, evidence also exists for some production in the mouth and esophagus.^{93,94} Melatonin is produced by the enterochromaffin cells in the stomach and intestinal tract, which also produce serotonin.⁹² After feeding, levels of melatonin in the mucosa of the mammalian gut are 100-400 times higher than in peripheral blood. This increase in intestinally-derived melatonin appears to be in response to diet-derived tryptophan.⁹⁵ Melatonin manufactured in the gut is then delivered to the liver and gall bladder where concentrated levels in the portal vein are higher than in the peripheral circulation.^{93,96}

Melatonin has been identified as an important gut motility signal and an effective signaling molecule for communication between the gut and the liver.⁹⁷ Both significant amounts of melatonin and melatonin-binding sites are present in the esophageal mucosa.⁹⁸ Orally administered melatonin has a local effect on the esophageal mucosa in animal models, increasing microcirculation and modulating nitric oxide production.⁹⁹ Melatonin stimulates the production of nitric oxide and prostaglandin E2, both of which protect the esophageal mucosa from damage induced by stress and excessive free radical production.⁹⁹ Melatonin also inhibits gastric acid secretion, while increasing gastrin release.⁹⁹ Gastrin then stimulates the contractile activity of the LES; both actions protect the esophagus by minimizing contact with refluxate. Melatonin has also been shown to prevent acid-pepsin-induced esophagitis in animals.¹⁰⁰

In experimentally-induced reflux esophagitis, melatonin reversed inflammatory lesions and reduced lipid peroxidation that occurs as a result of gastric juice and bile-containing duodenal contents.

Melatonin was also found to reduce inflammatory cytokine levels of tumor necrosis factor-alpha (TNF- α), interleukin (IL) -1 β , and -6 and to normalize levels of glutathione and superoxide dismutase, the latter two of which are antioxidants depleted in experimental models of reflux esophagitis.¹⁰¹

Human trials of melatonin for GERD are limited, but the results are significant. One study compared 176 patients on a nutrient/melatonin combination with 175 patients on 20 mg omeprazole.¹⁰² The nutrients provided included tryptophan, vitamin B₆, vitamin B₁₂, methionine, betaine, and folic acid. The nutrients were selected to promote the synthesis of s-adenosyl-L-methionine (S-AdoMet), an increase of which might increase serotonin and noradrenaline and act as an analgesic (Table 5). Melatonin was selected due to its efficacy in animal models of GERD. Treatment effect was measured by the length of time to become asymptomatic (defined as no heartburn or regurgitation) for 24 hours.

**Table 5. Daily Dosage of Melatonin/
Nutrient Supplement**

Melatonin	6 mg
L-Tryptophan	200 mg
Vitamin B12	50 μ g
Methionine	100 mg
Betaine	100 mg
Folic acid	10 mg
Vitamin B6	25 mg

Pereira RS. Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and amino acids: comparison with omeprazole. *J Pineal Res* 2006;41:195-200.

Ninety percent of patients taking the nutrient/melatonin combination experienced relief after seven days, while 66 percent of those on omeprazole had similar relief after nine days. After 40 days, 100 percent of the patients in the melatonin/nutrient group reported relief of symptoms compared to 66 percent of the omeprazole group. At the end of the 40-day trial, the 60 patients in

Table 6. Results of GERD Study Comparing Melatonin with Omeprazole

		Melatonin	Omeprazole	Melatonin & Omeprazole	
Symptoms	Heart burn				
	control	0	0	0	
	pretreatment:				
	yes	7	7	8	
	duration	1.3 ± 0.4	1.2 ± 0.3	1.4 ± 0.4	
	4 weeks	3(57.1%)	2(71.4%)	1(87.5%)	
	8 weeks	0(100%)	0(100%)	0(100%)	
	Epigastric pain				
	control	0	0	0	
	pretreatment:				
	yes	6	6	6	
	duration	1.4 ± 0.5	1.3 ± 0.4	1.3 ± 0.4	
4 weeks	3(50%)	2(66.7%)	1(83.3%)		
8 weeks	1(83%)	0(100%)	0(100%)		
LES Study	LES pressure (mmHg)				
	control	22.8 ± 1.3	22.8 ± 1.36	22.8 ± 1.3	
	pretreatment	10 ± 1.58	10.5 ± 2.86	10.3 ± 1.68	
	4 weeks	14.5 ± 1.58	10.4 ± 4.05	14.5 ± 1.26	
	8 weeks	20.2 ± 1.56	10.5 ± 2.85	20.5 ± 1.22	
	Relaxation duration (seconds)				
	control	5.0 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	
	pretreatment	6.8 ± 0.12	6.5 ± 2.74	6.8 ± 0.16	
	4 weeks	5.9 ± 0.16	6.3 ± 2.7	5.8 ± 0.13	
	8 weeks	5.3 ± 0.12	6.3 ± 2.65	5.2 ± 0.12	
	pH (at 5 cm above the LES)	control	7.8 ± 0.4	7.8 ± 0.4	7.8 ± 0.4
		pretreatment	2.3 ± 0.36	2.1 ± 0.38	1.98 ± 0.37
4 weeks		5.2 ± 0.5	5.9 ± 0.48	6.1 ± 0.55	
8 weeks		6.7 ± 0.65	7.2 ± 0.32	7.5 ± 0.31	
BAO(mmol/h)	control	2.6 ± 0.6	2.6 ± 0.6	2.6 ± 0.6	
	pretreatment	24.7 ± 0.5	25.1 ± 0.6	24.9 ± 0.7	
	4 weeks	20.1 ± 0.4	17.2 ± 0.7	15.8 ± 0.9	
	8 weeks	16.6 ± 0.6	11.5 ± 0.6	10.2 ± 0.9	
Serum Gastrin(pg/ml)	control	41.8 ± 7.1	41.8 ± 7.1	41.8 ± 7.1	
	pretreatment	22.1 ± 4.2	21.5 ± 4.6	21.9 ± 4.7	
	4 weeks	27.2 ± 2.3	32.1 ± 2.1	33.6 ± 2.7	
	8 weeks	32.3 ± 2.1	35.9 ± 1.8	36.8 ± 2.1	
Melatonin level at day time (pg/ml)	control	36.1 ± 2.3	36.1 ± 2.3	36.1 ± 2.3	
	pretreatment	18.2 ± 5.54	18.5 ± 3.75	18.3 ± 3.8	
	4 weeks	28.26 ± 2.26	19.2 ± 3.47	28.83 ± 1.82	
	8 weeks	34.5 ± .35	17.9 ± 3.72	34.5 ± 2.35	

Adapted from: Kandil TS, Mousa AA, El-Gendy AA, Abbas AM. The potential therapeutic effect of melatonin in gastro-esophageal reflux disease. *BMC Gastroenterol* 2010;10:7.

the omeprazole group who still reported symptoms were given the melatonin/nutrient combination for another 40 days. At the end of this treatment period 100 percent of these PPI non-responders (omeprazole) reported that all symptoms had resolved. Side effects reported in the omeprazole group (n=175) were diarrhea (7 patients), headache (2 patients), hypertension (3 patients), and somnolence (4 patients). The single side effect experienced by those in the melatonin/nutrient group was somnolence, which occurred in 159 of 176 subjects.¹⁰²

Another smaller human study consisted of 60 symptomatic GERD patients diagnosed by endoscopy and compared to a control group comprised of persons without GERD.¹⁰³ All GERD patients in the study had decreased LES pressure, increased LES relaxation duration, lowered esophageal pH, lowered serum gastrin levels, and elevated gastric basal acid output. GERD patients were treated with 3 mg melatonin alone, 20 mg omeprazole alone, or melatonin and omeprazole. Repeat symptom survey and all other indices of GERD were measured at four and eight weeks.

The effect of melatonin and omeprazole and the differences among the three groups are detailed in Table 6. Heartburn and epigastric pain were decreased after four weeks and completely resolved after eight weeks in all treatment groups. One of the primary differences among the treatment groups was that only the two groups that included melatonin as part of the protocol had significant improvements in LES function; the omeprazole-alone group did not. All treatment groups experienced an increase in serum gastrin (reflecting improved gastric motility) and a significant decrease in basal acid output. Treatment with omeprazole or omeprazole plus melatonin resulted in a significant improvement in esophageal pH and gastrin in addition to a decrease in gastric acid output compared to the melatonin-only group after four and eight weeks. Measurements at the beginning of the trial revealed that patients with GERD had about half the daytime serum melatonin levels compared to controls. Both nighttime and daytime melatonin levels increased to near normal in both groups on melatonin, but did not change in the omeprazole-only group.¹⁰³

Botanicals for GERD

Lonicerae: Chinese Honeysuckle Flower

The flower of *Lonicerae* (jin yin jua, Chinese honeysuckle) was evaluated in an animal model of GERD. When rats were pretreated with a powdered water-extract preparation at a dose of 125-, 250-, or 500 mg/kg and sacrificed nine hours later, there were significant improvements in esophageal lesion scores and thickness of the esophageal mucous membrane. The mechanism of action was believed to be an antioxidant effect. The gastric mucosa of treated animals had significantly higher levels of glutathione and lower levels of myeloperoxidase; the antioxidant, tissue-protective effects were similar to animals given alpha-tocopherol. There have been no published human studies of Chinese honeysuckle and GERD.¹⁰⁴

Spearmint/Peppermint

While ingesting spearmint does not appear to improve or worsen GERD symptoms,⁵² peppermint oil might have some benefits. Peppermint oil is reported to accelerate the early phase of gastric emptying, increase relaxation time of the pyloric valve, and decrease the resting lower esophageal sphincter pressure.¹⁰⁵

Iberogast®

STW 5 (Iberogast) is a commercial ethanolic extract formula that includes nine botanicals: *Iberis amara*, *Matricaria chamomilla*, *Carum carvi*, *Mentha piperita*, *Glycyrrhiza glabra*, *Melissa officinalis*, *Chelidonium majus*, *Silybum marianum*, and *Angelica archangelica* (Table 7). Iberogast has been shown to both inhibit the function of the proximal stomach (through the actions of the botanicals chamomile flowers, licorice root (*Glycyrrhiza*), and garden Angelica root), while greater celandine (*Chelidonium*), lemon balm leaf (*Melissa*), caraway fruit (*Carum*), and bitter candytuft (*Iberis*) increased the motility of the distal stomach.¹⁰⁶ While these mechanisms theoretically improve gastric motility, Iberogast has not been shown to increase gastric emptying in human trials.¹⁰⁷

Iberogast has been evaluated in six randomized controlled trials for the treatment of functional dyspepsia. In three trials that were selected for meta-analysis, 273 patients classified as having “functional dyspepsia” had symptoms of GERD (acid regurgitation, epigastric pain, or dysmotility symptoms). The trial dosages were consistent – 1 mL three times daily for four weeks. At the end of the trials 83/138 treated patients reported that

their symptoms had changed from severe to either mild or absent, while only 33/135 in the placebo group had the same response. At the end of treatment only seven percent of the treatment group said their symptoms remained “severe” or “very severe,” while 26 percent of the placebo group still complained of the “severe” or “very severe” nature of their symptoms. STW 5 was most effective for the specific complaints of epigastric pain, retrosternal pain, and acid regurgitation. Adverse events using the botanical combination of STW 5 during the trials were similar to placebo. The adverse events reported during the 14 years of these trials are seven cases of dermatitis that included both disseminated neurodermatitis and angioedema, six cases of digestive intolerance and one case of allergic asthma.¹⁰⁶

While STW 5 appears to be effective in treating some of the symptoms associated with GERD, trials have not attempted to measure factors such as changes in LES pressure or esophageal healing. Further research with endoscopic evaluations to determine whether Iberogast influences the healing of esophageal ulceration is warranted. STW 5 has been on the German market for 40 years, has a good safety profile,¹⁰⁶ and might be appropriate for symptomatic relief in persons with GERD.

Table 7. Herbal Constituents of Iberogast

Latin Name	Common Name	Part Used	Amount (per 100 mL)
<i>Matricaria recutita</i>	German chamomile	flower	20 mL
<i>Iberis amara</i>	clown's mustard (or bitter candy)	tuft	15 mL
<i>Angelica archangelica</i>	garden angelica	root and rhizome	10 mL
<i>Carum carvi</i>	caraway	fruit	10 mL
<i>Melissa officinalis</i>	lemon balm	leaf	10 mL
<i>Chelidonium majus</i>	greater celandine	aerial part	10 mL
<i>Glycyrrhiza glabra</i>	licorice	root	10 mL
<i>Silybum marianum</i>	milk thistle	fruit	10 mL
<i>Mentha piperita</i>	peppermint	leaf	5 mL

Raft-forming Agents

Raft-forming agents, the constituents of which are natural substances including alginate, pectin, and carbenoxolone (a synthetic derivative of glycyrrhizin), have been used in the symptomatic treatment of GERD. Alginate-based raft-forming agents have been used for treating heartburn and esophagitis for over 30 years. Alginate, in the presence of gastric acid, forms a gel. The bicarbonates added to the alginate formula are converted to carbon dioxide in the presence of gastric acid, which becomes trapped within the gel as bubbles and converts it to a lighter substance that can rise to the surface of gastric contents and float (thus the name “raft-forming agent”). This combination has been shown to move into the esophagus and provide a barrier to reduce acid contact with the esophageal mucosa.¹⁰⁸

Pectin-based raft-forming agents are effective for reducing esophageal pH and preventing reflux of food and gastric contents.¹⁰⁹ Trials in GERD patients with hiatal hernia and reflux have shown benefit symptomatically and endoscopically with carbenoxolone-based raft-forming agents.¹¹⁰ Alginate-based raft-forming agents have been demonstrated to prevent relapse of healed reflux esophagitis.¹¹¹ Pectin-based raft-forming agents have been tested in a comparison trial with PPIs and found to be faster acting and as effective at reducing reflux of both food and acid, although the PPI (esomeprazole) was significantly more effective based on the patient satisfaction reports (92 percent versus 58 percent on the pectin-based raft-forming agent).¹¹² Pyrogastone is a raft-forming antacid that contains alginate, magnesium trisilicate, aluminum hydroxide, sodium bicarbonate, and carbenoxolone. Pyrogastone has been

Table 8. Summary of Studies on Raft-forming Agents for GERD

Study	n	Design	Length	Dosage	Indicators	Outcome
Young et al	29/30	DBRC in endoscopy-confirmed GERD; pyrogastone vs. alginate raft	8 weeks	1 tid after meals and 2 at bedtime	Symptom rating scale, endoscopy	Pyrogastone: 82% improvement in 8 weeks vs. 63% on antacid/alginate
Reed et al	37	DBRC in endoscopy-confirmed GERD; pyrogastone vs. alginate raft	8 weeks	same	Symptom rating scale, endoscopy	Pyrogastone: 89% symptom remission in 8 weeks; 95% endoscopy confirmed esophageal ulcer remission compared with 67% controls (antacid/alginate alone)
Markham et al	104	Endoscopy confirmed GERD; Retrospective analysis in three groups: pyrogastone, pyrogastone plus metoclopramide, both with cimetidine	42 months	same	Symptom rating scale, endoscopy	Addition of either metoclopramide or cimetidine did not improve outcome; pyrogastone alone resulted in symptom relief in 85% of 96 patients in 4-8 weeks; endoscopic healing in 76% of 55 patients in 4-8 weeks
Maxton et al	80	Endoscopy confirmed GERD; randomized to pyrogastone or cimetidine	12 weeks	same	Symptom rating scale, endoscopy	Pyrogastone: 40% healed at 6 weeks vs. 37% on cimetidine; both equivalent at 12 weeks

DBRC= double-blind, randomized, control trial

compared to alginate formulations, motility agents (metoclopramide), and histamine H₂-receptor antagonists (cimetidine). In comparison studies, pyrogastrone was more effective for improving endoscopic findings and symptom rating scales than alginate alone, and as effective as both metoclopramide and cimetidine together (Table 8).¹¹³⁻¹¹⁶ Raft-forming agents lack major side effects and are considered useful in treating mild-to-moderate forms of GERD.¹¹³

D-Limonene

D-limonene is found in citrus oils and used as a fragrance and flavoring agent in body products and beverages. As such it is considered safe for ingestion and generally recognized as safe (GRAS). Clinical trials have determined no toxicity or side effects in humans at 100 mg/kg.¹¹⁷ In unpublished data, 19 patients with GERD or chronic heartburn were given 1,000 mg d-limonene daily or every other day. After 14 days, 89 percent of patients reported a complete remission of symptoms. Following this pilot trial, 13 participants with GERD or chronic heartburn were randomized to 1,000 mg d-limonene once daily or every other day or placebo. By day 4, 29 percent of participants on treatment experienced significant relief and by day 14, 86 percent experienced complete relief of all symptoms, compared to 29 percent on placebo.¹¹⁸ The mechanism of action of d-limonene in GERD and chronic heartburn is unknown, although *in vitro* research suggests it may protect mucosal surfaces from gastric acid and support normal peristalsis.^{118,119}

Esophagitis and Oxidant Stress

Because the severity of esophageal damage cannot be predicted based on the amount of time acid contacts the esophageal mucosa, nor can the pH of esophageal refluxate predict the severity of symptoms, researchers have proposed that factors other than the acidity of refluxate or the amount and duration of exposure to refluxate might determine esophageal damage. Several studies demonstrate mucosal resistance, inflammation, and free radical damage are major determinants in the progression of reflux esophagitis.¹²⁰⁻¹²² The esophageal epithelium is morphologically and embryologically related to skin epithelium, and skin epithelium is recognized as a major immunological organ. The esophagus has similar keratinocytes and epithelial cells that are able to secrete proinflammatory cytokines (e.g., IL-8, IL-10, nuclear factor-kappaB [NF-κB], IL-6, and platelet

adhesion factors).¹²³ Esophageal biopsies demonstrate elevated levels of these cytokines in GERD, with significantly higher levels in Barrett's esophagus and adenocarcinoma than patients with erosive GERD.¹²³

Artemisia asiatica

Higher levels of reactive oxidant species are found in the esophageal tissue of patients with GERD, especially in Barrett's esophagus and esophageal adenocarcinoma.¹²⁴ In an animal model, oxidative stress was found to be more important than acid exposure in development of esophageal ulcerations.¹²⁵ In this animal model, the use of ethanol-extracted *Artemisia asiatica*, given at two dosages of 30 mg/kg or 100 mg/kg, acted as an antioxidant and was more effective in preventing esophageal erosion than ranitidine (Zantac®).¹²⁵

Curcumin, Quercetin, and Vitamin E

In a study designed to simulate acid exposure experienced by GERD patients, curcumin prevented the expression of inflammatory cytokines in human esophageal tissue.¹²⁶ In another animal model, rats with experimentally-induced reflux esophagitis were given quercetin (100 mg/kg) or alpha-tocopherol (16 IU/kg) and compared with rats on omeprazole. Both quercetin and alpha-tocopherol lowered the level of esophageal inflammation and decreased acid and pepsin production in the stomach. Both antioxidants also raised levels of glutathione and other antioxidant enzymes while decreasing collagen production, indicating an anti-inflammatory and antifibrotic effect.¹²⁷

Conclusion

Current conventional approaches to GERD management rely extensively on the use of PPIs. While these medications can be effective in treating non-erosive GERD, their utility for many GERD patients is less evidence-based. Over-reliance on PPIs is also potentially problematic because they are often used not only as a means of treating GERD, but as a means of diagnosis, with the response to a trial of a PPI routinely relied upon as the primary method of GERD diagnosis. If a patient responds favorably to a PPI, it is presumed that GERD has been effectively addressed. However, a remission of symptoms subsequent to PPI treatment does not always reflect healing of underlying pathology. The simplistic model of GERD, in which acid exposure equals degree of erosion, does not bear out in the literature. Animal models and *in vitro* research linking oxidative

stress to esophageal damage continue to challenge the current model of pathogenesis. These underlying issues need more investigation and will ideally be considered in future research designed to prevent and treat GERD.

While older medications, like raft-forming agents based upon alginates, pectins, and glycyrrhizin analogs have been proven to be effective and safe in mild-to-moderate disease, they have fallen out of favor, replaced by newer, more expensive agents.

Melatonin is a potentially attractive alternative therapy for GERD. It might directly address several underlying mechanisms (oxidative stress, inflammation, motility, and gastrointestinal signaling). Its primary side effect is, not surprisingly, somnolence, which occurs in a majority of persons. While it has not been investigated, it is at least possible that the increased quality of sleep that occurs because of this side effect contributes in part to the therapeutic response to melatonin in GERD patients.

The use of compounds such as curcumin and quercetin has not been explored in human GERD trials, but the existing *in vitro* and animal data suggest these compounds warrant further investigation. The botanical combination Iberogast has shown efficacy in existing trials and has a low side effect profile. Further research on this botanical combination is warranted.

Evidence suggests acupuncture might play a therapeutic role in combination with PPIs for treatment of GERD. Its efficacy as a stand-alone treatment for this condition has not been investigated. More research on acupuncture in combination with other therapies and as a stand-alone approach should be conducted.

There is insufficient evidence to make any definitive dietary recommendations for persons with GERD. Limited evidence suggests potential benefits from consuming a low-carbohydrate diet. Evidence also suggests that dietary changes that produce weight loss might benefit GERD.

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