Gastroesophageal reflux disease (GERD) is a chronic recurrent condition affecting millions of Americans. A recent study investigating the economic and social burden of gastrointestinal (GI) disease in the United States indicated that GERD was the most common GI-related diagnosis given at office visits in 2006. This study also showed that sales of proton pump inhibitors (PPIs) exceeded $10 billion per year, and the number of prescriptions for PPIs per year has doubled since 1999. Numerous environmental and genetic risk factors have been implicated in the pathogenesis of GERD. GERD commonly presents with heartburn and acid regurgitation, although there are numerous atypical presentations, such as chronic cough, noncardiac chest pain, laryngitis, and poor sleep quality. This disease is associated with several other conditions, including Barrett’s esophagus, esophageal carcinoma, gastritis, esophagitis, respiratory conditions, sleep disorders, and various ear-nose-throat (ENT) conditions. Conventional treatment often includes the use of PPIs and other acid blockers. Natural therapies and lifestyle interventions are important to consider, owing to the chronic nature of GERD.

PREVALENCE

Studies attempting to assess the prevalence of GERD widely vary in their results, depending on criteria used for diagnosis. A large survey performed by the National Heartburn Alliance in 2000 estimated that 60 million Americans have GERD symptoms at least once per month, and 25 million adults have daily symptoms. This survey revealed that 95% of these individuals have had symptoms for more than one year, and 54% have had symptoms for more than five years. Forty percent of these individuals reported symptoms two to four times per week, and 33% reported symptoms five times per week or more. This survey also showed that GERD symptoms greatly affect activities of daily living, as more than 80% of the respondents reported decreased enjoyment of food, more than 60% reported that symptoms affected their ability to sleep well, and approximately 40% reported that their symptoms affect concentration at work and family activities.

RISK FACTORS

Both genetic and environmental factors appear to influence the presence of GERD. Numerous studies have shown that obesity, weight gain, and increasing body mass index (BMI) are associated with GERD. Hiatal hernia is also a risk factor for GERD symptoms. Studies indicate that individuals with large hiatal hernias have shorter and weaker lower esophageal sphincters (LES), increased amount of reflux, less-efficient acid clearance, less-effective peristalsis, and increased severity of esophagitis compared with individuals with small or no hiatal hernia. Research also indicates that smoking, excess alcohol consumption, irritable bowel syndrome, and a family history of upper GI disease are risk factors. Pharmaceutical usage such as
anticholinergics, antidepressants, and inhaled bronchodilators are also related to the disease. This study also associated lack of education and manual work with the presence of GERD. Additional studies have suggested that increased intake of table salt, sweets, or white bread is also a risk factor. Exercise and diets high in fruit and dietary fiber appear to be protective against the condition. However, high-intensity exercise has been shown to decrease LES pressure and induce GERD symptoms in otherwise asymptomatic individuals. Caffeine ingestion also decreases LES pressure and decreases distal esophageal mean amplitude of contractions and peristaltic velocity, which can increase reflux. Ingestion of carbonated beverages has also been observed in a study to decrease the resting pressure, overall length, and abdominal length of the LES in healthy individuals temporarily. This study showed that 62% of individuals who drank carbonated beverages had significant decreases in these parameters to meet the criteria for incompetence of the LES.

In addition, persistent wheezing, asthma, and airway hyper-responsiveness in childhood and adolescence have been shown to significantly increase risk for GERD symptoms at age 26 independent of BMI. A study with a Spanish population indicated that long-term GERD symptoms of 10 years or longer are associated with obesity and having a direct family member with GERD symptoms. GERD symptoms of 1 year or less were more closely correlated with having a spouse with GERD symptoms or taking 1–5 aspirins per week.

**DIAGNOSIS**

Diagnosis of GERD is often based on symptoms. It is characterized by chronic intermittent heartburn as a burning sensation in the chest and throat as well as acid regurgitation presenting as a sensation of acid in the throat or mouth. GERD may also present with atypical symptoms of esophageal and extra-esophageal origin such as chronic cough, sleep disturbance, chest pain, asthma, and hoarseness. In fact, one study showed that 50% of individuals with noncardiac chest pain had abnormal pH tests or positive endoscopy confirming the presence of GERD. A positive response to PPI therapy is frequently used to confirm the diagnosis of GERD. Additional diagnostic tests are performed for an individual with an atypical presentation, a high risk for complications, or a poor response to initial therapy. Initially, a barium swallow and upper GI series are commonly performed. Esophageal pH monitoring is an important diagnostic tool for GERD. Ambulatory pH monitoring detects abnormal levels of acid in the esophagus and can be used to correlate esophageal acid exposure with symptoms. The Bravo capsule is a wireless pH monitoring device that has been shown to be more tolerable, accurate, and sensitive than the catheter-based pH monitoring. The Bilitec system measures duodenogastroesophageal reflux by evaluating bilirubin absorbance; this system is useful particularly for the subset of patients that may be affected by duodenogastroesophageal reflux. These patients report reflux symptoms with normal acid exposure in the esophagus on high-dose PPI therapy. Intraluminal impedance monitoring detects the composition, distribution, and clearing of both acid and nonacid esophageal reflux. Combined esophageal pH-impedance monitoring...
allows detection of nearly all gastroesophageal reflux episodes, acid as well as nonacid, which provides better diagnostics, particularly with patients on acid-suppression therapy.\textsuperscript{14} Esophageal manometry is also performed to measure the pressure at the LES. Esophagoscopy, more commonly called endoscopy, is used to diagnose esophagitis, and a biopsy can differentiate esophageal strictures from cancer. Endoscopy should be performed on patients with chronic GERD symptoms to rule out Barrett’s esophagus.

**PATHOPHYSIOLOGY AND ASSOCIATED CONDITIONS**

Transient LES relaxation is the primary mechanism of GERD. It results from a vaso-vagal reflex triggered by stretch receptors of the proximal stomach. Studies have indicated that most reflux episodes are acidic. However, according to one study, 28\% of episodes were only weakly acidic and 10\% of episodes were weakly alkaline.\textsuperscript{15} Numerous factors may influence the symptoms of GERD. Delayed gastric emptying, volume of gastric content, quantity and acidity of refluxed contents, ability of the esophagus to clear this material, LES function, and the resistance of the esophageal tissue can influence reflux symptoms.\textsuperscript{16} Some researchers have proposed that patients with GERD can be categorized further as having erosive esophagitis, nonerosive reflux disease, and Barrett’s esophagus.\textsuperscript{17}

**Gastritis**

There is conflicting evidence regarding the role that *Helicobacter pylori* may play in GERD pathology. There are various studies that have looked at treatment of gastritis by eradicating *H. pylori* and the effects of treatment on concurrent GERD symptoms. The results of these studies vary from showing improvement to showing worsening of GERD symptoms.\textsuperscript{18} Research regarding inflammation in the gastroesophageal junction, or cardia, has indicated that the presence of erosive GERD or *H. pylori* gastritis is associated with the inflammation.\textsuperscript{19} In addition, GERD and carditis are associated with intestinal metaplasia at the gastroesophageal junction.\textsuperscript{20}

**Esophagitis**

Esophagitis is common with GERD and may be classified as erosive or nonerosive with the severity based on the number and location of mucosal breaks. Other types of esophagitis, such as eosinophilic esophagitis, present with similar symptoms as GERD and are commonly misdiagnosed. The common presentation of eosinophilic esophagitis is dysphagia and food impaction. Additional symptoms may include epigastric pain, emesis, weight loss, and failure to thrive.\textsuperscript{21} The diagnosis is based on a histologic finding of greater than 20 eosinophils per high-powered field in the esophageal squamous mucosa. This condition also presents with motor disturbances that may cause food impaction in the absence of strictures. Manometry shows high amplitude long-duration waves in the distal esophagus particularly at night. The symptoms often respond to elimination or elemental dietary regimens and antiallergy treatment.\textsuperscript{22} Standard skin-prick tests measure type I hypersensitivity reactions, which are typically mediated by immunoglobulin E (IgE). (It is possible to have a positive skin test but normal blood levels of IgE on a radioallergosorbent test [RAST].) However, these tests do not diagnose many food-allergy reactions, which are frequently IgG-mediated. Thus, IgG testing can offer additional insights that are frequently missed with standard skin-prick tests.
Respiratory Conditions

GERD is associated with numerous respiratory conditions. Approximately 10% of patients presenting to ENT specialists have conditions that may be attributed to GERD. One study revealed that GERD is present in 75% of individuals with refractory ENT symptoms, and PPI therapy provided symptom relief or reduction in the majority of these individuals. Asthma is associated with the presence of GERD symptoms, and although the relationship has not been well-studied. It is estimated that prevalence of GERD in people with asthma is between 60%–80% in adults and 50%–60% in children. Although the direct correlation is unknown, researchers have suggested that reflux aggravates asthma, which in turn induces further reflux. GERD is associated with a chronic nonproductive cough in some individuals; the cough occurs primarily during the day and while these patients are in an upright position. One study demonstrated that chronic cough was caused by reflux in 21% of cases. In addition, the researchers showed that chronic cough was the sole presenting symptom in GERD 43% of the time.

Otitis media may also be linked to GERD. A study examining otitis media with effusion in adults demonstrated that pepsinogen concentration was higher in middle-ear effusion in patients who reported GERD symptoms. In addition, treatment for GERD with PPIs provided some patients with GERD symptom relief as well as decreasing the concentration of pepsinogen in the effusion. Additionally, research has indicated that patients with chronic rhinosinusitis have an increased prevalence of GERD. These chronic rhinosinusitis symptoms in many patients are reduced when their GERD is treated. Laryngeal symptoms may be associated with GERD. Often, they present as hoarseness, frequent throat clearing, a postnasal drip, excess phlegm, sore throat, dysphagia, a globus sensation, or cough. Chronic laryngitis and chronic sore throat are associated with GERD in as many as 60% of patients. In addition, one study showed that at least 50% of patients presenting with laryngeal and voice disorders had laryngopharyngeal reflux. Less-common GERD-related laryngopharyngeal disorders include paroxysmal laryngospasm, subglottic stenosis, vocal-cord granuloma, and laryngeal and pharyngeal carcinoma.

Oral Health

GERD has been shown to affect overall oral health. One study showed that children with GERD have increased dental erosion, salivary yeast, and salivary Mutans streptococci compared with healthy children. In addition, research indicates that children with GERD have more dental caries and more severe erosion compared with healthy children.

Sleep Apnea

Sleep disturbance is common in individuals with GERD. Patients with obstructive sleep apnea (OSA) have GERD symptoms significantly higher than the general population. Studies have indicated that the severity of GERD symptoms is correlated positively to the severity of OSA. One study showed that treatment with continuous positive airway pressure (CPAP) in individuals with GERD and OSA reduced supine esophageal-acid contact time to within normal levels in 81% of the study patients. In addition, researchers have shown that treatment of GERD in patients who have OSA decreases the number of arousals during sleep.

Barrett’s Esophagus and Cancer

Barrett’s esophagus is a precancerous condition showing intestinal metaplasia of the lower esophagus and mucosecretory cells on histologic examination. It is the precursor to esophageal
adenocarcinoma. Approximately 8%–10% of individuals with GERD have Barrett’s esophagus. In fact, the cancer risk for an individual with Barrett’s esophagus is 30 times higher than in the general population. Risk factors for Barrett’s esophagus include GERD for at least five years’ duration, male gender, Caucasian race, and age over 50. A study with U.S. veterans showed that GERD increases the risk of both laryngeal and pharyngeal cancers independent from other risk factors.

CONVENTIONAL TREATMENT

Pharmaceuticals

Pharmaceutical acid blockers are usually the initial recommendation for both diagnosis and treatment. Treatment recommendations are usually based on a step-up or step-down approach depending on the severity of symptoms. Step-up treatment typically involves an eight-week trial of a histamine H2-receptor antagonist taken two times per day as needed, changing to a PPI if symptoms are not controlled. The step-down approach begins with an eight-week trial of a PPI taken 30 to 60 minutes before the first meal of the day and then decreasing to the lowest possible dosage that provides relief. Studies have indicated that both PPI therapy and H2 blockers provide symptom relief for the majority of patients. One study showed that eight weeks of therapy with the PPI omeprazole relieved symptoms in 74%, and eight weeks of the H2 blocker ranitidine relieved symptoms in 50% of individuals with reflux esophagitis. Low-dose antacids have also been shown to decrease reflux symptoms better than a placebo.

Long-term therapy with acid blockers has not been well-studied. Some research has indicated that nutrient deficiencies may arise with these treatments. Research has also suggested that long-term therapy with both PPI and H2 blockers increases the risk of vitamin B12 deficiency significantly in elderly adults. In fact, one study demonstrated that therapy with H2 blockers caused a 53% decrease in absorption of protein-bound vitamin B12. H2 blockers have also been associated with decreased absorption of folic acid, iron, and zinc. Research has demonstrated that treatment with the H2 blocker cimetidine significantly decreases intestinal calcium transport as well as altering vitamin D metabolism. There is also evidence that long-term use of PPIs increases the risk of hip fracture significantly.

Baclofen is a gamma-aminobutyric acid (GABA) receptor B agonist currently being investigated as a possible treatment for GERD symptoms. Studies have indicated that baclofen reduces the rate of transient LES relaxations significantly, reduces the rate of gastroesophageal acid-reflux episodes, increases basal LES pressure, and increases gastric pH. Studies have also suggested that the drug is well-tolerated by patients. Atropine has also been studied as a

<table>
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<th>Commonly Prescribed Pharmaceuticals for GERD</th>
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<tr>
<td><strong>Histamine H2-receptor antagonists</strong></td>
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<tr>
<td>Cimetidine (Tagamet)</td>
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<td>Famotidine (Pepcid)</td>
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<td>Ranitidine (Zantac)</td>
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<td>Nizatidine (Axid)</td>
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<td><strong>Proton pump inhibitors</strong></td>
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treatment for GERD symptoms. Evidence suggests that administration of atropine decreases transient relaxation in the LES and significantly decreases the number of reflux episodes. However, atropine can only be administered short-term, via intramuscular injections or intravenously.

**Surgery**

Surgery is considered based on severity of disease, response to pharmaceutical treatment, risk of complications, and individual patient needs. The most frequent antireflux procedure performed is laparoscopic fundoplication, although surgery can also be done to correct hiatal hernias and other anatomical causes of GERD. Laparoscopic fundoplication places a gastric wrap around the gastroesophageal junction, strengthening the barrier function. Research has indicated that fundoplication relieves heartburn and typical symptoms in 93% of patients, yet only 56% of individuals had relief of their atypical symptoms. This procedure does not appear to replace the use of acid-blocking medication or decrease the incidence of carcinoma over standard medication therapy.

**Lifestyle Modification**

Lifestyle modifications can have a great impact on GERD symptoms. Diet recommendations include avoiding foods that trigger symptoms. Common culprits include acidic foods, such as tomatoes, coffee, tea, and citrus foods. Additionally, avoidance of foods that decrease LES pressure, such as high-fat foods, chocolate, peppermint, and alcohol, may be necessary. Research has shown that diets high in the antioxidant vitamin C are associated with less risk of GERD symptoms, Barrett’s esophagus, and esophageal adenocarcinoma. In addition, a small study showed that very-low-carbohydrate diets reduce GERD symptoms and decrease lower esophageal acid exposure in obese individuals with GERD. In fact, this study showed that diets containing less than 20 g of carbohydrates per day significantly reduced symptoms in less than six days. Another study demonstrated that chewing sugar-free gum for one half-hour after a meal reduced postprandial esophageal reflux possibly by increasing the frequency of swallowing. A study with children who had GERD symptoms that were unresponsive to treatment showed that feeding an elemental formula reduced or resolved all patients’ GERD symptoms as well as improving histologic changes in the esophagus. Commonly, it is suggested to patients to sleep with the head of the bed elevated as well as sleeping in the left-lateral decubitus position. Numerous studies have investigated the effect of weight loss on GERD symptoms. Research has indicated that weight loss and decreased visceral fat mass correlated significantly with decreased esophageal-acid exposure. Smoking cessation is also recommended.

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<th>Alternative Supplements for Treating GERD</th>
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<tr>
<td>Vitamin C</td>
<td><em>Glycyrrhiza glabra</em> (licorice)</td>
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<td>Melatonin</td>
<td>Digestive enzymes</td>
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<tr>
<td>Fish oil</td>
<td><em>Atropa belladonna</em> (belladonna)</td>
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<td>D-limonene</td>
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ALTERNATIVE TREATMENT

Antioxidants

Antioxidants have been shown to be protective in numerous diseases, such as GERD, gastric ulcers, and GI cancers. Oxidative stress of the esophageal mucosa is a contributing factor in the pathology of GERD. A study was performed with individuals with both erosive and nonerosive GERD pre- and post-antireflux surgery measuring oxidative stress. This study showed that individuals with GERD have lower glutathione levels in the distal esophagus compared with controls. In addition, myeloperoxidase activity in the distal esophagus decreased after antireflux surgery but never returned to levels found in the control group. Supplementation to increase glutathione levels with the precursors N-acetyl-cysteine and selenium may be beneficial. Additional studies have shown that oxygen-free radicals measured by arachidonic acid peroxidation metabolites are significantly higher in patients with GERD compared with controls. Studies have also indicated that free-radical oxidative damage plays a role in gastric and duodenal ulcers as well as gastric carcinoma.

Although studies directly supporting antioxidant supplementation with GERD are lacking, substantial evidence supports using antioxidant therapy for patients with gastric ulcers and cancer, and shows that the therapy may also provide benefit for patients who have GERD. Research has shown that the hormone and potent antioxidant melatonin prevented gastric ulceration and reduced endogenous hydroxyl radicals by 88%. In fact, melatonin was shown to be more effective than ranitidine for preventing stress-related ulcers in animal models.

Fish oil supplementation has also been shown to protect gastric mucosa and decrease the severity of gastric ulceration in animal studies. Fish oil increased antioxidant enzyme activity, decreased acid-pepsin secretion, increased mucin secretion, and decreased lipid peroxidation in the gastric mucosa.

A study was performed with an antioxidant dietary supplement containing melatonin, L-tryptophan, vitamin B₆, folic acid, vitamin B₁₂, methionine, and betaine. The supplement or omeprazole was given to individuals with GERD. In this study, 100% of individuals who took the supplement had complete regression of their GERD symptoms within 40 days compared with less than 66% of individuals who had regression of symptoms treated with omeprazole.

D-Limonene

D-limonene is a monoterpenic in citrus oil. Numerous studies have shown that D-limonene exerts anti-cancer, antimicrobial, and anti-inflammatory effects. In particular, studies have shown that this constituent of citrus oil is protective against GI cancers, including cancers of the stomach and colon, decreasing both growth and metastasis. Although direct evidence of D-limonene’s effects on esophageal cancer is lacking, it is certainly possible that this monoterpenic may be protective against Barrett’s esophagus and esophageal adenocarcinoma. Alternative practitioners often recommend D-limonene for treatment of GERD with generally good results, although studies are lacking.

Licorice

Glycyrrhiza glabra (licorice) root has historically been used as a demulcent and anti-inflammatory botanical for treating conditions such as gastric and duodenal ulcers. Studies have shown that ingestion of deglycyrrhizinated licorice (DGL) may increase mucous production
and accelerate healing of duodenal and gastric ulcers.\textsuperscript{68,69} In addition, a small study showed that DGL also accelerates healing of aphthous ulcers.\textsuperscript{70} Although studies that correlate DGL with GERD directly are lacking, it is reasonable to assume that DGL may provide symptom relief in patients with GERD. Clinically, alternative health care providers often prescribe additional demulcent herbs for their healing and soothing properties, including such herbs as \textit{Aloe vera} (aloe), \textit{Ulmus fulva} (slippery elm), and \textit{Althaea officinalis} (marshmallow).

\textbf{Mastic}

\textit{Pistacia lentiscus} (mastic) resin is used medicinally for treating duodenal and gastric ulcers. Animal studies show that it decreased \textit{H. pylori} colonies thirtyfold.\textsuperscript{71} Research has also indicated that mastic resin oral supplementation protects gastric mucosa from experimentally induced damage as well as decreasing free acidity.\textsuperscript{72} In addition, a small study showed that mastic supplementation provided symptomatic relief of duodenal ulcers in 80\% of individuals who were treated with the supplement, and 70\% experienced healing with endoscopy.\textsuperscript{73} The antisecretory and cytoprotective activity of mastic may provide benefit for individuals with GERD, although direct evidence is lacking.

\textbf{Minerals}

Calcium carbonate, magnesium, aluminum, and phosphate salts are frequently used in over-the-counter antacids. Studies have indicated that antacids are effective for treating GERD symptoms, reducing acid regurgitation, and relieving both daytime and nighttime heartburn.\textsuperscript{74} Mineral supplementation, using calcium and magnesium, may reduce GERD symptoms, although direct evidence is lacking.

\textbf{Digestive Enzymes}

Supplemental digestive enzymes may reduce GERD symptoms. Delayed gastric emptying and a large volume of food in the stomach are associated with GERD symptoms, and
supplementation using digestive enzymes may reduce these factors. Digestive enzymes are commonly included in combination products, including lipase, amylase, protease, maltase, lactase, sucrase, phytase, and cellulase. Clinically, some patients actually benefit from hydrochloric acid and pepsin supplementation, including individuals who have low levels of stomach acid and delayed gastric emptying.

**ALLERGY TREATMENT**

Eosinophilic esophagitis is frequently misdiagnosed as GERD. Allergy treatment may be indicated in individuals who are not responsive to typical GERD therapies. Allergy testing to measure both IgE and IgG antibodies is indicated. In addition, dietary supplementation, using products to treat allergic reactions directly may also be necessary. Quercitin is a bioflavonoid often used in allergies because it has antihistamine, anti-inflammatory, and antioxidant effects. Vitamin C has been shown to be protective against GERD and to have antioxidant and some antihistamine properties.

**Zinc Carnosine**

Zinc carnosine has been shown to speed healing in many types of gastrointestinal lesions. Many studies refer to polaprezinc, a chelate compound consisting of zinc and L-carnosine. Studies show that polaprezinc has antioxidant activity and decreases the gastric inflammation caused by *H. pylori* infection. Polaprezinc has been shown to protect gastric mucosa from damaging free radicals as well as speed healing of gastric lesions in animal models. Additionally, studies show that zinc carnosine improves intestinal integrity and decreased lab-induced gastric and small-intestine injury.

**L-Glutamine**

L-Glutamine is an amino acid utilized as an energy source by intestinal epithelium. Research has shown that supplementation with glutamine prevented the development in chemical-
induced gastric lesions in stressed rats.\textsuperscript{78} Also, glutamine has been shown to decrease duration and severity of mucosal lesions induced by chemotherapy.\textsuperscript{79}

\textit{Belladonna}

\textit{Atropa belladonna} (belladonna) is a botanical often used for its anticholinergic activity. One of the constituents of belladonna is atropine. Although anticholinergics have been shown to aggravate GERD, atropine has been shown to be beneficial. It is possible that belladonna may be useful for treating GERD owing to the herb’s atropine component.

CONCLUSIONS

GERD is a chronic recurring condition that makes a great impact on the quality of life of individuals who have this condition. As a result of the economic and social burdens of GERD in the United States, it is important for patients to have access to alternative therapies and lifestyle modifications. Currently, research in this area is minimal.

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