Clinical manifestations and complications of gastroesophageal reflux disease (GERD)

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SUMMARY
Gastroesophageal reflux-induced diseases are among the most common disorders and are associated with classical oesophageal manifestations of gastroesophageal reflux disease (GERD) including a range of symptoms such as heartburn, acid regurgitation and chest pain, and also organic manifestations such as oesophagitis, oesophageal strictures and ulcerations, Barrett’s oesophagus and oesophageal adenocarcinoma. Recognition of its impact on other organ systems, extra-oesophageal reflux diseases, such as the ear, nose and throat (ENT) region and the bronchopulmonary system, as well as its contribution to symptoms such as chest pain and sleep disturbances, is also increasing. This paper addresses the symptoms, diseases and complications in which the abnormal reflux of gastric content to the oesophagus and adjacent organ systems is believed to be a frequent contributory factor.

Keywords: Gastroesophageal reflux; oesophagitis; otolaryngology; pulmonary disease; chest pain

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INTRODUCTION
In the US, more than 40% of the population reports, at least sporadically, symptoms of gastroesophageal reflux (e.g. heartburn and/or acid regurgitation) (1–3). A survey conducted in New Zealand indicated a 30% prevalence of gastroesophageal reflux and a combined prevalence of 45% for reflux plus dyspepsia (4). Twenty per cent of the adult US population has weekly heartburn (1). Despite the presence of large numbers of individuals with abnormal gastroesophageal reflux in the general population, primary care physicians (PCPs), who provide most of their care, continue to have difficulties in recognising the wide range of complications faced by patients with GERD. Some of these complications are potentially serious and many involve extra-oesophageal tissues as well as the oesophagus itself. Furthermore, gastroesophageal reflux is often not accurately documented, with patients treated purely on a symptomatic basis without diagnosing the gastroesophageal reflux per se or the extra-oesophageal manifestations of reflux. This may reflect an erroneous trivialisation of gastroesophageal reflux disease (GERD) itself and may lead to some of these patients not being accurately treated.

Oesophageal manifestations and complications of GERD include erosive oesophagitis, oesophageal stricture, Barrett’s oesophagus and oesophageal adenocarcinoma (Table 1). The wide range of extra-oesophageal complications includes sleep disturbance, cough, laryngeal and other upper respiratory tract symptoms and disorders (e.g. hoarseness/laryngitis), chronic obstructive pulmonary disease (COPD), asthma, and other lower respiratory tract conditions, plus unexplained chest pain, angina, sinusitis, otalgia and dental erosion (Table 2).

WHAT IS GERD?
Gastroesophageal reflux occurs when there is a transient decrease in tension in the lower oesophageal sphincter, allowing gastric contents to leak into the oesophagus (5–7). Small amounts of acid reflux occur physiologically, but if the time spent at pH < 4 is prolonged, the gastroesophageal reflux is considered to be abnormal. Prolonged exposure of the oesophagus to acid and digestive enzymes found in gastric fluid, or duodenal contents regurgitated into the stomach (e.g. bile salts), may induce and promote irritation and result in symptoms and morphological changes to the oesophageal mucosa (8). As oesophageal mucosal tissues possess limited intrinsic resistance to refluxate, prevention of oesophageal symptoms and damage relies upon the integrity of the anti-reflux barrier, which comprises the lower oesophageal sphincter and the crural diaphragm.

A number of studies have suggested that eradication of Helicobacter pylori infection, for example in patients with...
MECHANISMS IN GERD

Oesophageal manifestations in GERD may be classified as (i) symptomatic GERD, without oesophagitis (also known as non-erosive reflux disease – NERD); (ii) GERD with erosive oesophagitis and (iii) GERD with Barrett’s oesophagus, depending on the visible signs of oesophageal damage during oesophagoscopy. The major oesophageal complications of gastroesophageal reflux are listed in Table 1. Many patients with GERD lack overt signs of oesophagitis upon endoscopy. However, with more advanced techniques, ‘minimal changes’ of the oesophageal mucosa, due to inflammatory events, might be detected in a proportion of these patients (20).

The presence of reflux symptoms in the absence of visible signs of oesophageal damage may be due, at least in part, to increased permeability of the oesophageal squamous epithelium to hydrogen ions in gastric refluxate (21). This may be a consequence of changes in the flow of these ions across epithelial intercellular tight junctions, resulting in the dilated intercellular spaces seen in ultrastructural studies (22).

Persistent reflux of gastric contents into the oesophagus can induce breaks, disruptions and erosions of the mucosal cell layer (23,24), as mucosal defences become unable to withstand and repair local damage. The resistance of the stratified squamous epithelium of the normal oesophagus to damage is governed by several factors (25). For mucosal injury and oesophagitis to occur, stomach contents must reach the oesophageal mucosa and must overcome oesophageal clearance mechanisms, including oesophageal motility and saliva secretion. In addition, gastric contents must overcome the intrinsic buffering capacity of the mucous lining the epithelium and penetrate this protective film. The secretion of buffering compounds by the oesophageal mucosa is decreased among patients with reflux oesophagitis (26,27), suggesting an important role for this factor in mucosal protection against refluxed stomach contents.

Table 1 Structural oesophageal manifestations and complications of gastroesophageal reflux

| GERD without oesophagitis | GERD with: |
|---------------------------|------------|
|                           | Oesophagitis, erosions |
|                           | Oesophageal stricture |
|                           | Oesophageal ulcers and bleeding |
|                           | Barrett’s oesophagus |
|                           | Oesophageal adenocarcinoma |

gastric or duodenal ulcers, may cause or exacerbate GERD (9,10), although others have not confirmed this association. Helicobacter pylori infection often leads to forms of gastritis in which acid production is diminished, and several studies have documented a lower prevalence of GERD in patients with these forms of gastritis (11,12), or have found an increase in acid production in patients with GERD, following H. pylori eradication (13). However, no such association was seen in recent larger studies of the effects of H. pylori eradication on GERD (14–18). Therefore, based on the available clinical evidence, a causal relationship between H. pylori eradication and GERD seems unlikely and certainly not of clinical relevance (19).

OESOPHAGEAL MANIFESTATIONS AND MECHANISMS IN GERD

Several schemes have been used to classify the severity of oesophagitis, including the Savary-Miller, Los Angeles (LA) and ‘MUSE’ (Metaplasia, Ulceration, Strictures and Erosions) Systems. The LA-classification system is the current gold standard for classification and grades lesions as grade A (one or more mucosal breaks ≤5 mm long, none extending between tops of mucosal folds); grade B (one or more mucosal breaks >5 mm long, none extending between the tops of two mucosal folds); grade C (mucosal breaks extending between the tops of two or more mucosal folds but involving <75% of oesophageal circumference); or grade D (mucosal breaks involving ≥75% of oesophageal circumference). The advantage of this grading system is that it has been validated by physiological studies and clinical trials, showing different healing rates according to the LA grading of severity. However, the LA-classification system only covers erosive lesions and so other abnormalities, such as Barrett’s oesophagus, must be recorded separately.

It should be noted that oesophagitis that is visible only via high-magnification endoscopes and special staining/illumination techniques (i.e. minimal changes) and or by histology is not, as yet, included in oesophagitis-classification schemes, but is the subject of continuing investigation. Furthermore, as oesophageal endoscopy is not commonly available in primary care, erosive oesophageal damage in patients with GERD can be expected to remain undetected over long periods.

Table 2 Extra-oesophageal complications of gastroesophageal reflux

| Pulmonary                                      |
|------------------------------------------------|
| Chronic obstructive pulmonary disease and asthma|
| Cough                                          |
| Ear, nose and throat                           |
| Hoarseness                                     |
| Laryngitis                                     |
| Sinusitis                                      |
| Other                                          |
| Unexplained chest pain                         |
| Angina                                         |
| Sleep disturbance                              |
| Dental erosion                                 |

Dental erosion

Table 2 Extra-oesophageal complications of gastroesophageal reflux

Classification Systems for Endoscopic Grading of GERD with Oesophagitis

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Prevalence of Oesophagitis in Subjects with Symptoms of Gastroesophageal Reflux

A study of 789 patients in Germany, Ireland and the UK presenting with symptoms that, in the opinion of the PCP suggested pathological gastroesophageal reflux, showed that endoscopically evident oesophagitis was present in 45.5% of those examined (28). A recent study of some 1000 patients in Canada (the CADET Prompt Endoscopy study) showed that approximately 45% of all patients consulting a general practitioner with uninvestigated upper gastrointestinal (GI) symptoms, were shown to have damage to the oesophageal mucosa (mainly erosive oesophagitis), and two in three had some form of upper GI injury (29). In an ongoing, population-based study (n = 1001) in Northern Sweden, 15% of a representative sample of the adult population had oesophagitis at baseline, of which one-third were, in fact, asymptomatic (30).

Oesophageal Stricture

Oesophageal stricture, typically associated with difficult swallowing (dysphagia) or with painful swallowing (odynophagia), occurs when attempts by the body to repair oesophageal damage induce excessive fibrosis (31,32), leading to oesophageal wall thickening and luminal constriction. Although dysphagia is the most common presenting symptom of oesophageal stricture, it may not be present if the stricture produces only relatively minor oesophageal narrowing. Oesophageal stricture is found in approximately 10% of patients with severe reflux oesophagitis (8), and approximately 70% of all oesophageal strictures are likely to be related to reflux (33).

Strictures usually occur in the distal oesophagus and typically tend to be 2–4 cm long, but may involve the entire length of the thoracic oesophagus (8). Strictures generally develop over a period of months but occasionally evolve more rapidly, over several weeks. Most strictures cease to worsen when the oesophagus is narrowed to a diameter of 1.5–2 cm (8), which is often sufficient to impair swallowing and produce dysphagia. Strictures always demand careful differential diagnosis from oesophageal neoplasia.

Barrett’s Oesophagus

In some patients with abnormal gastroesophageal reflux, the oesophageal mucosa responds with the development of metaplastic columnar-specialised intestinal epithelium (Barrett’s oesophagus) (34–39) – an assumed risk factor for the development of oesophageal adenocarcinoma (35,37,40–43). The average age of patients diagnosed with Barrett’s oesophagus is approximately 55 years (44–46), although it appears to have a bimodal age distribution with another, smaller peak between birth and 15 years (47,48).

Significant increases in the prevalence of Barrett’s oesophagus have been associated with increasing reflux frequency (35). Prospective studies have indicated a clinical prevalence of 11–12% for Barrett’s oesophagus among patients with symptomatic reflux or symptomatic reflux oesophagitis (38,49). This is markedly higher than the 1.6% prevalence reported in a sample of the adult Swedish population (50), or the population prevalence rate of 376 cases per 100,000 population (0.376%) derived from autopsy data in the USA (51). Barrett’s oesophagus can also occur in the absence of reflux symptoms, as can oesophagitis. In a study conducted in the hospitals of the US Department of Veteran Affairs of selected patients undergoing sigmoidoscopy for colorectal cancer, voluntary upper GI endoscopy revealed Barrett’s oesophagus in 24% of patients (52). Barrett’s oesophagus and oesophagitis coexist in a proportion of patients, and these are particularly likely to have oesophagitis of grade C or D (LA classification).

Oesophageal Adenocarcinoma

Although there is a paucity of data to link reflux and Barrett’s oesophagus directly, there is nevertheless a strong association between oesophageal adenocarcinoma and both the severity of reflux and the length of Barrett’s oesophagus (34). Some hypotheses propose that the risk of oesophageal adenocarcinoma may be independent of Barrett’s oesophagus and is, instead, associated directly with symptoms of gastroesophageal reflux (41,53). Other evidence also suggests a role in Barrett’s oesophagus pathogenesis for bile or small intestinal and pancreatic secretions reaching the oesophagus via duodenogastric and gastroesophageal reflux (37,54).

Oesophageal adenocarcinoma is suggested to be an advanced stage in the sequence of oesophageal epithelial changes that can occur in patients with gastroesophageal reflux (34,37,40–43,55). Most cases of oesophageal adenocarcinoma occur in white men aged over 55 years (45,46,56–59), suggesting that a genetic element is involved in determining risk.

The incidence of oesophageal adenocarcinoma continues to increase – almost quadrupling, for example, among white males in the US between the mid-1970s and the late 1990s (60). Analysis of data indicates that the incidence of oesophageal adenocarcinoma in this population has, in fact, been increasing more rapidly than that of any other cancer, albeit from a low level (61). A recent survey of UK data collected between 1992 and 1996 has indicated an age-standardised annual incidence of 5.24 per 100,000 population (95% CI 5.02–5.45) (62). The same study also showed a fivefold greater incidence of oesophageal adenocarcinoma among men than among women.

Despite a lack of evidence to link reflux directly to adenocarcinoma, data from patients with adenocarcinoma of the oesophagus have shown a strong association with a history of acid reflux, oesophagitis, hiatus hernia or dysphagia (63).
Furthermore, in patients with long-standing, severe reflux symptoms, the odds ratio for oesophageal adenocarcinoma was particularly high, this risk rising with increasing frequency and duration of reflux symptoms (41). Prospective studies of patients with long-segment Barrett’s oesophagus have shown oesophageal cancer incidence rates of 0.25–1.9% per year in this patient subgroup (64). Currently, oesophageal adenocarcinoma is associated with an extremely high 5-year mortality in the 80–90% range (65).

**EXTRA-OESOPHAGEAL MANIFESTATIONS AND COMPLICATIONS OF GASTROESOPHAGEAL REFLUX**

Gastroesophageal reflux may be associated with manifestations and complications affecting a wide range of extra-oesophageal tissues and organ systems. These are collectively known as extra-esophageal reflux disease (Table 2). In the large German ProGERD study of patients presenting with heartburn, nearly one-third (32.8%) had extra-oesophageal reflux disorders at baseline, irrespective of whether they had concomitant oesophagitis or not. The most common extra-oesophageal reported were chest pain (14.5%), chronic cough (13.0%), laryngeal disorders (10.4%) and asthma (4.8%) (66). A summary of some key findings that link gastroesophageal reflux with pulmonary diseases is shown in Table 3, while findings linking reflux with a number of extra-esophageal and extra-pulmonary pathologies are summarised in Table 4.

**Asthma, COPD and Chronic Cough**

Surveys suggest that 30–90% of asthmatic adults have reflux symptoms or abnormal oesophageal acid exposure (67–69), and many studies show an association between these two conditions (70–78). The value of identifying reflux in individual patients with asthma is now becoming more widely recognised. The recognition of reflux in asthma patients is important because some bronchodilators, which are often used to treat asthma symptoms, may themselves exacerbate reflux by contributing to relaxation of the lower oesophageal sphincter (79). Such commonplace asthma therapy may therefore indirectly exacerbate respiratory symptoms in some patients with asthma.

Several mechanisms might link reflux with asthma. As well as reflux bronchoconstriction caused by the aspiration of refluxed stomach contents into the bronchi, acid regurgitation to the oesophagus may cause increased bronchial reactivity via a vagally transmitted reflex initiated by reflux.

A number of investigations have indicated an association between oesophageal acid reflux and COPD. In a study involving 109 children, reflux was diagnosed in 62% of those with obstructive bronchitis (84). Significantly, impaired vital capacity, forced vital capacity and forced expiratory volume have been recorded in patients with reflux as identified by 24-h pH monitoring (85). A recent study indicates that the prevalence of reflux symptoms is related to the degree of obstruction of airway flow in patients with stable COPD (86). An increased odds ratio for COPD has been reported in individuals with erosive oesophagitis or stricture (87).

Gastroesophageal reflux may also be responsible for many cases of chronic cough, as it is among the three conditions commonly associated with this bothersome condition (the others being asthma and postnasal drip) (88). In one study that included 11 patients with severe gastroesophageal reflux, chronic cough was reduced by 47% during the day and by 80% during the night by fundoplication (89), demonstrating a causal relationship between gastroesophageal reflux and cough.

**Unexplained Chest Pain**

Individuals with acid reflux may also experience ‘unexplained chest pain’, i.e. chest pain in patients for whom the results from medical history, physical examination and an electrocardiogram (ECG) make any acute cardiac disease unlikely (90). It is believed to be one of the most common extra-oesophageal manifestations of reflux disease and is common among patients with GERD. Reflux-induced chest pain can be difficult to separate from heartburn on symptom assessment, but can occur separately from heartburn. It can be speculated that reflux-related chest pain may be a pain dimension of heartburn in some reflux patients. Among 28 patients newly referred for cardiological assessment for angina-like chest pain, 12 (43%) had pathological 24-h oesophageal pH profiles and 10 (36%) had symptomatic reflux (91). Data from the ProGERD study, referred to earlier, have shown a frequency of unexplained chest pain of 14.5% among patients

| Symptom/Sign                  | Link with gastroesophageal reflux                                                                 | Reference     |
|------------------------------|--------------------------------------------------------------------------------------------------|---------------|
| COPD/asthma                   | Significantly increased rate of reflux in 30–90% of adult asthmatics                             | (67–69,86,131) |
| Obstructive bronchitis        | 62% of children also had reflux                                                                 | (84)          |
| Cough                        | GERD, a major cause of chronic cough                                                               | (88)          |

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

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consulting a PCP for heartburn (66). The proportion of chest pain patients with gastroesophageal reflux as the principal cause is currently unknown (92). This reflux complication has been estimated to be responsible for 2–5% of all emergency medical presentations (93,94). The few prospective prevalence studies that have been conducted suggest that the population-based prevalence for unexplained chest pain is 23–40%, and that it is significantly associated with the presence of reflux symptoms (1,95).

Gastroesophageal reflux-related chest pain is particularly worrying for patients, because its characteristic severe retrosternal pain, which may radiate to the jaw or throat, closely resembles that of myocardial infarction. It is therefore vital to differentiate chest pain that might have a cardiac source from that of probable oesophageal or musculoskeletal origin by means of electrocardiography, exercise testing or angiography, and the taking of a thorough patient history.

**Linked Angina**

Limited evidence suggests a role for gastroesophageal reflux in stimulating anginal attacks (so-called linked angina) in patients with impaired coronary circulation. Intra-oesophageal acid instillation has been shown to significantly lower exercise tolerance among patients with exertional angina (96). Intra-oesophageal acid infusion has also been associated with a significant reduction in coronary blood flow among patients with CAD (p < 0.01) (97), and similar effects of intra-oesophageal acid instillation have been observed in patients with syndrome X (98). A link between gastroesophageal reflux and angina has also been indicated in a study showing an association between oesophageal pH lowering and reduction in heart rate (99). In addition, the abolition of this association by atropine suggests vagal involvement in oesophageal acid-mediated bradycardia. The lack of a significant reduction in coronary blood flow among heart transplant patients upon intra-oesophageal acid instillation similarly indicates neurological involvement in acid-related decreases in coronary blood flow (97). Vagal involvement has also been suggested as one possible mechanism behind reflux-related pulmonary symptoms as mentioned above.

**Laryngeal Signs and Symptoms Associated with Gastroesophageal Reflux**

Four to 10 per cent of patients presenting to otolaryngologists have reflux symptoms (100,101), and reflux is associated with cough, hoarseness, chronic laryngitis and vocal cord ulceration (73,102–105). Laryngeal symptoms may be alleviated by proton pump inhibitor treatment in some cases (106), further supporting a link with acid reflux.

Gastroesophageal reflux has also been linked to laryngeal carcinoma. Measurement of oesophageal pH in 21 patients with laryngeal or hypopharyngolaryngeal squamous cell carcinoma showed reflux in 81% of individuals, which was significantly higher than the 19% of control patients with reflux symptoms (107). In addition, abnormal oesophageal/pharyngeal pH has been measured in 71% of patients with laryngeal carcinoma identified as part of a study of patients with suspected reflux-related upper airway/digestive tract disorders (108).

Although reflux into the proximal oesophagus may cause laryngeal disorders via a direct effect of gastric acid and peptic enzymes on the larynx and adjacent tissues (109–112), acid reflux into the distal oesophagus can induce vagal stimulation and thereby also produce proximal laryngeal disorders. Vagal stimulation can, for example, mediate reflex responses such as chronic throat clearing that may themselves result in laryngeal symptoms (113–116).

**Sleep Disturbance**

Insomnia, interrupted or poor quality sleep, is a common complication of gastroesophageal reflux. Recent data suggest that 50–80% of reflux patients might have disturbed sleep (117–120). Some cases appear to be associated with a nocturnal breathing disorder such as snoring or obstructive sleep apnoea (75,121). Many others are probably simply due to full

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**Table 4** Dental, otological and laryngopharyngeal manifestations and complications of gastroesophageal reflux

| Symptoms/signs                        | Link with gastroesophageal reflux                                                                 | Reference |
|---------------------------------------|--------------------------------------------------------------------------------------------------|-----------|
| Laryngeal or hypopharyngolaryngeal carcinoma | Reflux present in 81% of cases                                                                 | (107)     |
| Laryngeal carcinoma                   | Abnormal oesophageal or pharyngeal pH in 71% of cases                                            | (108)     |
| Sinusitis                             | Reflux present in 63% of cases                                                                 | (125)     |
| Sinusitis                             | Sinusitis present in 4% of children with reflux                                                 | (73)      |
| Otalgia                               | 6/6 children also had reflux                                                                    | (122)     |
| Otitis media                          | 5/5 adults also had reflux                                                                      | (123)     |
| Dental erosion                        | 20–55% prevalence in patients with reflux                                                      | (126)     |
| Sleep disturbance                     | Present in 51% of patients with reflux                                                           | (117)     |
or partial awakening in response to reflux-induced thoracic discomfort such as regurgitation or heartburn.

Rare Complications of Reflux Disease

A range of other, less common, extra-oesophageal complications of reflux has also been reported. Otitis is thought to be associated with gastroesophageal reflux in rare cases. In a study of six children presenting with ear pain, all had gastroesophageal reflux, as shown by oesophageal pH monitoring and, in some cases, endoscopy. All the six children experienced resolution of otalgia following acid–reflux therapy (122). Similarly, a study of five adults with chronic secretory otitis media provided evidence of gastroesophageal reflux in all cases and demonstrated resolution of otitis with omeprazole treatment (123).

Patients with reflux may also present with sinusitis (124). Ambulatory pH monitoring has shown the presence of reflux in seven of 11 (63%) patients with sinusitis confirmed by computed tomography, compared with two of 11 (18%) controls (125). Another study has shown that 4.2% of children with reflux also presented with sinusitis, compared with 1.4% of controls (73). In accordance with otitis, more data are needed to clarify the putative association between gastroesophageal reflux and sinusitis.

Dental erosion may accompany reflux in patients who experience frequent acid regurgitation into the mouth (126–129). The prevalence of dental erosion among individuals with reflux has been estimated at 20–55%, compared with a prevalence of 2–19% in the general population (126). In one study, oesophageal pH monitoring indicated reflux in 83% of individuals with dental erosions (129). The same study also showed that 55% of patients with reflux had dental erosion, compared with 10% of those without reflux.

DISCUSSION

The spectrum of GERD encompasses typical (oesophageal) and atypical (extra-oesophageal) symptoms and affects a large proportion of individuals. A large proportion of physicians still fail to fully recognise the occurrence of a wide range of manifestations and complications, some of which are potentially serious, linked directly to the coexistence of gastroesophageal reflux. Some complications of gastroesophageal reflux, such as dysphagia, chronic cough, laryngitis and sleep disturbance can be troublesome or painful to the patient, thereby impairing well being. Other complications of gastroesophageal reflux, such as Barrett’s oesophagus, oesophageal adenocarcinoma, asthma and pulmonary fibrosis should be regarded as potentially life threatening sequelae of perhaps seemingly benign acid reflux.

The prompt identification of the oesophageal and extra-oesophageal consequences of gastroesophageal reflux GERD and its extra-oesophageal manifestations makes possible the consequent implementation of effective anti-reflux interventions. Today, the gold standard is adequate acid inhibition with a proton pump inhibitor. In our opinion, the widely held view that gastroesophageal reflux and its associated symptoms are trivial is certainly unfounded in many patients and does not properly reflect the true nature of this common disease. In fact, trivialisation may lead to suboptimal treatment of these patients, unduly leaving patients with residual symptoms. Recent US data suggest that every second GERD patient is somewhat dissatisfied with his/her treatment (130).

During our work, collecting data concerning the impact of gastroesophageal reflux on different tissues and organ systems, it has become evident that there is great confusion in terms of classification, definitions and terminology of reflux disease and its complications. These are important confounders in the struggle to elucidate gastroesophageal reflux as an important pathophysiological factor in a large number of different diseases and symptoms with severe negative impacts on health and quality of life.

CONCLUSION

A broad range of seemingly unconnected disorders, some benign but with substantial discomfort to the patient and others potentially life threatening, has been linked to the presence of gastroesophageal reflux. Increased recognition of the true impact of GERD and EERD, particularly among PCPs, should help to increase the timely use of effective reflux-based management strategies for these apparently disparate conditions.

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