

Does gastroesophageal reflux contribute to the development of chronic sinusitis? A review of the evidence

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SUMMARY. Although recent studies suggest that gastroesophageal reflux disease (GERD) may contribute to a variety of ear, nose and throat and pulmonary diseases, the cause-and-effect relationship for the vast majority remains far from proven. In this article, the evidence supporting a possible causal association between GERD and chronic sinusitis has been reviewed. The evidence would suggest that: (i) a higher prevalence of GERD and a different esophagopharyngeal distribution of the gastric refluxate occurs in patients with chronic sinusitis unresponsive to conventional medical and surgical therapy compared to the general population; (ii) a biologically plausible pathogenetic mechanism exists whereby GERD may result in chronic sinusitis; and (iii) clinical manifestations of chronic sinusitis respond variably to antireflux therapy. While these findings suggest that GERD may contribute to the pathogenesis of chronic sinusitis in some patients, it is apparent that the quality of the evidence supporting each of these three lines of evidence is low and therefore does not conclusively establish a cause-and-effect relationship. A number of unresolved issues regarding prevalence, pathophysiological mechanism, diagnosis and treatment exist that deserve further investigation in order to solidify the relationship between GERD and chronic sinusitis. In conclusion, given the possible relationship between GERD and chronic sinusitis, until more convincing data are available, it may be prudent to investigate for GERD as a potential cofactor or initiating factor in patients with chronic sinusitis when no other etiology exists, or in those whose symptoms are unresponsive to conventional therapies.

KEY WORDS: chronic sinusitis, gastroesophageal reflux, pH, treatment.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common condition that encompasses a wide spectrum of clinical presentations.^{1,2} Although recent studies suggest that GERD may contribute to a variety of ear, nose and throat and pulmonary diseases, the cause-and-effect relationship is far from proven^{3,4} (Table 1). This is particularly so as evidence accumulates in which it becomes apparent that epidemiological studies, while helpful to define associations, do not prove causality; diagnostic tests such as pH testing and laryngoscopy neither accurately discriminate among disease populations nor predict response to treatment, and treatment trials using antisecretory agents yield inconsistent results in these patients. If an upper or lower respiratory tract disorder is causally related

to GERD, certain criteria should be met:⁵ (i) an increased coexistence of both disorders should exist compared to the general population; (ii) a biologically plausible pathophysiological mechanism should explain how the disease processes interact; and (iii) clinical manifestations of the suspected GERD-related disorder should respond to antireflux therapy. In this article, the evidence supporting the relationship between GERD and chronic sinusitis will be reviewed.

Like GERD, chronic sinusitis is a common condition, affecting an estimated 14% of the population that impacts significantly on patient quality of life, productivity and health care resource utilization.^{6–8} Chronic sinusitis can be defined clinically by the presence of nasal symptoms, facial headache and malaise for at least 12 weeks and objective evidence of sinus disease, usually provided by nasal endoscopy or CT scan, at least 4 weeks after appropriate antibiotic therapy and without intervening acute sinus infection.⁹ The pathophysiologic mechanism leading to chronic sinusitis involves compromised

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Table 1 Proposed extraesophageal complications of GERD

Pulmonary
Asthma
Chronic cough
Aspiration pneumonia
Sleep apnea
Pulmonary fibrosis
Subglottic stenosis
Chronic obstructive lung disease
Pharynx/larynx
Hoarseness
Posterior laryngitis
Vocal cord granulomas, ulcers, nodules
Paroxysmal laryngospasm
Cancer
Globus sensation
Frequent throat clearing
Lateral neck pain
Sore throat
Excessive phlegm
Oral cavity
Dental erosions
Halitosis
Buccal/tongue burning
Nasal/sinus/middle ear
Chronic sinusitis
Chronic serous otitis media
Other
Torticollis
Atrial dysrhythmias
Sudden infant death syndrome

Table 2 Predisposing factors to chronic sinusitis

Upper respiratory tract infections
Allergic rhinitis
Anatomic abnormalities
Concha bullosa
Nasal polyposis
Septal deviation
Tumors
Foreign bodies
Systemic processes
Disorders of ciliary motility
Cystic fibrosis
Wegener's granulomatosis
Immunodeficiency disorders
Vasomotor reactivity
Other
Smoking
Swimming and diving
Overuse of nasal sprays
Environmental irritants
?Gastroesophageal reflux

sinus drainage via the ostiomeatal complex ultimately leading to inflammation. The cause of chronic sinusitis is frequently multifactorial with a wide variety of contributing factors¹⁰ (Table 2). Despite effective medical and surgical therapies, a significant portion of chronic sinusitis patients remains symptomatic.⁸

PREVALENCE OF GERD IN CHRONIC SINUSITIS

A relationship between acid reflux and chronic nasal symptoms has been suggested in both children and

adults. Contencin and Narcy first demonstrated a potential relationship between acid reflux and chronic rhinopharyngitis in infants and children by demonstrating an increased number of pH episodes < 6, increased percentage of time with pH < 6 and lower overall pH in patients compared to controls using prolonged nasopharyngeal pH monitoring.¹¹ Unfortunately, simultaneous esophageal pH monitoring was not performed, raising questions about the origin of the 'acidity'. More recent retrospective^{12,13} and prospective¹⁴ studies have demonstrated a high prevalence of GERD, pharyngeal reflux episodes in particular, along with improvement in sinus symptoms following initiation of GERD therapy in children with chronic sinusitis.

In one of the earliest reports of a possible association between GERD and chronic sinusitis in adults, DiBaise *et al.* in a retrospective case series of 19 patients with chronic sinusitis, found a high prevalence of classical reflux symptoms and abnormal esophageal pH tests.¹⁵ A subsequent prospective study by the same authors found a similarly high prevalence of GERD symptoms, albeit infrequent and mild, and abnormal pH test results in a group of chronic resistant sinusitis patients: 91% of the patients had either an abnormal pH test (82%) or classical GERD symptoms (82%).¹⁶ These results are supported by findings from a large case-control epidemiological study in which it was shown that adults with complicated GERD were more likely to have sinusitis (OR 1.60; 95% CI 1.51–1.70) than the controls.² In this important study, a nationwide Veterans Affairs Medical Center database was used to compare the comorbid occurrence of sinus, laryngeal and pulmonary diseases in patients with (101 366) or without (101 366) a diagnosis of erosive esophagitis or esophageal stricture. A similar case-control study including 1980 children with GERD and 7920 controls demonstrated a very similar association between GERD and pediatric sinusitis (OR 2.3; 95% CI 1.7–3.2).¹⁷ Chambers *et al.* provided additional support for this association by demonstrating that the presence of GERD was a predictor of poor symptomatic outcome following sinus surgery in adults.¹⁸ Finally, the role of pharyngeal reflux of gastric acid and the esophageal distribution of the gastric refluxate was investigated in patients with chronic sinusitis unresponsive to conventional sinus therapy and compared to healthy individuals. A significantly higher occurrence of gastroesophagopharyngeal reflux was found in the chronic sinusitis patients, suggesting that this pattern of reflux may contribute to the pathogenesis of chronic sinusitis in some patients.¹⁹ Therefore, it has been demonstrated using a variety of study designs and methods that GERD appears to be more prevalent in chronic sinusitis patients compared to the general population. Nevertheless, because none of these studies included control groups and GERD is highly

prevalent in the general population,¹ the strength of this association remains uncertain.

BIOLOGICALLY PLAUSIBLE PATHOPHYSIOLOGIC MECHANISM

The mechanism(s) by which GERD may affect the sinonasal cavity and lead to chronic sinusitis remains unclear; however, two major possibilities have been suggested.^{16,20} The direct noxious effect of the refluxate on the sinonasal mucosa could result in inflammation and cause edema and mucociliary dysfunction leading ultimately to sinus ostial obstruction and infection. Unlike the esophagus, the airways are not protected by antireflux clearance mechanisms and intrinsic mucosal properties and are therefore theoretically at risk of injury from minute amounts of the gastric refluxate. Evidence supporting this mechanism is mainly derived from the pediatric literature, including the previously described study of Contencin and Narcy,¹¹ demonstrating a higher prevalence of nasopharyngeal 'acidity' in children with chronic rhinosinusitis compared to controls. Phipps *et al.* improved on the methods from the previously mentioned study by performing ambulatory dual-channel pH recordings (sensor within esophagus and nasopharynx) in children with chronic sinusitis and found that 19/30 (63%) patients demonstrated abnormal esophageal acid exposure with six of these 19 (32%) also demonstrating nasopharyngeal reflux.¹⁴ In adults, ambulatory 3-site pH testing (distal esophagus, proximal esophagus and hypopharynx) was performed in 11 chronic refractory sinusitis patients and were compared to the results of 11 healthy individuals.¹⁹ Pharyngeal reflux episodes were found to occur more commonly in the chronic sinusitis group, suggesting a different esophago-pharyngeal distribution pattern of the gastric refluxate in these patients. We are unaware of any studies performed in adults with chronic sinusitis in which an attempt to document the presence of nasopharyngeal reflux was made. Nevertheless, Ozdek *et al.* recently investigated the presence of *Helicobacter pylori* in the sinonasal mucosa of patients with and without chronic rhinosinusitis using polymerase chain reaction.²¹ *H. pylori* DNA was detected in 4/12 chronic rhinosinusitis patients, three of whom described classical reflux symptoms, but none of the patients with concha bullosa. Among several potential explanations, these finding could relate to the extension of the gastric refluxate into the sinonasal cavity. In addition, another recent report demonstrated high concentrations of pepsin/pepsinogen in middle ear effusion samples from children with otitis media with effusion; once again suggesting that reflux of gastric material into the middle ear is possible.²² Regardless of the above, it would seem

more likely that the gastric refluxate could reach the nasopharynx, as opposed to entering the sinus cavity via the convoluted bony channels which connect the sinuses to the nose, leading to nasal mucosal inflammation and edema which may obstruct the sinus ostia resulting in sinusitis.

A second mechanism may be a reflux-induced autonomic nervous system hyperactivity resulting in sinonasal edema which interferes with sinus drainage and leads to stasis of secretions and secondary infection, much like the patient with vasomotor rhinitis.²³ Esophageal stimulation by hydrochloric acid has been shown to cause inflammation of the airways suggesting that neural pathways are present that communicate between the esophagus and respiratory tract.²⁴ Certainly, the neural connections are well amplified in the nose and sinuses and could form the basis of neurogenic inflammation of the sinuses in patients with rhinitis.²³ Additionally, electrical stimulation of the sympathetic nerves supplying the nose has been shown to result in reduction in resistance to nasal airflow, whereas stimulation of parasympathetic nerves resulted in an increase in nasal resistance.²⁵ In support of this hypothesis, Loehrl *et al.* found that in patients with chronic upper airway inflammation compared to age- and gender-matched controls, significant autonomic dysfunction was present.²⁶ This finding is similar to previous studies investigating autonomic function in patients with suspected reflux-related asthma,²⁷ albeit the former suggesting adrenal hypofunction and the latter demonstrating vagal hyperresponsiveness.

OUTCOME OF ANTI-REFLUX THERAPY IN CHRONIC SINUSITIS

Evidence of improvement in sinus symptoms following the institution of acid suppressive therapy has been demonstrated mainly in retrospective case series in both children^{12,13} and adults.¹⁵ In a study by Bothwell *et al.* 89% of children with medically refractory chronic sinusitis experienced symptom relief with acid suppressive therapy and were able to avoid sinus surgery.¹² In a more recent prospective study by Phipps *et al.* 79% of children with chronic sinusitis showed improvement after reflux treatment.¹⁴ In a retrospective case series involving adults with chronic sinusitis, about two-thirds of the patients noted improvement in sinus symptoms after initiating antisecretory therapy.¹⁵ Interestingly, it was found that patients with abnormal ambulatory esophageal pH tests were the only ones who experienced dramatic improvements in their sinus symptoms. In a subsequent, prospective, open-label pilot study, it was the same authors' objective to determine whether medical treatment of GERD could improve both subjective and objective features

of chronic resistant sinusitis in adults.¹⁶ While most patients noted an improvement in one or more sinus symptoms and global satisfaction after treatment with a twice-daily proton pump inhibitor for 3 months, the improvement was modest at best in the majority. The improvement seemed to peak after about 8 weeks of therapy and the most dramatic effects noted were on the symptoms of sinus pressure and facial headache, with more modest effects on nasal congestion and drainage, and minimal effect on malaise. Complete symptom resolution occurred infrequently. There was a lack of parallel improvement in laryngeal and nasal endoscopy findings when compared to symptoms; a finding that may be related to an inadequate length of time at follow-up required for resolution of those physical changes.²⁸ Furthermore, ambulatory dual-channel esophageal pH testing results were not predictive of symptom improvement.

FUTURE DIRECTIONS

The evidence supporting a possible causal association between GERD and chronic sinusitis has been reviewed (Table 3). The evidence would suggest: (i) a higher prevalence of GERD and a different esophagopharyngeal distribution of the gastric refluxate occurs in patients with chronic sinusitis unresponsive to conventional medical and surgical therapy compared to the general population; (ii) a biologically plausible pathogenetic mechanism exists whereby GERD may result in chronic sinusitis; and (iii) clinical manifestations of chronic sinusitis respond to acid-suppressive therapy. While these findings suggest that GERD may contribute to the pathogenesis of chronic sinusitis in some patients, it is apparent that the quality of the evidence supporting each of these three lines of evidence is low and therefore does not establish a cause-and-effect relationship.

A number of unresolved issues regarding prevalence, pathophysiological mechanism, diagnosis and treatment exist that deserve further investigation in order to solidify the relationship between GERD and chronic sinusitis. Specifically, more information is needed regarding the prevalence and natural history of GERD-related chronic sinusitis in children and adults, both in those with and without

a history of previous sinus surgery. Further work is necessary to clarify how GERD influences the development of chronic sinusitis in those with and without a history of previous sinus surgery. The role of a potential interaction between GERD and confounding refluxogenic effects from such factors as smoking, asthma, increased intra-abdominal pressure associated with coughing/sneezing and use of medications that can affect the tone of the lower esophageal sphincter, that frequently occur concomitantly in these patients, also needs to be considered in order to avoid bias.²⁹⁻³¹ Additional study of the optimal diagnostic approach including the potential role of symptoms, pH testing, multichannel intraluminal impedance testing, pepsin levels, sinonasal ciliary function and nasal endoscopy is also needed. Finally, randomized, controlled trials of adequate sample size and duration of follow-up are needed to clarify the optimal treatment approach and to determine reliable predictors of treatment response. In particular, as sinus symptoms tend to fluctuate over time, short duration treatment responses without long-term follow-up may simply reflect the natural history of the disease process. The use of validated chronic sinusitis-specific instruments to measure symptoms and quality of life should be utilized in future clinical trials.^{32,33}

SUGGESTED CLINICAL APPROACH

While ambulatory esophageal pH testing has been considered by some to be the best diagnostic tool for identifying extraesophageal complications of GERD, several problems arise when pH testing is used to identify the potential role of reflux in patients with suspected extraesophageal GERD conditions, including: the optimal position of the proximal pH sensor (pharyngeal versus upper esophagus) if used; and the lack of well-established normal values, poor reproducibility and the occurrence of artifacts involving the proximal pH sensor. There also seems to be a tendency for false-negative tests; thus, a negative test may not confidently exclude the diagnosis. Last, and perhaps most important, a positive test only confirms that an abnormal amount of gastroesophageal reflux is present and does not prove a causal relationship. This can only be assured with confidence when the atypical symptom of suspected GERD

Table 3 Summary of evidence of a causal association between GERD and chronic sinusitis⁵

Criteria	Definition	Evidence
Strength	Large relative risk	+?
Consistency	Repeatedly observed by others in different situations	+
Biologic Plausibility	Makes sense according to current knowledge	+
Reversibility	Reduction in exposure leads to lower rates of disease	+?

+, evidence supports; +?, evidence supports but weak and doubtful; -, evidence absent.

shows sustained, dramatic improvement following treatment of GERD. Therefore, at the present time, there are no sufficiently reliable diagnostic tests that can accurately predict which patients have GERD-related extraesophageal complications. As a result of this complex relationship among symptoms, presence of GERD and causality, a therapeutic trial with a proton pump inhibitor seems to be most useful in identifying a causal relationship between reflux and suspected extraesophageal presentations (Fig. 1). This approach has been supported by recent reports suggesting that an empiric trial of a twice-daily proton pump inhibitor for 2–3 months may be more cost-effective than early testing;^{34,35} although, it is important to keep in mind that these data relate to patients with chronic cough and asthma and have not been evaluated in the situation of chronic sinusitis. Furthermore, it is difficult to establish cost-effectiveness in the absence of clear-cut effectiveness. If no response is seen after this extended therapeutic trial, esophageal pH testing, dual-channel gastroesophageal pH testing or combined multichannel intraluminal impedance, then pH testing while on acid suppressive therapy is suggested in order to assess its adequacy.^{36,37} For those who do respond, gradual titration of the therapy downward is recommended.

CONCLUSION

While a number of lines of evidence suggest that GERD may contribute to the pathogenesis of chronic sinusitis in some patients, it is apparent that the quality of

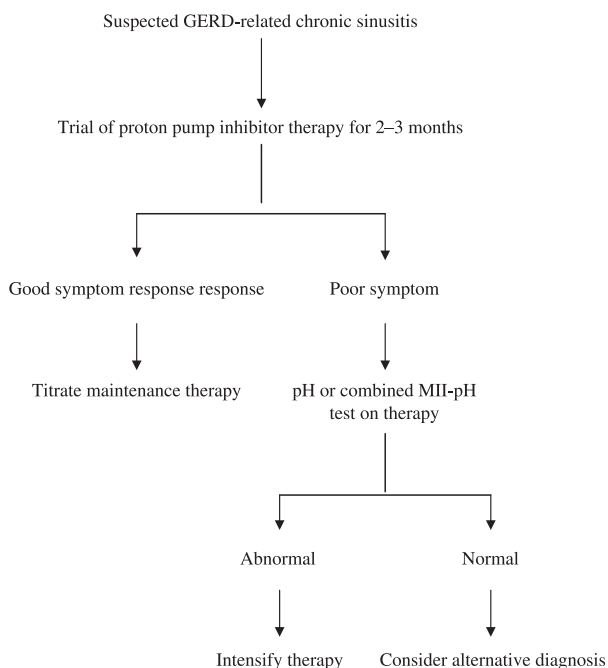


Fig. 1 Suggested algorithm for the management of the patient with suspected GERD-related chronic sinusitis. MII-pH, combined multichannel intraluminal impedance-pH test.

the supporting evidence is low and therefore does not establish a cause-and-effect relationship. Until additional evidence to support a causal relationship between GERD and chronic sinusitis exists, acceptance of this relationship must remain tempered. Nevertheless, given the possible relationship between GERD and chronic sinusitis, until more convincing data are available, it might be prudent to investigate for GERD as a potential cofactor or initiating factor in patients with chronic sinusitis when no other etiology exists, or in those whose symptoms are unresponsive to conventional therapies.

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