Gastroesophageal Reflux Disease-Related Asthma: Neurogenic Inflammation and Non-pharmacological Management

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Abstract

Asthma is a chronic inflammatory airway disease characterized by bronchoconstriction, airway remodeling, and increased responsiveness to non-specific stimuli. Adult-onset asthma is often associated with environmental and individual risk factors rather than allergens. One important contributing factor is gastroesophageal reflux disease (GERD), which can worsen asthma symptoms through microaspiration of gastric contents and vagally mediated reflex mechanisms. GERD is a chronic gastrointestinal disorder characterized by the reflux of gastric acid into the esophagus, influenced by factors such as obesity, smoking, certain medications, and stress. Evidence shows a strong association between GERD and asthma, with studies reporting that up to 80% of asthma patients experience reflux symptoms such as heartburn and regurgitation. Acid exposure in the esophagus can trigger neurogenic inflammation through activation of vagal pathways and release of neuropeptides, leading to airway hyperresponsiveness and bronchospasm. In addition, chronic exposure to refluxate may directly injure airway epithelium and increase inflammatory cell infiltration. Understanding this pathophysiological relationship is essential for improving asthma control. Non-pharmacological management plays a key role in reducing GERD-related asthma symptoms. Effective strategies include avoiding trigger foods, maintaining a minimum three-hour interval between meals and sleep, elevating the head during sleep, achieving weight loss in overweight individuals, and smoking cessation. These interventions have been shown to reduce reflux episodes and improve respiratory outcomes.

Keywords: Asthma, GERD, neurogenic inflammation, non-pharmacological treatment

Abstrak

Asma merupakan penyakit inflamasi kronis pada saluran napas yang ditandai dengan bronkokonstriksi, remodeling jalan napas, serta peningkatan respons terhadap rangsangan nonspesifik. Asma onset dewasa lebih sering berkaitan dengan faktor lingkungan dan individu dibandingkan alergen. Salah satu faktor penting adalah gastroesophageal reflux disease (GERD) yang dapat memperburuk gejala asma melalui mikroaspirasi isi lambung dan refleks yang dimediasi saraf vagus. GERD merupakan gangguan gastrointestinal kronis yang ditandai dengan refluks asam lambung ke esofagus, yang dipengaruhi oleh obesitas, kebiasaan merokok, penggunaan obat tertentu, dan stres. Berbagai penelitian menunjukkan hubungan kuat antara GERD dan asma, dengan sekitar 80% pasien asma mengalami gejala refluks seperti heartburn dan regurgitasi. Paparan asam di esofagus dapat memicu inflamasi neurogenik melalui aktivasi jalur vagal dan pelepasan neuropeptida, sehingga menyebabkan hiperreaktivitas jalan napas dan bronkospasme. Selain itu, paparan kronis refluks juga dapat merusak epitel saluran napas dan meningkatkan infiltrasi sel inflamasi. Pemahaman hubungan ini penting untuk meningkatkan kontrol asma. Penatalaksanaan nonfarmakologis berperan penting dalam mengurangi gejala asma akibat GERD. Strategi yang efektif meliputi menghindari makanan pemicu, memberi jarak minimal tiga jam antara makan dan tidur, meninggikan posisi kepala saat tidur, menurunkan berat badan pada individu obesitas, serta berhenti merokok. Intervensi ini terbukti dapat mengurangi episode refluks dan memperbaiki kondisi pernapasan pasien.

Kata kunci: Asma, GERD, inflamasi neurogenik, tatalaksana nonfarmakologis

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Introduction

Asthma is a chronic inflammatory disease of the airways characterized by coughing, wheezing, shortness of breath, and chest tightness. Asthma induces bronchoconstriction, which decreases the diameter of the airways.[1] In individuals with severe asthma, other mechanisms such as airway remodeling (which includes airway smooth muscle hyperplasia, goblet cell metaplasia, and increased subepithelial collagen deposition) may play an important role in the pathophysiology of more severe disease.[2] Asthma symptoms are caused by airway inflammation and increase the ability of smooth muscle cells to react to non-specific stimuli.[1]

Asthma tends to start at an early stage (childhood-onset asthma), however, some individuals develop asthma later in life. Late-onset asthma is progressively worse and has a less significant association with allergens than childhood-onset asthma. Environmental pollutants, stress, obesity, and hormone

disturbance could be factors that might lead to adult-onset asthma.[3] One of the causes related to adult-onset asthma is gastric acid reflux.[4]

Gastroesophageal reflux disease (GERD) and asthma frequently overlap, and complicated interactions occur in which GERD may exacerbate asthmatic symptoms or vice versa. Establishing a direct correlation between GERD and asthma is challenging.[4] Patients with any of the following symptoms should be suspected of having GERD-induced asthma: asthma presenting in adulthood, uncontrolled asthma despite appropriate medication, onset of heartburn or regurgitation before asthma, and asthma symptoms appearing after eating or in the supine position. According to some research, approximately 80% of individuals with asthma suffer from heartburn and regurgitation.[5] A study found that patients with GERD were 1.15 times at risk of having asthma compared to those without GERD. A systematic review stated that the average number of gastric reflux symptoms in asthmatic patients is more than 50%.[6]

GERD and Asthma Incidence

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal condition characterized by the reflux of stomach acids into the esophagus. Several risk factors have been observed and linked to the pathogenesis of GERD. Mechanical abnormalities such as esophageal dysmotility, lower esophageal sphincter tone impairment, and delayed gastric emptying contribute to GERD pathogenesis.[7]

Risks associated with GERD symptoms with the highest prevalence such as female, obesity, tobacco use, excessive intake of alcohol, connective tissue disorders, pregnancy, and postprandial supination.[8] Various drugs side effects such as anticholinergic drugs, benzodiazepines, non-steroidal anti-inflammation drugs (NSAID), calcium channel blockers, antidepressants, and other gastrointestinal affecting drugs.[9] GERD is also related to stress and is also recognized as a risk factor for asthma. Stress was found to be associated with a higher risk of asthma incidence in several studies. The study included participants in stressful working environments who were 50% more likely to have adult-onset asthma.[3] Stress was shown to affect and activate several cellular pathways that may be implicated in GERD-related asthma pathogenesis. It regulates inflammatory signals by releasing hormones and neuropeptides that can interact with immune cells.[10]

GERD develops through several mechanisms that affect the esophagogastric junction barrier. It is often characterized by heartburn and regurgitation. It may also appear with typical extra-esophageal symptoms such as chest pain, chronic cough, laryngitis, or asthma.[7] Chronic inflammation of lung tissue caused by reflux irritation can result in airway obstruction, poor gas exchange, acute lung injury, and a serious worsening of respiratory syndrome. These processes cause T-helper type 2 cells to release proinflammatory cytokines, resulting in increased airflow resistance and inflammation.[10]

Several studies propose a basic mechanism caused by gastric reflux (acid, pepsin, and pancreatic enzymes) that enters the esophagus and causes microaspiration and lung inflammations. Bronchoconstriction due to acid exposure is triggered via muscarinic receptors, which release acetylcholine, leading to airway inflammation. Macrophages, neutrophils, eosinophils, and lymphocytes are increasingly found in GERD-induced airway inflammation.[11]

Gastroesophageal Reflux Affects Neurogenic Inflammation in The Airway

Asthma and GERD may interact through different kinds of mechanisms. Reflux may trigger asthma by disrupting the airway via aspiration-driven reactions or indirectly through neurogenically released inflammation. Reflux of gastric fluids may provoke bronchoconstriction by a vagus-mediated reflex, neurally increased bronchial responsiveness, or microaspiration.[12]

Neurogenic inflammation in the lungs can result from vagus-mediated processes or microaspiration. Acid exposure to the esophagus can cause a decrease in peak expiratory flow, increasing resistance in the

airway. Other studies suggest that acid reflux may be a precursor to more severe bronchospasm with future consequences.[13]

Neurogenic inflammation may contribute to the onset and progression of chronic inflammatory airway disorders, including asthma. Numerous neuropeptides, including substance P, neurokinin A, and calcitonin gene-related peptide, have a role in neurogenic inflammation. Other physiologically active peptides, such as neuropeptide tyrosine, vasoactive intestinal polypeptide, endogenous opioids, and novel tachykinins such virokinin and hemokinins have been found to modify the immune response.[14]

Neuropeptides, including substance P and CGRP, can cause inflammation in the respiratory system. Over many years, neurogenic inflammation in the airways has been recognized as a potential contributor to pulmonary diseases. Airway nerves activate when receptors on their terminal varicosities engage with endogenous inflammatory mediators or external irritants.[15]

Several mediators of inflammation modify sensory and cholinergic nerve function during airway inflammation. Sensory nerve fibers in the airway regulate all major aspects of human respiratory function. Intraesophageal acid administration in the in vivo experiment induced the release of tachykinins into the airway, causing bronchospasm.[16]

Tachykinin levels and gastric acid reflux parameters were also identified in a group of patients with chronic cough and mild asthma. Elevated tachykinin levels in reflux patients were detected, together with a strong correlation between distal esophageal acid exposure and bronchial levels of substance P and neurokinin A, indicating vagus-induced stimulation of bronchial sensory nerves. Tracheal microaspiration was the most likely mechanism to explain the effects of GERD on asthma. Lung epithelium may also sustain injury during direct contact with aspirated acid, resulting in a release of cytokines and increased inflammation.[14]

Non-pharmacological Management for Asthmatic Patients Induced by GERD

GERD is maintained with a combination of lifestyle adjustments and medical treatments. Management for acid reflux will prevent acid from reaching the airways, reduce night-time Asthma attacks that are often worse at night while sleeping, and induce better response to asthma medications.[17] Non-pharmacological management, such as avoiding particular dietary triggers like carbonated beverages, spicy foods, fatty foods, and caffeine, may alleviate reflux-like symptoms. The majority of patients recognized at least one food that caused reflux-like symptoms, and symptoms improved after being advised to avoid their specific trigger foods.[18] Patients experiencing symptoms should keep a three-hour interval between meals and night sleep. Observational studies have shown a correlation between reflux-like symptoms and dinner-to-bed intervals of less than three hours.[19]

Acid regurgitation can also be avoided by keeping the head end of the bed elevated, which may help with nighttime reflux symptoms. The study reported that more than 70% of the participants in the head-elevation group are more likely to report an overall improvement in symptoms at 6 weeks after. Participants in the study also had statistically significant reductions in acid exposure by measuring the acid pH in the esophagus and reflux episodes during night time sleep.[20]

The next step is by losing body weight for individuals with overweight or obesity and those who have recently gained weight. Obesity is also related to an increase in the abdominothoracic pressure gradient. In patients with severe obesity, intra-abdominal pressure measurements from up to 12 cmH_2O were potentially leading to reflux of gastric content into the esophagus. The waist-hip ratio is an anthropometric number indicating the level of visceral adipose tissue. Higher waist-hip ratios are also related to higher Intra-abdominal pressure, which leads to increased esophageal acid exposure and worse acid clearance.[21] This finding is consistent with studies showing that obese people with less visceral adipose tissue release less stomach

acid and have less esophageal reflux. Visceral fat secretes cytokines such as interleukin-6 and tumor necrosis factor-α, which may contribute to GERD etiology. Evidence suggests that weight loss reduces reflux-like symptoms and decreased reflux episodes as measured by esophageal pH-metry.[22]

Smoking cessation is strongly recommended for a person who has frequent GERD-related asthma symptoms regardless of medication. Tobacco smoking increases the risk of reflux-like symptoms by reducing lower esophageal sphincter pressure, triggering coughing, and diminishing salivation. The mechanism underlying smoking-induced acid reflux is uncertain. The probable explanation is that nicotine alters the lower esophageal sphincter. Nicotine will loosen the lower esophageal sphincter, triggering the regurgitation of gastric contents and acid exposure in the lower esophagus.[23] Studies have found that former heavy smokers had a considerably higher incidence of gastric acid reflux than non-smokers. Studies showed that the risk of acid regurgitation has greatly increased among former smokers with a high amount of smoking, and the incidence declines as the amount of smoking is reduced or stopped.[24]

Conclusion

The causal relationship between gastroesophageal reflux disease (GERD) and asthma is complex, with direct and indirect mechanisms contributing to airway inflammation and bronchoconstriction. Microaspiration of gastric contents, particularly acid and pepsin, causes lung irritation, increased airway resistance, and worsened asthma symptoms.

Understanding the underlying mechanisms of GERD-related asthma, including neurogenic inflammation, allows for a more comprehensive treatment strategy. Non-pharmacological management strategies, including dietary modifications, weight reduction, head-of-bed elevation, and smoking cessation, play a significant role in reducing reflux symptoms and improving asthma control.

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