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Asthma and Chronic Obstructive Pulmonary Disease (COPD): Gastro-Oesophageal Reflux Disease (GERD)

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***Abstract*---Background:** Gastro-oesophageal reflux disease (GERD) is characterized by the retrograde movement of gastric contents into the oesophagus, leading to troublesome symptoms and potential lesions. Its prevalence is increasing globally, particularly in Western countries, with significant links to respiratory disorders like asthma and chronic obstructive pulmonary disease (COPD). **Aim:** This review aims to explore the association between GERD, asthma, and COPD, examining the prevalence, diagnostic challenges, and potential treatment implications. **Methods:** A systematic review of literature published between 1966 and 2016 was conducted using the PubMed database, focusing on the keywords: GERD, asthma, COPD, prevalence, and treatment. Relevant bibliographies were also reviewed to identify additional studies. **Results:** The prevalence of GERD in asthma patients ranges from 30% to 90%, while up to 40% of COPD patients may experience GERD symptoms. Mechanisms proposed for this association include aspiration of refluxate, airway reflex stimulation, and inflammatory mediators affecting lung health. **Conclusion:** The coexistence of GERD with asthma and COPD significantly impacts patient quality of life and complicates diagnosis and management. Management strategies should integrate lifestyle modifications and tailored treatment plans, considering the interactions between these conditions. Ongoing research is crucial to further elucidate the pathophysiological mechanisms underlying these associations and optimize treatment approaches.

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Introduction

Gastro-oesophageal reflux (GER) refers to the retrograde movement of gastric contents into the oesophagus, which is a natural physiological event. When GER results in troublesome symptoms or lesions within the oesophagus, it is classified as gastro-oesophageal reflux disease (GERD) [1]. The prevalence of GERD is on the rise, particularly in Western Europe, North America, and South America, where rates range between 20% and 40% [2-5]. GERD can present with various typical symptoms, such as heartburn and regurgitation; however, the reflux of acid, pepsin, and bile acids may have broader implications beyond these established oesophageal symptoms, potentially resulting in extra-oesophageal manifestations.

In recent decades, there has been growing attention to these atypical manifestations, or extra-oesophageal syndromes (EOS), of GERD in both clinical practice and academic literature. The relationship between GERD and various respiratory conditions has become a focal point of extensive debate. The first description of an association between GERD and respiratory disorders occurred in 1966, linking GERD to asthma pathophysiology [6]. The findings from the significant European ProGERD study indicated that approximately 4.8% of patients with GERD may also have asthma [7]. Similarly, a North American study found that asthma (9.3%) ranks as the third most prevalent EOS [8].

The extent of oesophageal mucosal damage and the severity of GERD-related symptoms are primarily dictated by the degree and duration of acid exposure in the oesophagus, which is largely contingent on the failure of protective mechanisms. The lower and upper oesophageal sphincters (LOS and UOS) serve to safeguard the pharyngeal and laryngeal regions from refluxate. Additionally, the oesophago-glottic closure reflex acts to protect the airway from contact with the refluxate [9, 10]. Furthermore, both swallow-induced or primary peristalsis and secondary peristalsis are crucial for oesophageal clearance. In instances of reflux, oesophageal peristalsis facilitates volume clearance and allows swallowed saliva to reach the distal oesophagus to neutralize acid [11]. Primary peristalsis appears to be predominantly present when individuals are upright and alert. Due to the inhibition of swallowing during sleep, secondary peristalsis assumes greater significance during nighttime [12, 13, 15]. Any disruption to these protective mechanisms could potentially contribute to the pathophysiology underlying EOS [15-20].

Diagnosis of GERD

The presence of GER can be assessed through various methods; however, diagnosing EOS resulting from reflux is complicated by the absence of universally accepted gold standard diagnostic criteria [21]. GER can be quantified by evaluating symptom frequency and severity [22]. While several questionnaires can

be utilized, the limitations of a questionnaire-based approach include its inherent subjectivity and the lack of established cut-off points [23]. Ambulatory oesophageal pH or impedance-pH monitoring is considered the gold standard for quantifying GER. Combined multichannel intraluminal impedance and pH monitoring not only detects both acid and non-acid reflux but also offers additional information regarding the composition of the refluxate (liquid, gas, or mixed) [24, 25]. Nevertheless, the diagnostic accuracy of this technique is somewhat limited, particularly concerning EOS [26, 27]. Vaezi et al. demonstrated that the proximal pH probe's reproducibility in detecting acid reflux in the proximal oesophagus was merely 55% among patients with proximal oesophageal acid reflux. This led the authors to conclude that a negative test result does not rule out proximal reflux that may cause atypical reflux symptoms due to possible micro-aspiration [26]. Additionally, the thresholds used in pH or pH-impedance monitoring to define GERD are not consistently applied, as highlighted by Roman et al. [28]. Upper endoscopy serves as an excellent tool for evaluating potential reflux-related consequences, as it offers direct and objective assessments of GERD lesions. However, a substantial proportion of GERD patients exhibit no macroscopic lesions, and this technique does not distinguish between microscopic alterations in the oesophageal mucosa that could underlie symptoms in certain individuals. Dilated intercellular spaces (DIS), an early morphologic indicator of GERD reflecting the disruption of oesophageal mucosal integrity [29], are not visible during routine endoscopy. Bredenoord et al. concluded that endoscopy possesses high specificity but low sensitivity for diagnosing GERD [25].

Empirical use of proton pump inhibitors (PPIs) may be advantageous since symptom resolution can potentially eliminate the need for further diagnostic assessments [25, 30]. However, a favorable response to high doses of PPIs is not specific and does not definitively confirm a GERD diagnosis [30]. Lastly, examining the presence of salivary pepsin in individuals with symptoms indicative of GERD may reduce unnecessary anti-reflux therapy and the need for additional diagnostic methods. Nonetheless, Sifrim et al. demonstrated significant overlap between healthy controls and GERD patients, which presents a major limitation of this test [31]. This review aims to provide an overview of the association between GERD, asthma, and chronic obstructive pulmonary disease (COPD). According to the Montreal classification, asthma is regarded as a well-established association with GERD [1]. Although the link between GERD and COPD remains relatively ambiguous, there is considerable evidence suggesting a connection between GERD and exacerbations of COPD.

Relation Between GERD and COPD

The relationship between gastro-oesophageal reflux disease (GERD) and chronic obstructive pulmonary disease (COPD) is complex and has become a significant area of research in recent years. Here are key points regarding their association:

1. Prevalence and Coexistence

Studies have indicated that individuals with COPD often have a higher prevalence of GERD compared to the general population. Research shows that the coexistence of these two conditions can exacerbate symptoms and impact the

overall quality of life. Some estimates suggest that up to 40% of patients with COPD may also experience GERD symptoms.

2. Mechanisms of Interaction

Several mechanisms have been proposed to explain the relationship between GERD and COPD:

- **Aspiration of Refluxate**: In individuals with GERD, gastric contents (which may include acid, pepsin, and bile) can be aspirated into the lungs. This aspiration can lead to inflammation and aggravate existing respiratory conditions, potentially contributing to the exacerbation of COPD symptoms.
- **Airway Reflexes**: GERD may stimulate airway reflexes, causing bronchoconstriction and increased airway reactivity. The vagus nerve may play a role in this reflex, as it innervates both the gastrointestinal tract and the respiratory system.
- **Inflammatory Mediators**: The inflammation associated with GERD may affect the lungs. The reflux of acidic content can lead to the release of inflammatory mediators that may aggravate pulmonary inflammation and damage the airway epithelium in COPD patients.

3. Symptom Overlap

Both GERD and COPD can present with similar symptoms, such as coughing, wheezing, and shortness of breath, which can complicate diagnosis and management. Patients may experience overlapping symptoms, leading to challenges in determining which condition is primarily responsible for the symptoms.

4. Impact on Quality of Life

The coexistence of GERD and COPD can significantly impact patients' quality of life. Patients may experience more frequent and severe symptoms, which can lead to increased healthcare utilization, reduced physical activity, and greater psychosocial stress.

5. Management Considerations

Management strategies for patients with both GERD and COPD must consider the interplay between the two conditions:

- **PPI Therapy**: Proton pump inhibitors (PPIs) are often used to manage GERD symptoms. While they can be effective, clinicians should be cautious, as some studies suggest a potential link between long-term PPI use and respiratory infections.
- **Lifestyle Modifications**: Lifestyle changes, such as dietary adjustments, weight management, and smoking cessation, can benefit both conditions. These modifications may help reduce GERD symptoms and improve overall respiratory health.
- **Individualized Treatment Plans**: It is crucial for healthcare providers to develop individualized treatment plans that address both GERD and COPD simultaneously, considering the unique symptoms and challenges faced by each patient.

6. Research Implications

Ongoing research is necessary to further elucidate the relationship between GERD and COPD, including potential pathophysiological mechanisms, optimal treatment strategies, and the effects of GERD management on COPD outcomes. The scientific database PubMed was utilized to identify pertinent full-text articles, focusing on the keywords: GERD, asthma, COPD, prevalence, and treatment. The

authors systematically reviewed articles published from 1966 to 2016, particularly emphasizing publications from the last 15 years that addressed the prevalence, diagnosis, and treatment of GERD in the context of asthma and COPD. Additionally, bibliographies of the selected studies were examined to uncover additional relevant research not identified through the initial PubMed search. Case reports were excluded from this review, and only publications in English were considered.

PART I: Asthma

The American Thoracic Society (ATS) defines asthma as a condition characterized by a history of episodic wheezing, coughing, or dyspnoea, coupled with an increase in forced expiratory volume in one second (FEV1) of at least 20% from baseline following bronchodilator use or a reduction of 20% in FEV1 following methacholine bronchoprovocation (32). Given that both asthma and GERD are prevalent conditions, their coexistence is common. However, the occurrence of these two disorders is significantly more frequent than what would be expected by random chance alone (33-35). This correlation suggests a potential pathological relationship between the two diseases; nonetheless, evidence concerning the direction of causality remains insufficient (33, 36).

2.1.1 Prevalence of GERD in Asthma

The prevalence of GERD among individuals with asthma exhibits considerable variability, with estimates ranging from 30% to 90% (36-40). Factors contributing to this variability include the limited sample sizes in many studies and the varying criteria used for asthma diagnosis. However, the primary factor influencing this variability appears to be the detection methods for gastro-oesophageal reflux (GER) and the thresholds applied to identify increased reflux.

A comprehensive literature review indicates that the average prevalence of GERD in asthma patients is 46.54% based on symptoms alone and 52.70% based on pH monitoring and endoscopic evaluations, while control groups exhibit a prevalence of 23.59% based on symptom assessment. Notably, a synthesis of data from 28 epidemiological studies by Havemann et al. in 2007 revealed that the sample size-weighted average prevalence of GERD symptoms, specifically weekly heartburn and/or regurgitation, in asthma patients was 59.2%. In contrast, the prevalence in control patients from general medical clinics was 38.1%. Furthermore, the study noted that among asthma patients, the average prevalence of an abnormal oesophageal pH profile, oesophagitis, and hiatal hernia was 50.9%, 37.3%, and 51.2%, respectively, with pooled odds ratios indicating a significant association (odds ratios: 5.5, 95% CI 1.9–15.8). Research indicates that abnormal distal oesophageal acid exposure may occur in up to 80% of asthma patients (37, 39). Although the direction of causality remains unclear, investigations into the prevalence of asthma among GERD patients reveal an average asthma prevalence of 4.6% among those with GERD, compared to 3.9% in control subjects (pooled odds ratios: 2.3, 95% CI 1.8-2.8) (36). A significant longitudinal study using data from the UK General Practice Research Database found that patients with asthma have a heightened risk of developing GERD, but not vice versa, indicating no increased risk of asthma development in individuals with GERD (41).

The absence of objective 24-hour pH monitoring in various studies may lead to an underestimation of GERD prevalence, as "silent" reflux, which occurs without typical reflux symptoms, may be undetected using questionnaires alone (42). Additionally, some studies lack a healthy control group or include non-asthmatic subjects with other conditions, such as allergic rhinitis, potentially biasing the results (43, 44). The prevalence of silent reflux in asthmatic individuals shows substantial variability, ranging from 9.6% to 62% (38, 45, 46), which can be attributed to differing screening strategies for GERD.

Furthermore, research by Gislason et al. highlights that young adults with nocturnal reflux, defined as experiencing heartburn or belching during the night at least once a week, demonstrate a greater prevalence of asthma and respiratory symptoms compared to those without nocturnal reflux symptoms (47). This increased prevalence may partly result from the lack of protective responses to reflux during sleep. Consequently, it has been proposed that nighttime reflux could predispose patients to respiratory manifestations, suggesting its potential significance in the pathogenesis of extra-oesophageal complaints. In summary, a study conducted by Ladanchuk, and colleagues indicated a higher frequency of asthma diagnosis in patients with Barrett's oesophagus (Odds Ratio 2.15, 95% CI 1.15-4.03). However, no association was found between asthma diagnosis and oesophageal adenocarcinoma (Odds Ratio 0.78, 95% CI 0.396-1.68) (48).

Mechanisms of Association between GERD and Asthma

The relationship between gastroesophageal reflux disease (GERD) and asthma has been explored through two primary mechanisms: the **reflux theory**, which describes a direct association, and the **reflex theory**, which illustrates an indirect relationship.

Reflux Theory

The reflux theory posits a direct connection whereby micro-aspiration of gastric contents (including duodenal) leads to injury of the pulmonary system. Micro-aspiration can result in various pulmonary symptoms, as the aspirated material irritates the pharynx or larynx, potentially triggering a cough reflex that manifests as tracheal or bronchial symptoms. This process may escalate to acute lung injury and severe complications such as acute respiratory distress syndrome (ARDS).

Injury to the lungs due to micro-aspiration can be categorized into three distinct mechanisms:

1. **Mechanical obstruction** of airways caused by small particles present in the aspirate.
2. **Reversible non-infectious chemical pneumonitis**, also known as aspiration pneumonitis, or the development of aspiration-related bacterial pneumonia.
3. **Severe pulmonary inflammatory response**, characterized by proteinaceous edema, hypoxemia, and diminished lung compliance .

Under normal circumstances, physiological barriers such as a functional lower esophageal sphincter (LES) and upper esophageal sphincter (UES) can prevent refluxate from inflicting harm or triggering symptoms. Disruption of these protective mechanisms could contribute to the development of asthma symptoms among patients with GERD . To assess pulmonary micro-aspiration of gastric contents, one potential method involves analyzing pepsin and bile salts in bronchoalveolar lavage fluid (BALF). Elevated levels of these markers may suggest the aspiration of gastric contents. However, a significant challenge in utilizing these molecular indicators lies in standardizing their concentrations in BALF. The dynamics of pepsin or bile salt levels in BALF following an aspiration incident remain poorly understood. Factors influencing these levels may include:

1. Dilution effects at the time of sampling.
2. The volume and frequency of aspiration episodes.
3. The efficiency of clearance mechanisms within the lungs .

Both animal and human studies provide evidence supporting the reflux theory. An early study by Tuchman et al. (1984) demonstrated increased total lung resistance in cats following tracheal infusion of hydrochloric acid . Additionally, research conducted by Jack et al. revealed concurrent reductions in peak expiratory flow (PEF) and tracheal pH in asthma patients with symptomatic GERD . Pauwels et al. identified bile acids in the sputum of 28% of asthma patients, suggesting duodenogastric content aspiration, with increased bile acid levels correlating with lung function impairment. This highlights the detrimental impact of micro-aspiration . Although ethical considerations complicate studies directly addressing micro-aspiration in humans, the detection of pepsin and bile acids in sputum or BALF has provided objective evidence linking micro-aspiration to GER.

Reflex Theory

In contrast to the reflux theory, the reflex theory posits an indirect mechanism whereby distal esophageal reflux activates the vagus nerve, resulting in bronchoconstriction. This potential neural connection between reflux and asthma is not unexpected, given that the esophagus and the tracheobronchial tree share an embryonic origin, leading to similar neural innervation that may facilitate interaction between the two structures (20). This shared innervation explains how stimuli in the distal esophagus can trigger respiratory symptoms through vagally mediated reflexes (61-64).

Research indicates a significant association between respiratory symptoms and esophageal acidification due to acid reflux in a large cohort of asthma patients, with percentages ranging from 46% to 78%. These findings support the reflex theory (37, 65). Additionally, several studies have documented instances of bronchoconstriction following distal esophageal acid perfusion in both asthmatic and non-asthmatic patients (the latter comprising individuals with normal lung function yet experiencing dyspepsia and/or heartburn symptoms) (66-68). A pivotal study by Schan et al. (1994) utilized an upright Bernstein acid infusion test, comparing four patient groups: 20 individuals with concurrent asthma and GERD, seven asthmatics without GERD, 10 non-asthmatic GERD patients, and 10 healthy controls. The results revealed decreased peak expiratory flow (PEF)

across all groups after exposure to esophageal acid, corroborating prior findings in non-asthmatic subjects (61, 69).

Nevertheless, the existing literature is not uniformly supportive. Field et al. concluded that both spontaneous reflux and esophageal acid perfusion had minimal or no impact on lung function (70). Furthermore, Ekström et al. found that the daytime instillation of esophageal acid (15 cm above the lower esophageal sphincter) did not elicit clinically significant bronchospasm, respiratory symptoms, or an increase in airway reactivity in patients with moderate to severe asthma and GERD (n = 8). The changes in forced expiratory volume in 1 second (FEV1) in response to esophageal acid stimulation were small and inconsistent among participants. A notable limitation of this study was its small sample size and the absence of a placebo group for comparative analysis (71). These findings highlight the uncertainty surrounding how GERD exacerbates asthma symptoms without manifesting significant alterations in lung function.

Bronchial Hyper-responsiveness

Bronchial hyper-responsiveness refers to an abnormal bronchoconstrictive response following an airway stimulus, and it is present in nearly all adults with symptomatic asthma (72-74). Three research domains provide evidence suggesting that esophageal acid may affect hyper-responsiveness: (1) micro-aspiration of refluxate (reflux theory), (2) vagally mediated reflexes triggered by the esophagus (reflex theory), and (3) neuroinflammation initiated by the esophagus (75). In clinical practice, bronchial hyper-responsiveness is assessed through the administration of standardized stimuli during pulmonary function testing. The four most commonly used stimuli include methacholine, histamine, hyperventilation with dry cold air, and exercise, with the degree of responsiveness correlating with asthma severity (76).

Hervé et al. (1986) demonstrated that esophageal acid perfusion increased bronchial responsiveness, as measured after voluntary isocapnic hyperventilation and methacholine inhalation in seven asthmatic patients with GERD (66). Vincent et al. conducted 24-hour pH monitoring alongside lung function assessments in 105 asthma patients, revealing no significant differences in lung function parameters between GERD-positive and GERD-negative asthmatics. However, a strong correlation was observed between bronchial reactivity and the frequency of acid reflux episodes in GERD-positive individuals (77).

Wu et al. (2000) found that esophageal perfusion with hydrochloric acid (15 cm above the lower esophageal sphincter) did not significantly affect FEV1, PEF, or respiratory resistance in seven patients with bronchial asthma. However, it did heighten airway hyper-responsiveness, as indicated by a notable decrease in the concentration of methacholine required to achieve a 35% reduction in respiratory conductance (78). Limitations of this study included the absence of a control group and a small sample size of only seven patients. Collectively, these findings suggest that esophageal acidification may play a critical role in the exacerbation of asthma symptoms.

Reflux and Asthma Relationship

The connection between gastroesophageal reflux disease (GERD) and asthma has been extensively studied, raising a significant question: does GERD provoke asthma symptoms, or do asthma conditions contribute to the development of GERD? The elevated incidence of GERD among individuals with asthma may partially stem from the asthma condition itself or the treatments associated with it. For instance, Field et al. highlighted that coughing and increased respiratory effort can exacerbate GERD by creating a heightened pressure gradient across the lower esophageal sphincter (LES). Patients with asthma often exhibit lung hyperinflation, which results in diaphragm contraction that increases the pressure differential between the thorax and abdomen. This pressure surge can potentially lead to the herniation of the LES into the thoracic cavity, thereby compromising its barrier functionality. Additionally, asthma medications such as theophylline, β-agonists, and corticosteroids may promote reflux by reducing LES pressure, thus facilitating acid reflux.

Conversely, several investigations endorse the concept of reflux-induced asthma. This perspective is particularly plausible in certain scenarios, including the onset of asthma symptoms during adulthood, absence of a family history of asthma, lack of allergic components, experiences of heartburn and regurgitation prior to the emergence of asthma symptoms, exacerbation of asthma following meals, and lack of response to conventional asthma treatments. In summary, establishing a definitive causal relationship between GERD and asthma remains challenging, as GERD may provoke bronchospasm while asthma may concurrently induce GERD.

Treatment Modalities

Given the recognized association between GERD and asthma, it is anticipated that addressing GERD in asthmatic patients could be advantageous. Some evidence suggests that other esophageal symptoms (EOS) associated with reflux, such as hoarseness or cough, may assist in predicting which asthma patients with GERD might experience pulmonary function improvements when reflux is treated.

Lifestyle Modifications

Adopting lifestyle modifications can enhance reflux management. Recommendations include quitting smoking, achieving weight loss, altering dietary habits, elevating the head of the bed, and avoiding food intake less than three hours before bedtime. While these changes could potentially improve esophageal function and, by extension, alleviate bronchial symptoms in asthma patients, there is currently no randomized controlled trial data to substantiate this hypothesis.

H2-Receptor Antagonists

Histamine2 (H2) receptor antagonists, including cimetidine and ranitidine, reduce gastric acid secretion by blocking the H2 receptors located on parietal cells in the stomach. Traditionally, these agents have been utilized to diminish gastric and,

consequently, esophageal acid exposure. Research from the 1980s and early 1990s indicated that treatment with H2-receptor antagonists can lead to improvements in reflux symptoms and, in some instances, nocturnal asthma symptoms. However, these studies revealed only modest enhancements in asthma control, particularly among patients with a history of GERD, and showed no evidence of improved lung function.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) have also been evaluated for their potential benefits. For example, in a study by Meier et al., 15 patients demonstrated a ≥20% net improvement in forced expiratory volume in one second (FEV1) after receiving omeprazole, while Harding et al. observed improved peak expiratory flow (PEF) in 73% of 30 patients treated with varying doses of omeprazole. In contrast, some studies, including one conducted by Littner et al. with 99 patients, found no significant changes in asthma symptoms or pulmonary function after treatment with lansoprazole. Similar results were noted in a study by Mastronarde et al., which included 208 patients treated with esomeprazole. Conversely, Kiljander et al. reported improvements in asthma symptom scores among 545 patients treated with esomeprazole, along with minor enhancements in pulmonary function. A significant finding by Sandur et al. was the notable improvement in both nocturnal and daytime asthma symptoms among 28 patients treated with omeprazole.

Anti-Reflux Surgery

Surgical interventions, such as Nissen fundoplication, have been explored as a treatment option for GERD in asthma patients. According to Perrin-Fayolle et al., long-term gastrointestinal relief was reported in 95% of 44 patients, with varying degrees of pulmonary improvement. Larrain et al. observed clinical improvements and significant reductions in bronchodilator usage among patients undergoing Nissen fundoplication. However, some studies, including Ekström et al. and Sontag et al., indicated minimal effects on lung function while noting improvements in asthma symptom scores and overall clinical status. In conclusion, the treatment of GERD in asthmatic patients includes a variety of options ranging from lifestyle changes and medications to surgical interventions, each presenting varying levels of effectiveness in managing asthma symptoms.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are a well-tolerated category of medications that inhibit the proton pump (H+/K+ ATPase) in the stomach's parietal cells, thus reducing gastric acid secretion. They are regarded as the standard treatment for gastroesophageal reflux disease (GERD) due to their significant advantages over H2-blockers regarding symptom relief and healing of esophagitis [88]. Numerous studies have explored the impact of PPI treatment on asthma outcomes, but the findings have been inconclusive. The efficacy of PPI therapy in asthmatic patients has not been definitively established and remains uncertain. It has been shown that asthma patients with a confirmed diagnosis of GERD exhibited the most notable improvement in morning peak expiratory flow (PEF) rates; however, no

statistically significant differences were observed in forced expiratory volume in one second (FEV1) when comparing PPI treatment to a placebo.

In 2003, Gibson et al. conducted a systematic review of 12 randomized, placebo-controlled trials involving asthma patients, utilizing the Cochrane methodology, with five of these trials examining the effects of PPIs on asthma. One trial noted an increase in FEV1, another indicated a significant enhancement in asthma symptoms, and a third reported improvements in nocturnal asthma following PPI treatment [89]. Chan et al. performed a meta-analysis summarizing the outcomes of PPI therapy in asthma patients, concluding that there was a modest but significant improvement in morning PEF rates following PPI treatment. However, the authors noted that this enhancement is unlikely to hold clinical significance, as there was no overall improvement in lung function measured by FEV1, nor any substantial enhancement in asthma symptom scores [90].

Meier et al. conducted a double-blind, placebo-controlled, crossover study demonstrating that a 6-week treatment with omeprazole (20 mg, twice daily) improved pulmonary function (FEV1) in 4 out of 15 (27%) asthma patients with GERD. They suggested that a subset of asthma patients might benefit from omeprazole treatment, although cough, hoarseness, and nocturnal heartburn were not effective predictors of which patients would experience improvements in pulmonary function [91]. A 3-month trial of omeprazole (20 to 60 mg/day) resulted in a 20% increase in PEF and/or a reduction in pulmonary symptoms for 22 out of 30 (73%) asthma patients with concurrent GERD [92]. However, a limitation of this study is the absence of a placebo arm, despite including a 4-week pre-therapy phase.

In a recent investigation by Sandur et al., the effects of omeprazole on asthma symptoms, pulmonary function, and the need for asthma medications were assessed in 40 patients with difficult-to-control asthma. All patients underwent 24-hour pH monitoring, and pulmonary function tests were conducted before and after treatment. Among asthma patients with GERD, there were significant post-treatment improvements in reflux symptom scores, pulmonary symptom scores, and nighttime asthma symptom scores ($P < .0001$), along with a notable increase in FEV1 ($P < .001$). The authors concluded that PPI therapy enhances both nocturnal and daytime asthma symptoms in patients with asthma and concurrent GERD [93].

The conflicting findings from the aforementioned studies may stem from varying clinical endpoints related to the effectiveness of PPI therapy in asthmatics. Galmiche et al. identified key reasons for these inconsistent results: (1) limited high-quality, randomized, placebo-controlled trials reported; (2) the absence of defined inclusion criteria for selecting potential responders; (3) undefined optimal therapeutic regimens for this specific patient population; (4) frequent enrollment of heterogeneous populations in trials; and (5) insufficiently defined relevant clinical endpoints [29, 42]. In summary, there is inadequate evidence to support the empirical use of PPIs in asthma treatment [92, 94]. However, PPI therapy may be beneficial for a subset of patients, particularly those experiencing nocturnal asthma or nocturnal reflux, as indicated by a study conducted by Kiljander et al. [95].

Anti-Reflux Surgery

Research involving H2-antagonists or PPIs has yielded only marginal improvements in pulmonary outcomes for asthmatics with GERD. In contrast, anti-reflux surgery may provide a more effective solution for GERD, as it not only reduces esophageal acid exposure but also addresses ongoing non-acid reflux. Anti-reflux surgery has demonstrated not only symptomatic relief for reflux disease but also a reduction in asthma symptom scores and decreased asthma medication usage. However, the impact of anti-reflux surgery on pulmonary function remains unclear.

An early study by Perrin-Fayolle et al. in 1989 revealed an improvement in pulmonary symptoms for 29 out of 44 (66%) asthmatics with GERD more than five years post-Nissen fundoplication. The pulmonary improvement rate appeared higher in patients with intrinsic asthma (without an allergic component) and those experiencing predominantly nocturnal asthma crises linked to reflux episodes [96]. In a study by Larrain et al., six months following anti-reflux surgery, the use of asthma medications was significantly lower in 26 patients with non-allergic asthma and GER compared to 28 patients receiving placebo, and this effect persisted during long-term follow-up [86]. In 2000, a prospective study by Ekström and Johansson assessed the effects of anti-reflux surgery (transabdominal or laparoscopic fundoplication) in 13 patients with severe GERD and asthma. Although the surgery appeared to have no impact on lung function, there was a small yet non-significant reduction in asthma symptom scores, and the consumption of inhaled bronchodilators and other regular asthma medications decreased post-surgery [97].

In 2003, Sontag et al. conducted a randomized study enrolling 62 patients with both GERD and asthma: 22 patients received ranitidine (150 mg, three times daily), 16 underwent anti-reflux surgery (Nissen fundoplication), and 24 patients were in a control group that allowed symptomatic treatment with antacids. After two years of follow-up, anti-reflux surgery emerged as the only treatment that significantly improved asthma symptom scores and overall clinical status, albeit with minimal effects on pulmonary function and medication requirements [98]. Silva et al. examined the effectiveness of laparoscopic Nissen fundoplication in alleviating eosinophilic asthma in patients with GER. As anticipated, six months post-surgery, there was a notable reduction in heartburn, and more significantly, there was a marked difference in daily asthma crises [99]. While the studies mentioned suggest that anti-reflux surgery may enhance asthma symptom scores, the true benefits of this surgical approach on pulmonary function and the necessity for asthma medications remain ambiguous, as most studies have several limitations: a lack of control groups, inadequate documentation of asthma severity, and insufficient information on whether reflux was effectively managed postoperatively.

Conclusion

The intricate relationship between gastro-oesophageal reflux disease (GERD) and respiratory disorders, particularly asthma and chronic obstructive pulmonary disease (COPD), necessitates a nuanced understanding of their interplay. The

substantial overlap in symptomatology—such as coughing, wheezing, and dyspnea—complicates the diagnostic landscape, often leading to challenges in effective management. Given that patients with asthma and COPD frequently experience GERD, understanding the implications of this coexistence is vital for improving clinical outcomes. The prevalence of GERD among asthma patients is notably high, with estimates suggesting that between 30% and 90% of individuals with asthma also experience GERD symptoms. This relationship is often exacerbated by mechanisms such as aspiration of refluxate and the inflammatory response it triggers, which may worsen respiratory symptoms. In COPD patients, the prevalence of GERD may reach up to 40%, further complicating their clinical management. These dual diagnoses can lead to an increased frequency and severity of symptoms, adversely affecting the patients' quality of life and leading to greater healthcare utilization. Management strategies must consider the interplay between GERD, asthma, and COPD. Proton pump inhibitors (PPIs) are commonly employed to address GERD symptoms; however, their use must be balanced against potential risks, including respiratory infections. Lifestyle modifications, such as weight management and smoking cessation, are beneficial for both GERD and respiratory health and should be emphasized in treatment plans. In conclusion, recognizing and addressing the relationship between GERD and respiratory disorders is essential for healthcare providers. An individualized approach to treatment that considers the complexities of each patient's condition is crucial for optimizing outcomes. Future research is warranted to further clarify the pathophysiological mechanisms connecting these disorders and to develop effective management strategies that enhance patient care in those affected by both GERD and respiratory diseases.

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الربو ومرض الانسداد الرئوي المزمن :(COPD) مرض الارتجاع المعدي المريئي(GERD)

الملخص:
الخلفية :يتميز مرض الارتجاع المعدي المريئي (GERD) بالحركة العكسية لمحتويات المعدة إلى المريء، مما يؤدي إلى أعراض مزعجة وإمكانية حدوث إصابات. إن انتشاره في تزايد عالمي، خاصة في الدول الغربية، وله ارتباطات كبيرة مع اضطرابات الجهاز التنفسي مثل الربو ومرض الانسداد الرئوي المزمن.(COPD)
الهدف :تهدف هذه المراجعة إلى استكشاف العلاقة بين GERD والربو وCOPD، مع التركيز على الانتشار، التحديات التشخيصية، والآثار المحتملة للعلاج.
الطرق :تم إجراء مراجعة منهجية للأدبيات المنشورة بين عامي 1966 و2016 باستخدام قاعدة بياناتPubMed ، مع التركيز على الكلمات الرئيسيةGERD :، الربو، COPD، الانتشار، والعلاج. كما تمت مراجعة الببليوجرافيات ذات الصلة لتحديد دراسات إضافية.
النتائج :يتراوح انتشار GERD لدى مرضى الربو بين 30% إلى 90%، بينما قد يعاني حتى 40% من مرضى COPD من أعراض .GERD تشمل الآليات المقترحة لهذه العلاقة استنشاق المواد المرتجعة، تحفيز ردود الفعل الهوائية، والعوامل الالتهابية التي تؤثر على صحة الرئة.
الخاتمة :تؤثر التعايش بين GERD والربو و COPDبشكل كبير على جودة حياة المرضى وت complicates diagnosis and management.يجب أن تدمج استراتيجيات الإدارة تعديلات نمط الحياة وخطط العلاج المصممة خصيصًا، مع مراعاة التفاعلات بين هذه الحالات. يعد البحث المستمر أمرًا حاسمًا لتوضيح الآليات الفسيولوجية المرضية الأساسية وراء هذه العلاقات وتحسين طرق العلاج.
الكلمات الرئيسية :مرض الارتجاع المعدي المريئي، الربو، مرض الانسداد الرئوي المزمن، الانتشار، العلاج.