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The Impact of Gastroesophageal Reflux Disease (GERD) on Pharyngeal Mucosal Changes: A Case-Control Study in Indonesia

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A B S T R A C T

Introduction: Gastroesophageal reflux disease (GERD) is a prevalent digestive disorder with potential extra-esophageal manifestations, including laryngopharyngeal reflux (LPR). LPR can lead to various pharyngeal mucosal changes, impacting voice quality and overall well-being. This study aimed to investigate the association between GERD and pharyngeal mucosal changes in a population in Indonesia. **Methods:** A case-control study was conducted at a tertiary hospital in Indonesia, involving 100 participants diagnosed with GERD (cases) and 100 participants without GERD (controls). All participants underwent a comprehensive ear, nose, and throat (ENT) examination, including flexible nasopharyngoscopy, to assess pharyngeal mucosal changes. The Reflux Symptom Index (RSI) questionnaire was used to evaluate the severity of reflux symptoms. Data were analyzed using SPSS software, employing chi-square and logistic regression analyses to determine the association between GERD and pharyngeal mucosal changes. **Results:** The study found a significantly higher prevalence of pharyngeal mucosal changes in the GERD group compared to the control group (78% vs. 22%, $p<0.001$). Erythema, edema, and posterior pharyngeal wall cobblestoning were the most common findings in GERD patients. The severity of reflux symptoms, as measured by the RSI, was positively correlated with the presence and severity of pharyngeal mucosal changes. **Conclusion:** GERD is significantly associated with pharyngeal mucosal changes in the Indonesian population studied. These findings underscore the importance of recognizing and managing LPR in patients with GERD to prevent potential complications and improve quality of life.

1. Introduction

Gastroesophageal reflux disease (GERD) stands as a prevalent and chronic disorder of the digestive system, affecting millions worldwide. This condition arises when the acidic contents of the stomach repeatedly flow back into the esophagus, leading to a spectrum of symptoms and potential long-term complications. While heartburn and regurgitation are widely recognized as the hallmark symptoms of GERD, the impact of this disease extends beyond the confines of the esophagus. In recent decades, increasing attention has been directed towards the extra-esophageal manifestations of GERD, with laryngopharyngeal reflux (LPR) emerging as a significant concern. LPR, often referred to as "silent reflux," occurs when the refluxate ascends further to reach the pharynx and larynx. This retrograde flow of gastric contents, laden with acid, pepsin, and bile

acids, can inflict considerable damage upon the delicate mucosal lining of the throat. Consequently, LPR can precipitate a variety of pharyngeal mucosal changes, ranging from subtle erythema and edema to more pronounced alterations such as cobblestoning and granuloma formation. These mucosal changes can have profound implications for an individual's well-being, affecting voice quality, swallowing function, and overall quality of life. The prevalence of GERD exhibits considerable variation across different regions and populations. Studies have estimated the global prevalence of GERD to range from 8.8% to 25.9% in Europe, 18.1% to 27.8% in North America, 2.5% to 7.8% in East Asia, 8.7% to 33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America. These figures underscore the substantial global burden of GERD and its associated healthcare costs. In Indonesia, a rapidly developing nation in Southeast Asia, the prevalence of GERD has been reported to be 12.7%, indicating a significant impact on the Indonesian population.[1-4]

LPR, as an extra-esophageal manifestation of GERD, is estimated to affect approximately 10-20% of the general population. This condition often goes undiagnosed or misdiagnosed due to its atypical presentation, which may lack the classic symptoms of heartburn and regurgitation. Instead, individuals with LPR may present with a variety of laryngeal and pharyngeal symptoms, including hoarseness, chronic cough, throat clearing, globus sensation (a feeling of a lump in the throat), and dysphagia (difficulty swallowing). These symptoms can significantly impair an individual's ability to communicate, eat, and perform daily activities, leading to a diminished quality of life. The pathophysiology of LPR involves a complex interplay of factors that contribute to the reflux of gastric contents into the laryngopharynx. These factors include transient lower esophageal sphincter relaxations, impaired esophageal motility, hiatal hernia, and increased intra-abdominal pressure. Once the refluxate reaches the pharynx and larynx, its acidic and enzymatic components can initiate an inflammatory cascade, leading to mucosal injury and the characteristic pharyngeal mucosal changes observed in LPR. The pharyngeal mucosa, a delicate lining that covers the pharynx, plays a crucial role in protecting the underlying tissues from mechanical, chemical, and microbial insults. In healthy individuals, the pharyngeal mucosa appears smooth, pink, and moist. However, in the presence of LPR, the chronic exposure to gastric refluxate can disrupt the mucosal integrity, leading to a variety of changes. These changes can range from subtle erythema and edema to more pronounced alterations such as posterior pharyngeal wall cobblestoning, characterized by an irregular, bumpy appearance of the pharyngeal wall. In severe cases, LPR can even lead to the formation of granulomas, which are small, nodular lesions that represent a chronic inflammatory response.[5-7]

The diagnosis of LPR can be challenging due to the lack of specific symptoms and the absence of visible esophageal injury in many cases. A thorough clinical evaluation, including a detailed history and physical examination, is essential to identify potential signs and symptoms of LPR. Flexible nasopharyngoscopy, a minimally invasive procedure that allows direct visualization of the pharynx and larynx, is considered the gold standard for diagnosing LPR-related pharyngeal mucosal changes. This procedure enables the clinician to assess the extent and severity of mucosal abnormalities, aiding in the diagnosis and management of LPR. While the association between GERD and LPR has been extensively studied in various populations, limited data are available on the prevalence and impact of LPR-related pharyngeal mucosal changes in Indonesia. This knowledge gap highlights the need for further research to understand the burden of LPR in the Indonesian population and to develop effective strategies for its prevention and management.[8-10] This study aimed to address this gap by conducting a case-control study at a tertiary referral hospital in Indonesia.

2. Methods

This investigation adopted a case-control study design, a robust epidemiological approach well-suited for exploring the association between a risk factor (in this case, GERD) and an outcome of interest (pharyngeal mucosal changes). This design involves

comparing a group of individuals with the outcome (cases) to a group without the outcome (controls) to assess the presence and magnitude of the association. The study was conducted at a tertiary referral hospital in Indonesia. Tertiary hospitals, being at the apex of the healthcare pyramid, receive referrals of complex cases from primary and secondary care facilities, thereby offering access to a diverse patient population. This setting enhanced the study's ability to recruit participants with a wide spectrum of GERD severity and associated pharyngeal mucosal changes. The study was conducted over a one-year period, from January 2023 to December 2023. This extended duration facilitated the recruitment of an adequate sample size and allowed for the observation of seasonal variations in GERD symptoms and pharyngeal mucosal changes, if any.

Prior to the commencement of the study, ethical approval was obtained from the Institutional Review Board (IRB) of the participating hospital. The IRB reviewed the study protocol, ensuring its adherence to ethical principles and guidelines for research involving human subjects. All participants were provided with a detailed explanation of the study's purpose, procedures, potential benefits, and risks. Written informed consent was obtained from each participant before their enrollment in the study.

The study population comprised adult patients aged 18 years and above who were referred to the Otorhinolaryngology clinic of the hospital. A total of 200 participants were enrolled in the study, equally divided into two groups; Cases: 100 patients with a confirmed diagnosis of GERD; Controls: 100 participants without GERD. The diagnosis of GERD in the case group was established based on a combination of clinical, endoscopic, and therapeutic criteria. The following criteria were employed; Presence of typical symptoms: Participants were considered to have GERD if they reported experiencing classic symptoms such as heartburn and regurgitation. These symptoms are highly suggestive of GERD and are often used as the primary basis for diagnosis in clinical practice; Positive response to proton pump inhibitor (PPI) therapy: Participants who exhibited a significant improvement in their symptoms following a trial of PPI therapy were also considered to have GERD. PPIs are potent inhibitors of gastric acid secretion and are the mainstay of treatment for GERD. A positive response to PPI therapy further supports the diagnosis of GERD; Endoscopic evidence of esophagitis (if available): Upper gastrointestinal endoscopy, a procedure that involves visualizing the esophagus, stomach, and duodenum with a flexible endoscope, was performed in a subset of participants to assess for the presence of esophagitis. Esophagitis, characterized by inflammation and damage to the esophageal mucosa, is a common finding in GERD. While not all patients with GERD have endoscopic evidence of esophagitis, its presence provides strong support for the diagnosis. The control group consisted of patients who visited the Otorhinolaryngology clinic for reasons unrelated to GERD. These participants served as a comparison group to assess the prevalence of pharyngeal mucosal changes in the absence of GERD. The control group was carefully selected to ensure that they did not have any history of GERD symptoms or diagnosis. To ensure the homogeneity of the study population and minimize the influence of confounding factors, the following exclusion criteria were applied to both the case and control groups; History of head and neck surgery: Participants with a history of head and neck surgery were excluded to avoid the potential confounding effects of surgical interventions on the pharyngeal mucosa; History of radiation therapy to the head and neck region: Radiation therapy can cause significant damage to the mucosal tissues in the head and neck region, potentially mimicking the changes seen in LPR. Therefore, participants with a history of radiation therapy were excluded; Presence of other laryngeal or pharyngeal pathology: Participants with other laryngeal or pharyngeal conditions, such as tumors, infections, or vocal cord paralysis, were excluded to ensure that any observed mucosal changes could be attributed to LPR rather than other underlying pathologies; Current use of medications known to affect the pharyngeal mucosa: Certain medications, such as corticosteroids and antibiotics, can alter the appearance of the pharyngeal mucosa. To avoid potential confounding effects, participants currently using these medications were excluded.

A standardized data collection protocol was implemented to ensure consistency and accuracy in data acquisition. All participants underwent a comprehensive ear, nose, and throat (ENT) examination, including flexible nasopharyngoscopy, performed by an experienced otorhinolaryngologist. Flexible nasopharyngoscopy is a minimally invasive procedure that allows direct visualization of the pharynx and larynx using a flexible endoscope. The endoscope, a thin, flexible tube with a camera and light source at its tip, is gently inserted through the nasal cavity and advanced into the pharynx and larynx. The procedure is typically well-tolerated and can be performed in an outpatient setting. In this study, the nasopharyngoscopy was conducted using a state-of-the-art flexible endoscope (Olympus ENF-VT2) equipped with a high-resolution video camera. The video camera captured real-time images of the pharyngeal and laryngeal structures, allowing for detailed assessment of the mucosal surfaces. The otorhinolaryngologist performing the nasopharyngoscopy meticulously examined the following areas; Nasopharynx: The uppermost part of the pharynx, located behind the nasal cavity; Oropharynx: The middle part of the pharynx, located behind the oral cavity; Hypopharynx: The lowermost part of the pharynx, located above the larynx; Larynx: The voice box, containing the vocal cords. Particular attention was paid to assessing the pharyngeal mucosa for any signs of LPR-related changes, including; Erythema (redness): Erythema, or redness, of the pharyngeal mucosa is a common finding in LPR and indicates inflammation of the mucosal lining; Edema (swelling): Edema, or swelling, of the pharyngeal mucosa can occur due to fluid accumulation in the tissues, often as a result of inflammation; Posterior pharyngeal wall cobblestoning: Cobblestoning refers to an irregular, bumpy appearance of the posterior pharyngeal wall, often seen in LPR. This change is thought to be caused by chronic inflammation and lymphoid hyperplasia; Granuloma formation: Granulomas are small, nodular lesions that represent a chronic inflammatory response. They can occur in the larynx or pharynx in severe cases of LPR; Thickened mucus: Thickened mucus in the pharynx can be a sign of LPR, as the refluxate can stimulate mucus production. In addition to the ENT examination, all participants completed the Reflux Symptom Index (RSI) questionnaire. The RSI is a validated, self-administered instrument designed to assess the severity of reflux symptoms, encompassing both esophageal and extra-esophageal manifestations. The questionnaire comprises nine items, each scored on a Likert scale ranging from 0 to 5, with higher scores indicating greater symptom severity. The nine items assess the following symptoms; Hoarseness; Clearing your throat; Excess throat mucus or postnasal drip; Difficulty swallowing; Coughing; Breathing difficulties or choking episodes; Heartburn; Regurgitation; Dyspepsia (indigestion). The total RSI score is calculated by summing the scores for each item, resulting in a range from 0 to 45. The RSI has been shown to have good reliability and validity in assessing reflux symptoms and is widely used in clinical practice and research.

The data collected in this study were meticulously analyzed using SPSS software (version 26), a comprehensive statistical package widely employed in healthcare research. The following statistical techniques were employed: Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. These statistics included measures of central tendency (mean, median) and dispersion (standard deviation, range) for continuous variables, and frequencies and percentages for categorical variables. The chi-square test, a non-parametric statistical test, was used to compare the prevalence of pharyngeal mucosal changes between the GERD and control groups. This test assesses whether there is a significant association between two categorical variables. Logistic regression analysis, a multivariate statistical technique, was performed to determine the independent association between GERD and pharyngeal mucosal changes. This analysis allowed for the adjustment of potential confounding factors, such as age, sex, and smoking status, to isolate the specific effect of GERD on the outcome. Spearman's rank correlation coefficient, a non-parametric measure of association, was used to assess the correlation between the RSI score and the

severity of pharyngeal mucosal changes. This analysis evaluated the strength and direction of the relationship between these two variables. A p-value of less than 0.05 was considered statistically significant for all analyses. This threshold indicates that there is less than a 5% probability that the observed results occurred by chance alone.

3. Results

Table 1 presents the demographic and clinical characteristics of the 200 participants enrolled in the study, divided into two groups: the GERD group (n=100) and the control group (n=100). The average age of participants in the GERD group was 48.5 years, while the control group had a mean age of 46.3 years. This difference was not statistically significant (p=0.28), indicating that the two groups were comparable in terms of age. The distribution of males and females was similar in both groups, with no statistically significant difference (p=0.35). This suggests that sex is unlikely to be a confounding factor in the analysis of the association between GERD and pharyngeal mucosal changes. The prevalence of current, former, and never smokers was similar between the two groups, with no statistically significant difference (p=0.79). This indicates that smoking status is unlikely to influence the relationship between GERD and pharyngeal mucosal changes in this study. The mean BMI in the GERD group was 26.8 kg/m², slightly higher than the mean BMI of 25.5 kg/m² in the control group. However, this difference was not statistically significant (p=0.08). While BMI has been linked to GERD in some studies, it does not appear to be a major confounding factor in this particular study. The prevalence of comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia was slightly higher in the GERD group compared to the control group. However, none of these differences reached statistical significance (p>0.05). This suggests that these comorbidities, while potentially related to GERD, are unlikely to significantly confound the association between GERD and pharyngeal mucosal changes in this study.

Table 1. Demographic and clinical characteristics of participants.

Characteristic	GERD Group (n=100)	Control Group (n=100)	p-value
Age (years)			
Mean ± SD	48.5 ± 13.2	46.3 ± 12.8	0.28
Gender			
Male, n (%)	55 (55%)	48 (48%)	0.35
Female, n (%)	45 (45%)	52 (52%)	
Smoking status			
Current, n (%)	20 (20%)	18 (18%)	0.79
Former, n (%)	15 (15%)	12 (12%)	
Never, n (%)	65 (65%)	70 (70%)	
Body mass index (kg/m²)			
Mean ± SD	26.8 ± 4.1	25.5 ± 3.9	0.08
Comorbidities			
Diabetes Mellitus, n (%)	18 (18%)	10 (10%)	0.11
Hypertension, n (%)	25 (25%)	15 (15%)	0.06
Hyperlipidemia, n (%)	30 (30%)	22 (22%)	0.18

Table 2 provides a detailed breakdown of the prevalence of various pharyngeal mucosal changes observed in the GERD and control groups. The data clearly demonstrate a significantly higher prevalence of these changes in individuals with GERD, reinforcing the link between GERD and laryngopharyngeal reflux (LPR). A striking 78% of the GERD group exhibited some form of pharyngeal mucosal change, compared to only 22% in the control group (p<0.001). This stark difference highlights the substantial impact of GERD

on the pharyngeal mucosa. Erythema, or redness, was the most common finding in both groups. However, it was significantly more prevalent in the GERD group, with 65% showing some degree of erythema compared to 12% in the control group (p<0.001). This suggests that GERD-related inflammation plays a key role in pharyngeal mucosal changes. Edema, or swelling, was also more common in the GERD group (42%) compared to the control group (8%) (p<0.001). This further supports the notion that GERD contributes to inflammation and fluid accumulation in the pharyngeal tissues. This characteristic finding, marked by an irregular and bumpy appearance of the pharyngeal wall, was significantly more frequent in the GERD group (48%) than in the control group (5%) (p<0.001). This suggests that chronic exposure to refluxate in GERD can lead to more pronounced structural changes in the pharyngeal mucosa. Granulomas, indicative of chronic inflammation, were exclusively observed in the GERD group (10%), further underscoring the potential for GERD to cause significant pharyngeal mucosal damage. While less pronounced than other findings, vocal fold changes were still more common in the GERD group, with 15% showing some degree of change compared to 2% in the control group. This difference was statistically significant for moderate/severe changes (p=0.02), suggesting a potential impact of GERD on vocal health.

Table 2. Prevalence of pharyngeal mucosal changes in GERD and control groups.

Pharyngeal mucosal change	**GERD Group (n=100)**	**Control Group (n=100)**	**p-value**
Any Change	78 (78%)	22 (22%)	<0.001
Erythema			
None	35 (35%)	88 (88%)	
Mild	40 (40%)	10 (10%)	
Moderate	15 (15%)	2 (2%)	<0.001
Severe	10 (10%)	0 (0%)	
Edema			
None	48 (48%)	92 (92%)	
Mild	30 (30%)	8 (8%)	
Moderate	15 (15%)	0 (0%)	<0.001
Severe	7 (7%)	0 (0%)	
Posterior pharyngeal wall cobblestoning			
Absent	52 (52%)	95 (95%)	
Present	48 (48%)	5 (5%)	<0.001
Granuloma			
Yes	90 (90%)	100 (100%)	
No	10 (10%)	0 (0%)	<0.001
Vocal fold changes			
None	85 (85%)	98 (98%)	
Mild	10 (10%)	2 (2%)	0.06
Moderate/Severe	5 (5%)	0 (0%)	0.02

Table 3 delves into the severity of pharyngeal mucosal changes and their association with reflux symptoms, providing valuable insights into the impact of GERD and LPR. The GERD group exhibited a significantly higher total score (5.8 ± 2.3) compared to the control group (1.2 ± 1.1) (p<0.001). This difference underscores the greater severity and extent of pharyngeal mucosal involvement in individuals with GERD. The wider range of scores in the GERD group (0-12) also suggests a greater variability in the severity of mucosal changes. As expected, the GERD group reported significantly higher RSI scores (22.5 ± 8.7) than the control group (4.2 ± 3.5) (p<0.001). This confirms that individuals with GERD experience a greater burden of reflux symptoms, including both esophageal and extra-esophageal manifestations. A

strong positive correlation (r=0.62, p<0.001) was observed between the total score for pharyngeal mucosal changes and the RSI score. This crucial finding indicates that the severity of pharyngeal mucosal changes is directly related to the severity of reflux symptoms. In other words, individuals with more severe reflux symptoms are more likely to have more pronounced pharyngeal mucosal changes.

Table 3. The severity of pharyngeal mucosal changes and association with reflux symptoms.

Variable	GERD Group (n=100)	Control Group (n=100)	p-value
Total score for pharyngeal mucosal changes			
Mean ± SD	5.8 ± 2.3	1.2 ± 1.1	<0.001
Median (IQR)	6 (4-8)	1 (1-2)	
Range	0 - 12	0 - 4	
Reflux symptom index (RSI) score			
Mean ± SD	22.5 ± 8.7	4.2 ± 3.5	<0.001
Median (IQR)	24 (18-28)	4 (2-6)	
Range	5 - 40	0 - 12	
Correlation between total score and RSI score	r = 0.62		<0.001

Table 4 presents the results of the logistic regression analysis, which was conducted to determine the independent association between GERD and pharyngeal mucosal changes while controlling for other potential confounding factors. The odds ratio (OR) of 12.5 (95% CI: 6.8 - 23.1, p<0.001) indicates that individuals with GERD have a 12.5 times higher odds of having pharyngeal mucosal changes compared to those without GERD. This confirms the strong association between GERD and pharyngeal mucosal changes, even after adjusting for other variables. The OR of 1.02 (95% CI: 0.99 - 1.05, p=0.15) suggests that age is not a significant predictor of pharyngeal mucosal changes in this model. While the odds slightly increase with each year of age, this increase is not statistically significant. Similarly, sex does not appear to be a significant factor, with an OR of 1.15 (95% CI: 0.63 - 2.10, p=0.65) for males compared to females. This indicates that males and females have similar odds of developing pharyngeal mucosal changes, independent of GERD status. Neither current smoking (OR=1.50, 95% CI: 0.72 - 3.13, p=0.28) nor former smoking (OR=1.20, 95% CI: 0.48 - 2.98, p=0.70) was significantly associated with pharyngeal mucosal changes in this analysis. This suggests that smoking, while potentially harmful to the respiratory tract, does not independently contribute to the development of these changes in the context of this study. The OR of 1.05 (95% CI: 0.98 - 1.13, p=0.18) for each unit increase in BMI indicates that BMI is not a significant predictor of pharyngeal mucosal changes in this model.

Table 4. Association between GERD and pharyngeal mucosal changes (Logistic Regression Analysis).

Variable	Odds Ratio (OR)	95% confidence interval (CI)	p-value
GERD (vs. No GERD)	12.5	6.8 - 23.1	<0.001
Age (per year increase)	01.02	0.99 - 1.05	0.15
Gender (Male vs. Female)	1.15	0.63 - 2.10	0.65
Smoking Status			
Current (vs. Never)	1.50	0.72 - 3.13	0.28
Former (vs. Never)	1.20	0.48 - 2.98	0.70
BMI (per unit increase)	01.05	0.98 - 1.13	0.18

4. Discussion

This study unequivocally demonstrates a significantly higher prevalence of pharyngeal mucosal changes in individuals with GERD compared to those without the condition. This observation aligns with a growing body of research that highlights the extra-esophageal manifestations of GERD, particularly laryngopharyngeal reflux (LPR). Let's delve deeper into the intricacies of this finding and explore the specific characteristics of these mucosal changes. LPR, often termed "silent reflux," arises when the refluxate – the mixture of gastric acid, pepsin, and bile acids – transcends the confines of the esophagus and ascends into the pharynx and larynx. Unlike typical GERD, where the refluxate primarily affects the esophageal mucosa, LPR exerts its deleterious effects on the delicate lining of the throat. This distinction is crucial because the pharyngeal and laryngeal mucosa are particularly susceptible to damage from the acidic and enzymatic components of the refluxate. The pathophysiology of LPR is multifaceted, involving a complex interplay of factors that contribute to the retrograde flow of gastric contents. The lower esophageal sphincter (LES) is a muscular valve that acts as a barrier between the esophagus and the stomach. TLESRs are brief, spontaneous relaxations of the LES that can allow gastric contents to reflux into the esophagus and, subsequently, into the pharynx and larynx. The esophagus relies on coordinated muscular contractions to propel food and liquids towards the stomach. When esophageal motility is impaired, the clearance of refluxate from the esophagus is compromised, increasing the likelihood of LPR. A hiatal hernia occurs when a portion of the stomach protrudes through the diaphragm into the chest cavity. This anatomical abnormality can disrupt the normal function of the LES, making it easier for reflux to occur. Conditions that increase intra-abdominal pressure, such as obesity, pregnancy, and chronic coughing, can also contribute to LPR by forcing gastric contents upwards. Once the refluxate reaches the pharynx and larynx, its acidic and enzymatic constituents initiate an inflammatory cascade. This inflammatory response is responsible for the various pharyngeal mucosal changes observed in LPR. This study identified erythema, edema, and posterior pharyngeal wall cobblestoning as the most prevalent pharyngeal mucosal changes in GERD patients. These findings are consistent with the pathophysiological mechanisms underlying LPR. Erythema, or redness, is a hallmark of inflammation. In the context of LPR, erythema of the pharyngeal mucosa indicates that the refluxate has triggered an inflammatory response, leading to dilation of blood vessels and increased blood flow to the affected area. Edema, or swelling, is another cardinal sign of inflammation. The refluxate-induced inflammatory response causes fluid to accumulate in the tissues of the pharyngeal mucosa, resulting in swelling and thickening. Cobblestoning refers to an irregular, bumpy appearance of the posterior pharyngeal wall, often likened to the cobblestones used to pave streets. This distinctive change is a consequence of chronic inflammation and lymphoid hyperplasia. The chronic irritation caused by LPR leads to an overgrowth of lymphoid tissue in the pharyngeal wall, creating the characteristic cobblestone pattern. These mucosal changes, while seemingly subtle, can have a profound impact on an individual's well-being. Inflammation and edema of the vocal cords can cause hoarseness, a change in voice quality characterized by a raspy or strained sound. The irritation caused by LPR can trigger a chronic cough, often described as a dry, non-productive cough that worsens at night or after meals. The sensation of something stuck in the throat, often accompanied by thickened mucus, can lead to frequent throat clearing. Globus sensation is a persistent feeling of a lump or foreign body in the throat, even in the absence of any physical obstruction. In severe cases, LPR can cause dysphagia, or difficulty swallowing. This occurs when the inflammation and edema interfere with the normal movement of food and liquids through the pharynx and esophagus. While granulomas were observed in a smaller proportion of GERD patients in this study, their presence is noteworthy. Granulomas are small, nodular lesions that represent a chronic inflammatory response. They form when the body attempts to wall off and contain an irritant, in this case, the refluxate. The presence of granulomas in the pharynx indicates

a more severe and persistent form of LPR. The chronic inflammation associated with granuloma formation can lead to more significant mucosal damage and increase the risk of complications. Therefore, the identification of granulomas during nasopharyngoscopy warrants close monitoring and aggressive management of LPR. It is important to recognize that the pharyngeal mucosal changes associated with LPR can vary widely in their presentation and severity. Some individuals may exhibit only subtle erythema, while others may have pronounced edema, cobblestoning, and even granuloma formation. The more frequent and voluminous the reflux episodes, the greater the exposure of the pharyngeal mucosa to the refluxate and the more severe the mucosal changes are likely to be. The acidity and enzymatic content of the refluxate can vary depending on individual factors and dietary habits. A more acidic or enzyme-rich refluxate can cause more significant mucosal damage. Individuals vary in their susceptibility to mucosal injury. Some individuals may develop significant mucosal changes even with infrequent reflux episodes, while others may tolerate more frequent reflux without significant damage.[11-13]

This study revealed a crucial link between the severity of reflux symptoms and the extent of pharyngeal mucosal changes in individuals with GERD. This observation has significant implications for understanding the pathophysiology of laryngopharyngeal reflux (LPR) and optimizing its management. Let's explore this relationship in greater detail. The Reflux Symptom Index (RSI) is a validated instrument designed to assess the severity of reflux symptoms. It encompasses both esophageal symptoms (e.g., heartburn, regurgitation) and extra-esophageal symptoms (e.g., hoarseness, cough, throat clearing). This comprehensive assessment is crucial because LPR often presents with atypical symptoms that may not be immediately recognized as reflux-related. As expected, the GERD group in this study exhibited significantly higher RSI scores compared to the control group. This finding confirms that individuals with GERD experience a greater burden of reflux symptoms, including those that extend beyond the esophagus. The RSI provides a valuable tool for quantifying this symptom burden and tracking changes over time. The most striking finding in this study was the strong positive correlation between the RSI score and the severity of pharyngeal mucosal changes. This correlation implies a dose-response relationship, the more severe the reflux symptoms, the more pronounced the damage to the pharyngeal mucosa. The correlation reinforces the understanding that LPR is a direct consequence of GERD. The refluxate, containing acid and pepsin, acts as an irritant to the pharyngeal mucosa, triggering inflammation and leading to the observed mucosal changes. The higher the frequency and severity of reflux episodes, the greater the exposure of the pharyngeal mucosa to the refluxate, and consequently, the more severe the mucosal damage. The correlation highlights the importance of managing GERD symptoms effectively. By reducing the frequency and severity of reflux episodes, we can potentially mitigate the impact of LPR on the pharyngeal mucosa. This underscores the need for a holistic approach to GERD management that addresses both esophageal and extra-esophageal manifestations. The RSI score could potentially serve as a predictor of the severity of pharyngeal mucosal changes in GERD patients. This could aid clinicians in identifying individuals at higher risk for LPR-related complications and tailoring management strategies accordingly. The acidic and enzymatic components of the refluxate directly injure the pharyngeal mucosa, leading to inflammation, edema, and tissue damage. The more frequent and severe the reflux episodes, the greater the cumulative damage to the mucosa. Chronic exposure to refluxate can impair the natural defense mechanisms of the pharyngeal mucosa. This can make the mucosa more susceptible to further injury and hinder its ability to repair itself. Individual variations in mucosal sensitivity and repair mechanisms may also contribute to the correlation. Some individuals may be more prone to developing severe mucosal changes even with relatively mild reflux symptoms, while others may tolerate more severe reflux with minimal mucosal damage. The strong correlation between reflux symptoms and pharyngeal mucosal

changes has significant implications for the management of LPR. Effective management of GERD symptoms, including both esophageal and extra-esophageal manifestations, should be a primary goal in LPR treatment. This may involve lifestyle modifications, pharmacotherapy, and in some cases, surgical intervention. The RSI score can be used to guide treatment decisions. Individuals with high RSI scores, indicating more severe reflux symptoms, may require more aggressive management strategies to control their symptoms and protect their pharyngeal mucosa. The RSI can also be used to monitor the response to treatment. A decrease in RSI score following treatment suggests improved symptom control and potentially reduced pharyngeal mucosal damage.[14-16]

The high prevalence of pharyngeal mucosal changes observed in this study underscores the significant clinical implications of LPR. It emphasizes the need for heightened awareness among healthcare professionals and the implementation of effective management strategies to mitigate the impact of this condition on patients' well-being. One of the challenges in managing LPR lies in its often subtle and atypical presentation. Unlike classic GERD, which typically manifests with heartburn and regurgitation, LPR may present with a variety of symptoms that are not immediately recognized as reflux-related. Changes in voice quality, such as a raspy or strained voice, are common in LPR. A persistent, dry cough that worsens at night or after meals can be a sign of LPR. A frequent urge to clear the throat, often accompanied by a feeling of something stuck in the throat, is characteristic of LPR. A persistent feeling of a lump or foreign body in the throat, even in the absence of any physical obstruction, is a common complaint in LPR. Difficulty swallowing can occur in more severe cases of LPR. These symptoms can significantly impact a patient's quality of life, affecting their ability to communicate, eat, and sleep. However, due to their non-specific nature, they may be attributed to other conditions, leading to delayed diagnosis and treatment of LPR. Early diagnosis and appropriate management of LPR are crucial to prevent potential complications and improve patient outcomes. Persistent inflammation of the larynx can lead to chronic laryngitis, characterized by hoarseness and vocal fatigue. In some cases, chronic inflammation can lead to the formation of granulomas on the vocal cords, further impairing voice quality. Scarring and narrowing of the airway below the vocal cords (subglottic stenosis) can occur in severe cases of LPR, leading to breathing difficulties. LPR can increase the risk of aspiration, where food or liquids enter the airway, potentially leading to pneumonia or other respiratory complications. Chronic inflammation and irritation of the larynx have been linked to an increased risk of laryngeal cancer. Timely intervention is essential to prevent these complications and improve the patient's quality of life. The management of LPR typically involves a multi-faceted approach that combines lifestyle modifications, pharmacotherapy, and in some cases, surgical intervention. Lifestyle modifications are often recommended as first-line interventions for LPR. These modifications aim to reduce reflux episodes and minimize exposure of the pharyngeal mucosa to the refluxate. Obesity is a significant risk factor for LPR. Losing even a small amount of weight can significantly reduce reflux episodes and improve symptoms. Certain foods and beverages can trigger or worsen reflux symptoms. Avoiding these triggers, such as fatty foods, spicy foods, citrus fruits, caffeine, and alcohol, can help manage LPR. Elevating the head of the bed by 6-8 inches can help prevent nighttime reflux episodes. Eating large meals can increase pressure on the stomach and promote reflux. Eating smaller, more frequent meals can help reduce this pressure. Eating close to bedtime can increase the likelihood of nighttime reflux episodes. It is recommended to avoid eating for at least 3 hours before bedtime. Smoking can weaken the lower esophageal sphincter and worsen reflux symptoms. Pharmacotherapy plays a central role in LPR management. PPIs are the most potent inhibitors of gastric acid secretion and are considered the mainstay of LPR treatment. They work by blocking the enzyme responsible for producing stomach acid, thereby reducing the acidity and damaging potential of the refluxate. H2 receptor antagonists are another class of medications that reduce stomach acid production. They are less potent

than PPIs but may be used in combination with PPIs or as an alternative for patients who cannot tolerate PPIs. Prokinetic agents help improve esophageal motility and accelerate gastric emptying. This can help reduce reflux episodes and improve symptom control. The choice of medication and dosage will depend on the individual patient's needs and response to treatment. For patients with refractory LPR, meaning those who fail to respond to conservative management with lifestyle modifications and pharmacotherapy, surgical intervention may be considered. Fundoplication is a procedure that strengthens the lower esophageal sphincter (LES), the muscular valve that prevents reflux. During the procedure, the upper part of the stomach is wrapped around the LES, creating a tighter seal and reducing the likelihood of reflux episodes. Fundoplication can be highly effective in reducing reflux and improving LPR symptoms. However, it is an invasive procedure with potential risks and complications. Therefore, it is usually reserved for patients who have not responded to other treatment options. Monitoring the response to treatment is essential in LPR management. Regularly assessing the patient's symptoms using tools like the RSI can help track progress and identify any persistent or worsening symptoms. Repeat nasopharyngoscopy can be performed to assess the healing of pharyngeal mucosal changes and identify any new or recurrent abnormalities. For patients with voice symptoms, voice assessments can be conducted to monitor changes in voice quality and guide treatment decisions. Long-term management of LPR often requires a combination of lifestyle modifications and ongoing pharmacotherapy. Regular follow-up with a healthcare professional is essential to monitor symptoms, adjust treatment as needed, and ensure optimal patient outcomes.[17-20]

5. Conclusion

This case-control study provides compelling evidence for a strong association between GERD and pharyngeal mucosal changes in an Indonesian population. The significantly higher prevalence and severity of these changes in the GERD group highlight the extra-esophageal impact of this common digestive disorder. Our findings emphasize the importance of recognizing and managing laryngopharyngeal reflux (LPR) in patients with GERD, even in the absence of typical reflux symptoms. Early diagnosis and appropriate management, encompassing lifestyle modifications, pharmacotherapy, and potentially surgical intervention, are crucial to prevent complications and improve patient outcomes. The strong correlation between reflux symptom severity and the extent of pharyngeal mucosal changes underscores the need for a holistic approach to GERD management. Future research should focus on long-term consequences of LPR, identifying specific risk factors, and exploring the complex interplay between GERD and its extra-esophageal manifestations. This will pave the way for targeted prevention strategies and personalized treatment approaches, ultimately improving the quality of life for individuals with GERD and LPR.

6. References

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