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Gastroesophageal Refluxes As A Modificator Of Inflammatory Response In Bronchial Asthma And Tumor: The Role And Personalized Treatment Opportunities Of Water Pepsin

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Abstract

The presence of GERD in patients with BA and COPD is accompanied by a significant increase in the detection frequency and concentration of pepsin in the saliva. GERD varies in the inflammatory profile in BA and COPD, which confirms the need for a non-specific approach. Therapy with the addition of a prokinetic (itoprid) leads to a significant decrease in pepsin levels, a reduction in systemic inflammation, and an improvement in external respiratory function. Gastroesophageal reflux disease (GERD) is widespread among patients suffering from bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD), and is considered a factor aggravating the clinical course of respiratory pathology. However, the contribution of various types of reflux, including weak acid and mixed reflux, to the formation of the inflammatory response has not yet been sufficiently studied. The aim of the study was to evaluate the impact of GERD on the systemic inflammatory profile and external respiratory function indicators in patients with BA and COPD, as well as to determine the diagnostic significance of pepsin in saliva as a proximal reflux marker. The study included 120 patients (n=60 symptomatic, n=60 asymptomatic) distributed by the presence of GERD symptoms, with additional stratification by nosology. All patients underwent clinical assessment, spirometry, endoscopy, daily pH measurement, determination of C-reactive protein, and measurement of salivary pepsin content (bottom ≥ 16 ng/ml). The presence of GERD signs is associated with a significant increase in the frequency of pepsin and its concentration detection in BA and COPD ($p<0.001$). In patients with BA, GERD was accompanied by a more pronounced systemic inflammatory reaction. The inflammatory profile in COPD is primarily neutrophilic-eosinophilic in nature, demonstrating a less direct correlation with the clinical manifestations of GERD. Against the background of therapy with itopride, a statistically significant decrease in pepsin concentration, S-reactive protein levels, and an improvement in OFV1 indicators were noted ($p<0.05$).

Keywords. Gastroesophageal reflux, bronchial asthma, COPD, salivary pepsin, systemic inflammation, personalized treatment.

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1. Introduction

The comorbidity of gastroesophageal reflux disease with bronchial asthma and COPD is a clinically significant phenomenon that affects the severity of symptoms, the frequency of attacks, and the effectiveness of primary treatment. Interaction mechanisms include vagus-mediated

reflexes, direct damage to respiratory epithelium during microaspiration, and the maintenance of chronic inflammation.

Modern data indicate that pathological reflux is not limited to the acid component. Daily pH measurement records acidic, weakly acidic, and neutral episodes, but does not independently reflect the presence of gastral enzymes in the proximal parts.

Pepsin is a strictly digestive proteolytic enzyme that, when detected in saliva, indicates a retrograde decrease in gastric content regardless of its acidity. Identifying it allows for going beyond the acid-only concept of GERD and assessing the microaspiration component.

Materials and methods

The study was conducted using a prospective comparative design. 120 patients with a stable course without exacerbation of BA or COPD were included.

Depending on the presence of GERD signs, patients were divided into two groups (60 people each) with additional stratification according to nosology: BA+GERD (n=33), BA without GERD (n=32), COPD+GERD (n=27), COPD without GERD (n=28).

All patients underwent the following: assessment of clinical signs; spirometry with bronchodilation test (OFV1 assessment); esophagogastroduodenoscopy; one-time pH measurement; C-reactive protein determination; quantitative determination of pepsin in saliva (bowel ≥16 ng/ml).

The statistical analysis included the use of the Mann-Whitney U-test, the $\chi 2$-test, and multifactorial regression analysis. The differences were considered statistically significant at $p<0.05$.

Results

The presence of GERD was observed in BA and COPD with a significant increase in the frequency of pepsin detection and its concentration.

Table 1.

Salivary pepsin indicators in patients with BA and COPD with and without GERD symptoms

Indicator	BA+GERK	GERK-free BA	O'SOK+GERK	GERKsiz SOOK
Pepsin ≥16 ng/ml, n (%)	75.8%	31.3%***	85.2%	25.0%***^^
Pepsin, ng/ml, Me (Q1-Q3)	62 (28–115)	18 (9-34) ***	88 (41-162)	14 (8-29) ***^^
Max-pepsin, ng/ml	96 (44–176)	26 (12–51) ***	138 (65–241)	22 (11–46) ***^^
Postprandial test was positive	66.7%	25.0%***	74.1%	21.4%***^^

At the same time, pH-metry recorded not only acidic but also weakly acidic and neutral episodes. The detection of pepsin in the absence of pronounced acidity confirms the presence of the gastral component of reflux regardless of pH.

Consequently, this refers not only to acid reflux but also to mixed reflux. This is very important, as proton pump inhibitors reduce acidity but do not eliminate reflux itself or prevent the release of pepsin.

The presence of GERD symptoms in patients with bronchial asthma was associated with a more pronounced systemic inflammatory response—an increase in C-reactive protein and changes in the cellular composition of the blood.

At the same time, high levels of leukocyte and eosinophilic links in COPD were noted in patients without signs of GERD, which reflects other - primarily neutrophil-eosinophilic - characteristics of inflammation.

Thus, gastroesophageal reflux alters the inflammatory response not universally, but non-specifically.

Table 2.

Dynamics against the background of itopride therapy, including BA and GERD

Indicator	Before therapy	Post-therapy	p.
Pepsin, ng/ml	62 (28–115)	47 (21–86)	<0.05
Pepsin ≥16 ng/ml	75.8%	56.9%	<0.05
OFV1, %	72	90	<0.05
CRP, mg/l	4.2	3.2	<0.05

The presented data indicate a statistically significant decrease in the frequency and severity of proximal reflux against the background of treatment with itopride in patients with bronchial asthma and GERD symptoms. The average pepsin concentration in saliva decreased from 62 (28–115) to 47 (21–86) ng/ml ($p<0.05$), which was accompanied by a decrease in the proportion of patients with ≥16 ng/ml levels from 75.8% to 56.9% ($p<0.05$). The obtained changes indicate a decrease in the retrograde transport of gastric contents and, possibly, a decrease in the microaspiration component.

At the same time, a significant improvement in the functional indicators of the respiratory system was noted: the OFV1 level increased from 72% to 90% ($p<0.05$), reflecting an improvement in bronchial conductivity and increased disease control. At the same time, a decrease in S-reactive protein concentration from 4.2 to 3.2 mg/l ($p<0.05$) was noted, indicating a decrease in systemic inflammatory activity.

Table 3.

Dynamics against the background of itopride therapy, including COPD and GERD

Indicator	Before therapy	Post-therapy	p
Pepsin, ng/ml	88 (41-162)	66 (31–122)	<0.05
Pepsin ≥16 ng/ml	85.2%	63.9%	<0.01
OFV1, %	54	68	<0.05
CRP, mg/l	6.8	5.1	<0.01

The inclusion of itoprid in the standard treatment regimen for patients with symptoms of COPD and GERD was accompanied by a statistically significant decrease in the severity of proximal reflux. The average concentration of pepsin in saliva decreased from 88 (41-162) to 66 (31-122) ng/ml ($p<0.05$), while the frequency of detecting a level of diagnostic significance (≥16 ng/ml) decreased from 85.2% to 63.9% ($p<0.01$). These data indicate a decrease in gastral exposure of the upper respiratory tract and a decrease in the probability of microaspiration.

At the same time, a significant improvement in functional parameters was noted: the OFV1 index increased from 54% to 68% ($p<0.05$), indicating a clinically significant improvement in bronchial patency. A decrease in S-reactive protein levels from 6.8 to 5.1 mg/l ($p<0.01$) reflects a decrease in systemic inflammatory activity.

It should be noted that in patients with COPD, the baseline levels of pepsin and CRP were higher than in BA, which may reflect a more pronounced microaspiration component against the background of chronic neutrophilic inflammation. The results obtained confirm that the correction of motor disorders and the reduction of proximal reflux are capable of altering the inflammatory profile and functional state of the respiratory tract even in cases of structurally fixed bronchial obstruction.

Discussion

The results obtained allow for the consideration of gastroesophageal reflux disease not as a comorbid

condition, but as a pathogenetically significant factor capable of altering the nature and intensity of the inflammatory response in chronic respiratory diseases. The identified differences between the subgroups indicate a nozotropic effect of reflux on systemic and possibly local inflammation.

The presence of GERD symptoms in patients with bronchial asthma was more associated with the activation of systemic inflammation. This phenomenon may be associated with several complementary mechanisms. First, stimulating the afferent vagus receptors of the esophagus is capable of triggering bronchodilator reflexes and enhancing the hyperreactivity of the respiratory tract. Secondly, episodes of proximal reflux and microaspiration of the gastral contents can lead to damage to the epithelial barrier and activation of the innate immune response. Together, this stimulates additional inflammation against the background of already existing Th2-mediated immune dysregulation characteristic of asthma.

Unlike bronchial asthma, the inflammatory profile in COPD is initially characterized by the predominance of the neutrophil node and the reorganization of the respiratory tract. In this group, the effect of GERD is primarily mediated by a microaspiration mechanism. In patients with COPD, a high initial concentration of pepsin in saliva may reflect a high frequency of retrograde transport of gastric contents or a more pronounced impairment of airway clearance. At the same time, the relationship between clinical signs of GERD and inflammatory parameters is less linear, highlighting differences in pathogenetic boundaries in asthma and COPD.

Determining pepsin is of fundamental importance in episodes of weak acid and neutral reflux. This confirms that the acid-only concept of GERD is limited and indicates the presence of mixed reflux with the gastral enzymatic component. When using proton pump inhibitors, the reduction of acidity does not eliminate the retrograde transport of gastric contents and, accordingly, does not prevent the potential harmful effects of pepsin. In this regard, the universal appointment of IPP without preliminary phenotyping of reflux cannot be considered a pathogenetically grounded strategy.

Against the background of introducing prokinetic therapy, a decrease in salivary pepsin concentration was accompanied by a decrease in S-reactive protein levels and an improvement in external respiratory function indicators. Although the research design does not allow for final conclusions regarding cause-and-effect relationships, the data obtained indicate the potential role of reducing proximal reflux in indirectly reducing inflammatory activity and improving bronchial conductivity.

Conclusion

Thus, determining pepsin in saliva can be considered a clinically important tool for differentiating patients with comorbid respiratory and gastroesophageal pathology. Its use allows for the detection of proximal and mixed reflux that is not determined solely by acidity levels, thereby creating a foundation for a more personalized choice of antireflux therapy.

Treatment with the inclusion of a prokinetic (itoprid) leads to a significant decrease in pepsin levels, a reduction in systemic inflammation, and an improvement in external respiratory function.

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