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The Comparison of Pepsin Level in Gastroesophageal Reflux Disease Patients with or without Chronic Rhinosinusitis

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KEYWORDS
Pepsin Levels, Gastroesophageal Reflux Disease, Chronic Rhinosinusitis

ABSTRACT:
Introduction: Gastroesophageal Reflux Disease (GERD) is a digestive disorder that is often found around the world. GERD is a condition with disturbing symptoms and complications due to the rise of stomach contents into the esophagus. The presence of pepsin in the laryngopharynx has been shown to correlate with these reflux events, and pepsin levels tend to be elevated in patients with chronic rhinosinusitis (CRS).
Objective: To determine the comparison of pepsin levels in GERD patients with or without chronic rhinosinusitis
Method: This research used a cross-sectional design conducted at RSUP Dr. Wahidin Sudirohusodo Makassar from January to July 2023. The research samples included were GERD patients with or without CRS. All patient secretions were taken and pepsin levels were checked using the ELISA method. Data analysis used SPSS version 26.0.
Results: 46 people were included in this study (case group (n=23) and control group (n=23)). Most samples had fasting pepsin levels compared to those who did not have fasting pepsin levels (p=1.000), as well as pepsin levels 1 hour post-prandial (p=0.022). The median (min-max) fasting pepsin level in the case group was 150.12 (3.78–3236.89) and in the control group was 321.25 (5.46–5231.88) (p=0.160), while the 1 hour postprandial pepsin level in the case group was 106.75 (5.46-2691.91) and in the control group it was 388.13 (3.59–3420.89) (p=0.057).
Conclusion: There is no significant relationship between GERD and CRS with nasal pepsin examination.

1. Introduction

Gastroesophageal Reflux Disease (GERD) is a condition caused by stomach contents refluxing into the esophagus, resulting in symptoms such as heartburn, regurgitation, dysphagia, chest pain, and others.[1,2] In Asia, particularly Indonesia, the prevalence of GERD and associated complications is generally lower than in Western countries; nevertheless, current data show that the frequency is increasing. This is due to changes in lifestyle that enhance a person's risk of GERD, such as smoking and obesity. The global population-based prevalence of GERD is 13.98%.[3]

Bai et al (2013) studied 8,065 samples in China and discovered a rise in cases of reflux esophagitis coupled with an increase in the Gerd-Q score, hence it was advocated for the diagnosis of GERD.[4] A low Gerd-Q score, however, does not rule out the potential of reflux esophagitis.[5] Pepsin is involved in the pathogenesis of laryngopharyngeal reflux (LPR), a condition that begins in the gastrointestinal system and affects upper airway structures. CRS patients have greater pepsin levels in their nasal secretions and tissues, which are restricted to the epithelial layer or mucosal cells.[6,7]

Several experts referenced in EPOS and other meta-analyses indicated that LPR is one of the causes underlying the emergence of LPR, although this is still debatable, thus more research is required. Based on nasal pepsin analysis, the link between CRS and LPR has not been established. Aside from that, there has never been any research at RSUP Dr. Wahidin Sudirohusodo on the association between GERD and CRS based on nasal pepsin examination. The aim of this study is to confirm the relationship between GERD and CRS with nasal pepsin examination, so that if there is a relationship between GERD and CRS with nasal pepsin examination, it is hoped that nasal pepsin examination can be an alternative examination tool for diagnosing GERD that is non-invasive, easier and cheaper.

2. Methods

Research design

This study was conducted at RSUP Dr. Wahidin Sudirohusodo Makassar as an observational analytical study with a cross-sectional design.

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Place and time

This study was conducted at RSUP Dr. Wahidin Sudirohusodo. This study will run from January 2023 until July 2023.

Research Sample

This study's population consisted of all GERD patients. This study's sample consisted of people with GERD, either with or without CRS. The research sample was divided into two sections: the case group and the control group. The case group included individuals with GERD and CRS, while the control group included patients with GERD without CRS. Anamnesis, physical examination, and the GERD-Q questionnaire are used to diagnose GERD.

This study comprised patients aged 18-60 years who had not taken a proton pump inhibitor (PPI), antacids, or AH-2 for 96 hours. Patients who were pregnant or had undergone post-operative functional endoscopic sinus surgery (FESS) were not eligible for this study.

Research Permit

This study was carried out after receiving ethical approval from the Health Research Ethics Committee of Hasanuddin University's Faculty of Medicine, with reference number 237/UN4.6.4.5.31/PP36/2023. Every action in this study is carried out after obtaining written approval (informed consent) from the patient or family.

Research Methods

Secretions were collected from all research samples after receiving informed consent from the patient to participate in the study. Secretions from patients with GERD, with or without CRS, were collected in the morning (fasting) and 1 hour post-prandial.The Human PP (Pepsin) ELISA Kit (RD Biomed Ltd, Cottingham, UK) was then used to measure nasal pepsin. Pepsin levels were examined between the case and control groups after fasting and 1 hour post-prandial pepsin levels were obtained in all research samples.

Data analysis

Following the collection of all data, this research data was analyzed using the Statistical Package for the Social Sciences (SPSS) computer software version 26.0. Variable categories are represented by frequencies and percentages, whereas numerical variables are represented by mean values and standard deviation. The chi square test was used to assess bivariate analytic tests.

3. Results

The Research Sample's Characteristics

This study involved 46 patients, including 23 patients with GERD who also had CRS (case group) and 23 patients with GERD without CRS (control group). Based on the research sample characteristics, there were significant differences in the GERD with CRS and GERD without CRS age groups (p=0.001), as well as in the mean GERD-Q scores in the GERD with CRS and GERD without CRS groups (p =0.001). Meanwhile, there was no significant difference in gender between the GERD with CRS and GERD without CRS groups (p=0.767) (Table 1).

The majority of patients in both groups were found to have fasting pepsin levels, as well as 1 hour postprandial pepsin levels, based on the presence or absence of pepsin levels, but this difference was not statistically significant (p=1,000). Furthermore, the GERD without CRS group had higher pepsin levels 1 hour postprandial than the GERD with CRS group, and this difference was statistically significant (p=0.022) (Table 2).

Fasting pepsin levels in the GERD with CRS group were 150.12 (3.78-3236.89) and 1 hour postprandial pepsin levels were 106.75 (5.46-2691.91). Fasting pepsin levels and 1 hour postprandial pepsin levels did not change between the GERD and CRS groups (p=0.784). Fasting pepsin levels in the GERD group without CRS were 321.25 (5.46-5231.88) and 1 hour postprandial pepsin levels were 388.13 (3.59-3420.89). In the GERD group without CRS, there was no significant difference in fasting pepsin levels or 1 hour postprandial pepsin levels (P=0.751). Fasting pepsin levels in the GERD group with CRS and the GERD group without CRS did not differ significantly (p=0.160). There was no statistically significant change in mean pepsin levels 1 hour after eating between the GERD group with CRS and the GERD group without CRS (p=0.057) (Table 3). Figure 1 shows a comparison of fasting pepsin levels and 1 hour postprandial pepsin levels between the two groups

4. Discussion

According to the findings of this study, the average age of GERD with CRS is older than that of GERD without CRS. GERD is often thought to worsen as people get older.[8] Older folks have a higher chronic disease burden and take more drugs than younger persons.[9] The deterioration in gastro-esophageal function in older adults contributes to the rise in GERD incidence. With advancing age, the efficacy of esophageal peristalsis decreases, exposure to esophageal acid increases, and the pressure of the lower esophageal sphincter becomes increasingly ineffective. Anatomical problems with the gastro-esophageal junction will also become more common. As a result, GERD is more common in older people.[8] GERD is more common in female because the hormones progesterone and estrogen can reduce the lower esophageal sphincter (LES) pressure and cause

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GERD.[10,11] Similar to our study, it was discovered that there was a tiny variation in the number of GERD sufferers accompanied by or without CRS, with female sufferers slightly outnumbering male sufferers, albeit the results were deemed insignificant.

Pepsin was discovered in nasal cavity secretions of GERD patients with and without CRS in pepsin test while fasting and pepsin levels 1 hour post-prandial. These findings are consistent with the findings of Katle J, et al (2019), who discovered that both GERD patients with and without CRS exhibited substantial pepsin levels.[12] Pepsin is a proteolytic enzyme that aids in the digestion of proteins in the stomach. Because pepsin A is produced from pepsinogen, which is secreted by gastric main cells in the stomach, the presence of pepsin A in the esophagus, mouth, or respiratory system should be considered a sign of reflux. Pepsin is most hazardous when it is acidic. Pepsin, on the other hand, can cause harm at pH levels as low as 6.5 and does not undergo lasting denaturation until the pH approaches 8. This means that when the pH in the reflux is above 4, there is still active pepsin in it, but it is not detectable. Additionally, in theory, inactive pepsin could be reactivated and become dangerous through a drop in pH from drinking acid or a future event of acid reflux. The large increase in the amount of pepsin in GERD patients with or without CRS supports the concept of physiological reflux, especially postprandial.[12-14]

Reflux usually occurs after eating, and the related GERD symptoms are much worse 1 to 2 hours later.[12] The findings of this study show that there is a difference in average pepsin levels during fasting and 1 hour postprandial in GERD patients with CRS, with fasting pepsin levels being greater than 1 hour postprandial pepsin levels. Fasting pepsin levels are lower than 1 hour post-prandial pepsin levels in GERD patients without CRS, albeit this difference is thought to be insignificant. The difference in results observed in this study could be attributed to the food consumed 1 hour before assessing pepsin levels, as food is also a risk factor for GERD.[3]

According to Buana AW et al (2022), 20 (83.3%) of the CRS group were pepsin positive, while 5 (45.5%) were pepsin negative. There were 6 non-CRS patients who were pepsin negative (54.5%) and 4 who were pepsin positive (16.7%) (p=0.04). Based on the nasal pepsin examination results, there is a substantial association between CRS and GERD; a positive pepsin result in GERD causes CRS.[15] Meanwhile, we concluded in this study that it is not possible to say that GERD is the cause of CRS; various other variables must be investigated to verify it. Common problems include chronic rhinosinusitis and gastric reflux illness. As a result, it is not surprising that some people who experience this have both diseases.[16] GERD is thought to be a potential exacerbator of sinonasal inflammatory illness. There are three theories of how GERD could damage the sinonasal cavity. To begin, the inflammatory process is triggered by the presence of acid and pepsin, which directly impact the mucosa. Mucosal edema develops as a result, and mucociliary clearance is compromised. This reaction causes an obstruction in the sinus ostium, which leads to infection. The second is connected to vagal nerve-mediated neurological mechanisms. Autonomic nervous system dysfunction causes sinonasal edema and subsequent ostial blockage. In the latter method, Helicobacter pylori, which causes peptic ulcers and gastritis, may play a role in sinonasal infections. Although studies have found a link between rhinosinusitis and GERD, the mechanism by which GERD affects the sinonasal cavity and causes rhinosinusitis has not been thoroughly understood.[17,18] There is no convincing evidence to imply that gastric contents are refluxing into the nasal cavity. However, there is evidence of a gastronasal reflex, and given that PPIs have been shown in randomized controlled trials to relieve postnasal infusion symptoms in patients without CRS, it is possible that GERD produces nasal reflex symptoms.[16]

Pepsin is present in GERD. When the LES is compromised, gastric fluid, which contains pepsin, rises from the stomach to the esophagus. Gastric juices may reach the larynx if the upper esophageal sphincter (UES) also collapses. Important structures of the larynx, such as the vocal cords, can be damaged by hydrochloric acid and pepsin. It may even enter through the larynx and harm the lungs, as well as the nasal passages.[19] High levels of pepsin in patients with and without CRS, on the other hand, may reflect individual variances in sensitivity to reflux, including pepsin, i.e., specific levels of pepsin may cause disease in some people but not others.[12,20]

5. Conclusion

Pepsin is found in patients with GERD with or without CRS. There was no significant relationship between GERD with CRS or without CRS with nasal pepsin examination

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Attachment

Table 1. Research Sample Characteristics

GERD-Q Score	10.04±1.63	10.91±2.74	<0.001***

*Mann-whitney
** chi-square
***independent t-test

Table 2 Fasting and 1 Hour Postprandial Pepsin Levels

Variable		GERD with CRS	GERD without CRS	P-value
Fasting Pepsin	No Pepsin	9 (39.1%)	9 (39.1%)	
	Have Pepsin	14 (60.9%)	14 (60.9%)	1.000*
1 Hour Post Prandial Pepsin	No Pepsin	10 (43.5%)	3 (13.0%)	
	Have Pepsin	13 (56.5%)	20 (87.0%)	0.022*

*chi-square

Table 3 . Average Pepsin Levels of Research Samples During Fasting and 1 Hour Post Prandial

Variable	GERD with CRS	GERD without CRS	p-value
Fasting Pepsin (median (min-mix)	150.12 (3.78-3236.89)	321.25 (5.46-5231.88)	0.160*
1 Hour Post Prandial Pepsin (median (min-mix))	106.75 (5.46-2691.91)	388.13 (3.59-3420.89)	0.057*
p-value	0.784**	0.751**	

*Mann-whitney
**Wilcoxon

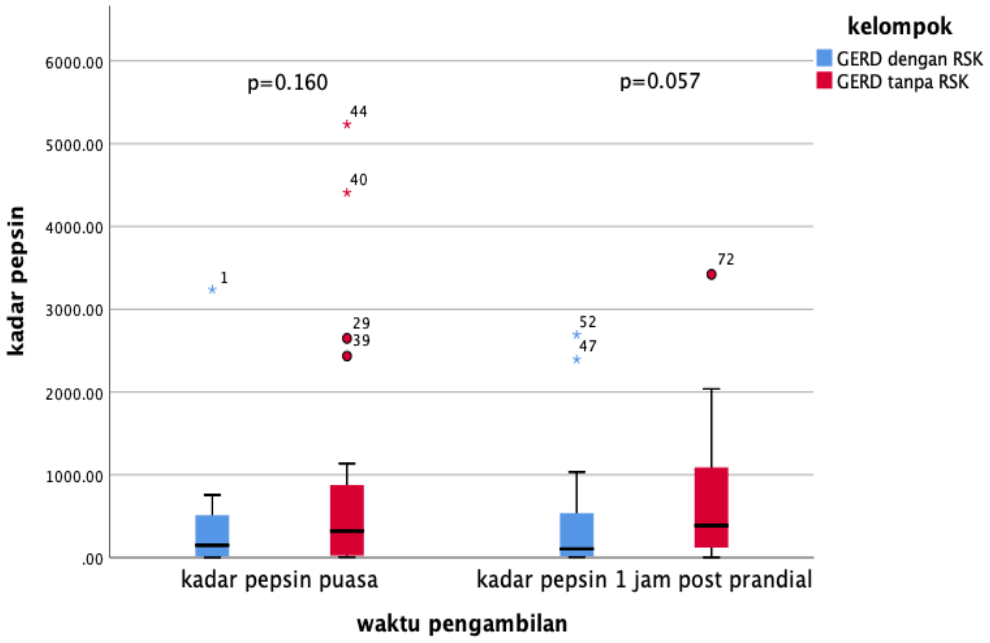

Figure 1. Differences in Pepsin Levels in GERD sufferers with or without CRS