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## Original article

# Association between Gastroesophageal Reflux Disease and Chronic Sinusitis: Salivary and Nasal Pepsin as a Biomarker

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## ABSTRACT

**Background:** The relationship between gastroesophageal reflux [GER] and chronic rhinosinusitis [CRS] has been discussed in several studies, but a direct relationship could not be established. However, both conditions are highly prevalent.

**Aim of the work:** The study aimed to evaluate the nasal and salivary pepsin as a biomarker for GER in CRS patients.

**Patients and Methods:** Fifty patients with CRS were included; 28 males and 22 females, and 50 healthy volunteers; 25 males and 25 females served as controls. Peptest was performed for all subjects.

**Results:** Pepsin positivity was found to have a slight increase in CRS salivary samples than the control group. However, the difference was insignificant [P >0.05], in contrast with nasal samples, which was estimated to have a statistically significant difference [P <0.05] in the second and third samples. As regard pepsin concentration in salivary samples, it was found to show a statistically significant difference [P <0.01] in all samples, while it was non-significant in all nasal samples [P >0.05].

**Conclusion:** CRS patients have a higher positive rate of pepsin in salivary and nasal secretions; however, no significant more pepsin in saliva or nasal secretions is regarded as CRS-patients than healthy controls.

**Keywords:** Chronic Rhinosinusitis; Salivary; Nasal; Pepsin; Gastroesophageal Reflux Disease.

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\* Main subject and any subcategories have been classified according to the research topic.

## INTRODUCTION

Chronic rhinosinusitis [CRS] is a worldwide challenging health problem<sup>[1]</sup>. The optimal medical treatment is based mainly on corticosteroids<sup>[2]</sup>. The resolution of gastroesophageal reflux disease [GERD] was found to improve CRS symptoms<sup>[3]</sup>. CRS sometimes become refractory to medical treatment. The associated factors include alteration of mucosa due to genetic, phenotypic factors, scars, allergy, smoking, and GERD<sup>[4]</sup>. Previous researches have proposed a link between acid reflux disease and CRS. However, such a relationship is difficult to be established due to the high prevalence of both CRS and GERD<sup>[5]</sup>.

There are many theories to explain the proposed relationship. The first one supposed that the inflammation of nasal mucosa was caused as a result of exposure to gastric acid, with impairment of mucociliary clearance and obstruction of sinus Ostia with infection recurrence<sup>[6]</sup>. Another theory is based on the fact that both areas are sharing the same nerve supply (vagus nerve). This relationship is well established in the lower airway and patients with rhinitis. However, it was not yet proved in patients with CRS<sup>[4,7]</sup>.

A third and final mechanism related to the direct association between helicobacter pylori and CRS. For example, Koc *et al.*<sup>[8]</sup> demonstrated that Helicobacter pylori were discovered in nasal polypi but not in the mucosa of healthy control subjects.

Besides, Morinaka *et al.*<sup>[9]</sup> found that Helicobacter pylori discovered in the CRS nasal mucosa and GERD complaints. However, no consensus was build about the role of helicobacter pylori in the nasal mucosa and CRS<sup>[10]</sup>.

Furthermore, previous trials failed to establish a good relationship between CRS and GERD<sup>[11,12]</sup>. Since the introduction of these researches, no specific reflux diagnostics are available, including endoscopy<sup>[13]</sup>. In addition, diagnostic invasive, and more expensive tests are slowly introduced [e.g., 24-hour pH monitoring probes]<sup>[14]</sup>.

Pepsin is one of the most important enzymes found in the gastric secretions. It is the sole biological indicator in GERD diagnosis<sup>[15]</sup>. The gastric mucosa exclusively manufactures pepsin. Its large molecular

size permits its detection<sup>[16]</sup>.

It had been proposed that the high concentration in saliva and/or nasal secretion is a strong predictor of GERD<sup>[17]</sup>.

Peptest is a test assigned to detect and measure pepsin levels in saliva and predict GERD in patients with CRS<sup>[13]</sup>. However, the use of such tests to establish an association between GERD and CRS is not well investigated.

## THE AIM OF THE WORK

The current work was designed to evaluate nasal and salivary pepsin values as a biomarker for GERD in CRS patients.

## PATIENTS AND METHODS

This prospective study conducted 50 patients with CRS; 28 males and 22 females, and 50 healthy volunteers; 25 males and 25 females were considered controls that match the studied group in age and sex. The study was performed in the Otorhinolaryngology departments in Al-Azhar Faculty of Medicine, Damietta, Egypt, for two years, from May 2017 to May 2019.

Ethical considerations: The patients gave informed written consent to use their clinical records in this study. The study protocol was also accepted by the local institutional board [IRB] of Damietta Faculty of Medicine.

All participants [patients and controls] were subjected to the well-known Peptest [RD Biomed Limited, UK] to evaluate the Pepsin concentration in the secreted salivary fluid.

This study's inclusion criteria were: patients' age > 18. CRS's diagnosis was based on the 3 months of persistent sinonasal manifestations and positive findings for sinusitis on CT. To be included, patients must have had persistent symptoms for up to 4 weeks before inclusion in the study. Other healthy subjects over the age of 18 were included as a control group.

On the other side, exclusion criteria were those who did not meet the inclusion criteria, subjects on gastric motility drugs up to the last week before the study initiation, patients with esophageal or gastric carcinoma, esophageal spasm, achalasia, dysphagia, previous esophageal or gastric surgery, and functional heartburn. All patients were instructed to abide by



corticosteroid therapy a day before investigation.

**RESULTS**

Test and sampling: Peptest®, a linked enzyme immunoassay for detecting salivary pepsin. The test is based on a technology known as “lateral flow.” It confirms anti-bodies’ presence in pepsin A [human variant pepsin], which is exclusively secreted by the gastric mucosa. A control band indicates a correct test detected on the device. The presence of another line indicates the existence of pepsin. The concentration is defined in ng/mL, and the lower value of detection was 16ng/mL<sup>[18]</sup>.

Three samples were collected in citrated tubes; the first acquired in an upright position just 15 minutes after waking up before breakfast or brushing teeth; the second was obtained one hour following the lunch, and the third one obtained one after dinner<sup>[19]</sup>. Samples were referred to the Lab for detection of pepsin concentration. Through immunohistochemistry (IHC), staining pepsin in nasal mucosa was assessed and fixed in formalin, but the second sample was frozen directly in liquid nitrogen and stored at -80°C for Western blot techniques exam. The presence of pepsin was differentiated histologically as negative, weak-positive, positive, and strong positive <sup>[20]</sup>.

Statistical analysis: Statistical tests were done by SPSS v23 statistical software [SPSS, Inc, Chicago, Illinois]. Descriptive statistics [mean, standard deviation, frequencies, and correlation coefficients] were calculated for all variables. To compare the two groups, a paired t-test was used to estimate the P values using Pearson’s correlation coefficient and  $\chi^2$  test, and a one-sample t-test and Wilcoxon test performed when appropriate. The positive rates of pepsin A in tissues were calculated with Fisher’s exact probability method.  $P < 0.05$  was considered statistically significant.

Our work included 50 patients with rhinosinusitis; 28 males and 22 females represent the patients’ group, their ages ranged from 18 to 56 years with a mean  $\pm$  SD of  $24.8 \pm 5.69$  years and 50 healthy subjects; 25 males and 25 females represent the control group with age ranged from 18 to 49 years and mean  $\pm$  SD of  $23.8 \pm 4.97$  years. The two groups were matched in sex and age [ $P > 0.05$ ] as estimated in table [1].

Body Mass Index (BMI), smoking, allergy, diabetes mellites were common risk factors of CRS and was found to show a statistically significant difference in comparison of the two groups [ $P < 0.05$ ] as shown in table [1].

Studying of pepsin positivity by Peptest in the three samples showed a slight increase in salivary samples in CRS than the control group. However, it showed a statistically insignificant difference [ $P > 0.05$ ], in contrast with nasal samples showed a statistically significant difference [ $P < 0.05$ ] in the second and third samples [Table 2].

As regard pepsin concentration in salivary samples showed a statistically significant difference [ $P < 0.01$ ] in the three samples, while it showed a non-significant difference in the three nasal samples [ $P > 0.05$ ] as shown in table [3].

On evaluating Peptest in this study, it was 83%, 61%, 76%, 58%, and 81% regarding the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy, respectively, in salivary samples. It was 84%, 60%, 75%, 62%, and 83% regarding the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy, respectively [Table 4]. So, the test is reliable in both salivary and nasal samples.

Table [1]: Demographic characteristics of the studied groups.

		CRS group [1] n = 50		Control group [2] n = 50		Test of significance	
		n.	%	n.	%	$\chi^2$	P
Gender	Males	28	56	25	50.0	0.094	0.217
	Females	22	44	25	50.0	0.018	0.635
Risk factors	Smoking	18	36	7	14	4.956	0.002*
	Allergy	32	64	3	6	9.489	0.001*
	Diabetes Mellitus	4	8	1	2	3.514	0.038*
		<i>Mean</i>	<i>±SD</i>	<i>Mean</i>	<i>±SD</i>	<i>t-test</i>	<i>P</i>
Age [years]:		24.8	5.69	23.8	4.97	0.0015	0.869
BMI		29.6	3.56	27.6	4.57	0.028	0.387

CRS: Chronic rhinosinusitis, BMI: Body mass index.  $\chi^2$  = Chi square test,  $P > 0.05$  = non-significant, \* $P > 0.05$  = significant.

Table [2]: Outcome of pepsin positive subjects as measured by Peptest.

Sample	CRS group [n = 50]		Control group [n= 50]		Test of significance	
	n.	%	n.	%	$\chi^2$	P
Salivary samples:						
• First postprandial	35	70.0	33	66.0	0.0659	0.253
• Second postprandial	34	68.0	32	64.0	0.0517	0.377
• Third sample	33	66.0	32	64.0	0.0018	0.617
Nose samples:						
• First postprandial	29	58.0	27	56.0	0.0291	0.1921
• Second postprandial	27	54.0	15	30.0	4.5221	0.019*
• Third sample	26	52.0	16	32.0	3.6171	0.038*

$\chi^2$  = Chi square test, \* P <0.05= significant.

Table [3]: Pepsin concentration in saliva and nasal samples as measured by Peptest.

Sample	CRS group [n= 50]		Control group [n= 50]		Test of significance	
	Mean	$\pm$ SD	Mean	$\pm$ SD	t-test	P
Salivary samples:						
• First postprandial	42.9	16.4	118	22.8	1.652	0.001*
• Second postprandial	34.8	18.1	159	14.9	3.827	0.000*
• Third sample	25.4	12.7	45.8	9.72	0.951	0.004*
Nose samples:						
• First postprandial	11.1	6.87	9.32	5.42	0.002	0.592
• Second postprandial	10.2	5.19	8.62	3.09	0.002	0.589
• Third sample	16.8	6.12	12.6	3.94	0.009	0.473

$\chi^2$  = Chi square test, \* P <0.05= significant.

Table [4]: Accuracy of Peptest positive in saliva and nasal samples.

Sample	PPV	NPV	Sensitivity	Specificity	Accuracy
Saliva	83%	61%	76%	58%	81%
Nasal	84%	60%	75%	62%	83%

PPV: Positive predictive value, NPV: Negative predictive value.

### DISCUSSION

Although the gastrointestinal refluxate constitution is variable and its constituents like acid or bile salts may or may be present. Pepsin is present in all gastric refluxate. Pepsin analysis may be carried out on samples as easily available as saliva and sputum, thereby assisting in testing certain patients like children<sup>[21]</sup>. This study aims to evaluate nasal and salivary pepsin as a biomarker for GER in CRS patients. We chose two groups, patients and controls, who were matched in age and sex, which coincided with previous studies <sup>[22-23]</sup>. CRS risk factors such as BMI, smoking, diabetes mellites, and allergy showed a significant difference in the patient group than the control one. This was in agreement with Marcus *et al.*

<sup>[24]</sup>, Workman *et al.* <sup>[25]</sup>, Kartush *et al.* <sup>[26]</sup>.

Pepsin in salivary secretion had positivity slightly more in the CRS group than controls, but they showed a non-significant difference. Also, pepsin in the nasal sample showed positivity only in the second and third samples in the CRS group than controls; they showed a statistically significant difference. This was parallel to Katle *et al.* <sup>[23]</sup>, who stated that saliva or nasal secretions of patients with CRS did not have more pepsin when Peptest measured it in comparing their results to healthy controls. They postulated that CRS people with anomalous proximal reflux did not have more positive samples than people without reflux for Peptest.

The saliva's pepsin concentration is variable over

the 24 hours but decreases rapidly after the reflux episode [27]. Thus, saliva samples should be obtained after reflux to detect the pepsin [28]. After meals are the most reflux occurrence, its symptoms are significantly higher 1 to 2 hours post-prandially [27]. We tested for pepsin three times a day, controlled by the waking up time and the time of next meals and not by reflux manifestations. We found pepsin concentration in salivary secretion showed significant values in patients' group than control, while nasal samples had pepsin concentration nearly the same in both groups and showed a non-significant difference between the two groups as regards the three samples.

In agreement with this study, Ren *et al.* [22] who found that pepsin concentrations in nasal secretions were significantly higher in CRS patients with GER supporting the hypothesis of pepsin's gastric origin in patients with reflux. In addition, pepsinogen, a precursor for pepsin, was not found in any nasal tissues. Thus, the possibility of local pepsin synthesis.

In contrast to these results, Katile *et al.* [23] found a lower pepsin concentration in patients than controls, and they explained this by GER inducing hyper-salivation that may dilute the pepsin concentration in those patients [29].

As per nasal mucosa, it was considered to have a limited protective capability against the refluxate and is sensitive to its injurious action. Pepsin is most the harmful effect of pepsin was estimated when it takes the acidic state. A pH up to 6,5 can cause injury and is not permanently denatured until the pH reaches the value of 8 [30].

Considering the Severity of rhinosinusitis and reflux episodes, it was estimated that exposure to refluxate is normally considered physiological but may cause many individuals' symptoms. Considering that the same vulnerability differences can also exist in the nose, whether a certain level of pepsin may contribute to CRS development in predisposed patients than others [31].

Our data showed a little difference in nasal and salivary pepsin between CRS-and controls and the insignificant difference in salivary and nasal pepsins' positivity, maybe in line with Katile *et al.* [23], though the results made due to the limited sensitivity and specificity of the Peptest.

Compared with the controls, Ren *et al.* [22] concluded that CRS patients tended to have pepsin in nasal and tissue secretion, which indicates a higher rate of extra-GER manifestation in CRS patients R.

Studies have determined that reflux contents could reach up to the nasopharynx. Hayat *et al.* [32] detected pepsin in saliva. He *et al.* [33] found pepsin in the middle ear fluid of children with otitis media, proposing that reflux could reach upward to the eustachian tube and enter the middle ear. Luo *et al.* [34] also reported that pepsin could reach and pass through the adenoid and enter the middle ear cavity.

This study had a small number of patients that give unreliable statistics. Future studies should be done on large scale studies to confirm these results.

Conclusion: CRS patients have a higher positive rate of pepsin in salivary and nasal secretions. However, we did not find a significant increase of pepsin in salivary or nasal secretions in patients with CRS than in controls.

#### Financial and Non-financial Relationships and Activities of Interest

None

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