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LARYNGOLOGY

Usefulness of pepsin saliva measurement for the detection of primary burning mouth syndrome related to reflux

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Abstract

Objectives To study the diagnostic value of salivary pepsin tests for detecting laryngopharyngeal reflux (LPR) in patients with primary burning mouth syndrome (BMS).

Methods Patients with BMS and asymptomatic individuals were consecutively recruited from September 2018 to June 2023. Patients underwent hypopharyngeal-esophageal impedance pH-monitoring (HEMII-pH) and saliva collections to measure pepsin. Stomatology evaluation was carried out to exclude other causes of BMS. Oral, pharyngeal and laryngeal signs and symptoms were evaluated with Reflux Sign Assessment (RSA) and Reflux Symptom Score (RSS). Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of pepsin test were calculated considering the highest values of pepsin tests at ≥ 16, ≥ 36, and ≥ 100 ng/mL cutoffs. Receiver operating characteristic curve (ROC) was evaluated.

Results Forty-nine patients with both BMS and LPR at the HEMII-pH and 21 asymptomatic individuals were recruited. Pepsin test was 83.7%, 79.6%, and 71.4% sensitive at cutoffs ≥ 16, ≥ 36, and ≥ 100 ng/mL, respectively. The ROC analysis reported that a threshold of ≥ 21.5 ng/mL was associated with sensitivity, specificity, PPV and NPV of 81.6%, 81.0%, 90.1% and 65.4%, respectively. The severity score of burning mouth symptom was significantly associated with the saliva pepsin concentration ($r_s = 0.263$; $p = 0.029$) and the oral RSA ($r_s = 0.474$; $p = 0.007$).

Conclusion Pepsin test is a valuable diagnostic approach for detecting LPR in patients with BMS. Patients with high level of saliva pepsin reported more severe burning mouth symptoms. Future studies are needed to confirm the role of LPR in the primary BMS.

Keywords Otolaryngology · Maxillofacial · Reflux · Laryngopharyngeal · Pepsin · Peptest · Burning · Mouth · Tongue · Impedance

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Introduction

Primary burning mouth syndrome (BMS) is a still poorly understood condition associated with recurrent or chronic burning of the oral mucosa without an obvious cause [1]. The symptoms associated with BMS can affects the cheeks, palate, tongue, gums, lips, or widespread areas of the mouth [1]. The pathophysiology of primary BMS is still unknown, although it has been hypothesized that several conditions may be involved in its the development: psychiatric disease, medications, vitamin deficiencies, structural and functional changes in the nervous system and disruption of circadian rhythm [2, 3]. Laryngopharyngeal reflux (LPR) is a prevalent condition in otolaryngology, dentistry and maxillofacial surgery [4], which was recently identified as an additional cause of BMS [5]. Patients with LPR commonly have laryngopharyngeal and oral symptoms and findings, which are

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related to the deposit of pepsin into the mucosa [6]. Pepsin is a proteolytic enzyme that is associated with the development of upper aerodigestive tract mucosa traumas, and related inflammatory reaction [6]. The LPR diagnosis is based on the identification of pharyngeal reflux events at the 24-h hypopharyngeal-esophageal multichannel impedance pH-monitoring (HEMII-pH) but this examination is costly, inconvenience and not available in all hospitals [4]. The quantification of saliva pepsin was therefore proposed as an addictive non-invasive diagnostic tool for the detection of LPR with several and different cutoffs regarding studies [7]. To date, there is no study investigating the accuracy, sensitivity, specificity and predictive values of pepsin test for the detection of LPR in patients with BMS.

The aim of this study was to investigate the diagnostic value of salivary pepsin tests for detecting LPR in patients with BMS and the correlations between salivary pepsin level and BMS severity.

Materials and methods

Patients and setting

Patients with primary burning mouth syndrome were consecutively recruited from September 2018 to June 2023 from the otolaryngological and maxillofacial consultations of four European hospitals (CHU Saint-Pierre Hospital & Cesar de Pape Hospital, Brussels, Belgium; Dour Medical Center, Dour, Belgium; Polyclinic Elsan of Poitiers, Poitiers, France). Patients benefited from medical and dental evaluation to exclude conditions associated with secondary burning symptoms, including aphtosis, dysplasia, lichen, atrophic glossitis, geographic tongue, mycosis, Sjogren syndrome, vitamin disorders, or hypersensitivity to dental materials. The following additional exclusion criteria were considered: smoker, alcohol addiction, neurological or psychiatric illness, upper respiratory tract infection within the last month, current use of anti-reflux treatment or inhaled corticosteroids, previous history of neck surgery or trauma, benign vocal fold lesions, malignancy, history of ear, nose and throat radiotherapy and active seasonal allergies or asthma. Only patients with a primary BMS and without laryngopharyngeal confounding condition were included in the present study.

After the consideration of inclusion and exclusion criteria, patients were evaluated by a board-certified otolaryngologist and underwent 24-h HEMII-pH monitoring and saliva sample collection. Gastrointestinal (GI) endoscopy was proposed to patients with heartburn, history of esophagitis, digestive complaints, or in elderly (age > 60 years).

A control group of asymptomatic individuals was composed. Asymptomatic individuals did not have burning mouth symptoms or laryngopharyngeal disorders and exhibited a reflux symptom score (RSS) < 13 [8]. Exclusion criteria were similar for asymptomatic individuals. The study was approved by institutional review board (CHUSP, n°BE076201837630).

24-h hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing

The HEMII-pH catheter model (Versaflex Z®, Digitrapper pH-Z testing System, Medtronic, Europe) was introduced transnasally and the length was chosen based on the esophageal length of the patient. The catheter was placed in the morning fasting (8:00 AM) at the hospital by an experienced practitioner. The HEMII-pH device was composed of 8 impedance segments and 2 pH electrodes. Six impedance segments were placed in the esophagus zones (Z1–Z6) at 19, 17, 11, 9, 7 and 5 cm above the lower esophageal sphincter (LES). Two impedance segments were placed 1 and 2 cm above the cricopharyngeal sphincter in the pharynx, respectively. The pH electrodes were placed 2 cm above LES and 1–2 cm below the cricopharyngeal sphincter, respectively. A hypopharyngeal reflux event was defined as an episode that reached two impedance sensors in the hypopharynx. Pharyngeal reflux events were defined as acid (pH < 4.0) or weakly/non-acid (pH ≥ 4.0). According to the Dubai consensus, the LPR diagnosis was based on the occurrence of ≥ 1 hypopharyngeal reflux episode [9]. Gastroesophageal reflux disease (GERD) diagnostic was based on the Lyon consensus guidelines. [10]

Pepsin detection

Patients and asymptomatic individuals collected saliva samples (1–5 mL) in the morning (fasting, after waking) and 2 h after the dinner (bedtime) simultaneously to the HEMII-pH recording. The saliva was collected into a 30-mL universal sample collection tube containing a pre-established concentration of citric acid to preserve the action of any pepsin present. They were invited to store the saliva collections in the refrigerator. The measurement of pepsin concentration in the saliva samples was carried out the day after the removal of the pH probe with the Peptest® device (RD Biomed Ltd., Hull, United Kingdom). The steps of pepsin measurement were performed in a standardized procedure, which has been previously described. The saliva pepsin concentration was measured using the Cube Reader®, which may detect pepsin down to 16 ng/mL. The Cube Reader® may measure a saliva pepsin concentration ranging from 0 to 500 ng/dL. [11]

Burning mouth, symptoms, and signs

The burning mouth sensation was assessed through a 25-point scale, considering the severity and the frequency of the symptoms [5]. Five points were attributed to the frequency of burning mouth (from 1 time weekly to daily), while severity was assessed through a 5-point Likert scale ranging from 1 (mild symptom) to 5 (very severe symptom). The frequency and severity were multiplicated to have the final 25-point score. Symptoms were evaluated with the RSS, which is a 22-item validated patient-reported outcome measure questionnaire, documenting frequency and severity of ear, nose, throat, digestive, and respiratory complaints [8]. Oral, pharyngeal and laryngeal signs were evaluated with the Reflux Sign Assessment (RSA) at the videolaryngostroboscopy. RSA is a 61-point finding score evaluating the severity of signs associated with LPR. [11]

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 27.0; IBM Corp, Armonk, NY, USA). The sensitivity (SE), specificity (SP), positive (PPV) and negative predictive value (NPV) of pepsin test were evaluated at cutoffs $\geq 16, \geq 36$, and ≥ 100 ng/mL, which are the most used cutoffs in the literature [7]. We considered the highest value of both pepsin tests (morning and bedtime). Moreover, the pepsin test cutoff for determining the presence and absence of LPR was examined by receiver operating characteristic (ROC) analysis. The relationships between the HEMII-pH findings, the pepsin saliva concentration and the clinical features were evaluated. The association was considered as low, moderate and strong for $r_s < 0.30$, 0.30–0.60, and $r_s > 0.60$, respectively. The consistencies between HEMII-pH, pepsin test, RSS and RSA were assessed with kappa-Cohen analysis. RSS > 13 [8] and RSA > 14 [11] were considered as suggestive of LPR.

Results

Forty-nine patients with BMS and positive LPR at the 24-h HEMII-pH were recruited. Twenty-one asymptomatic individuals were recruited from the CHU Saint-Pierre Hospital & Cesar de Pape Hospital, Brussels, Belgium; Dour Medical Center, Dour, Belgium; Polyclinic Elsan of Poitiers, Poitiers, France. Demographic and clinical features are reported in Table 1. Females accounted for 81.6% and 33.3% of cases in LPR and control groups, respectively. The age ranged from 31 to 85 years in the LPR group, while it ranged from 18 to 53 years in the asymptomatic group. The GI endoscopy was performed in 39 patients. The examination was normal in 33.3% of cases. Most hypopharyngeal reflux events were weakly acid (pH > 4.0). Ten patients (25.6%) had both LPR and GERD. The RSS and RSA data are reported in Table 1. LPR patients reported significant higher RSS and RSA than controls ($p = 0.001$). Symptoms of LPR patients were reported in Table 2.

Pepsin analyses

Saliva was collected in patients and asymptomatic individuals. Pepsin was undetectable in 15 asymptomatic individuals (71.4%), whereas 7 subjects reported at least one pepsin concentration ≥ 16 ng/mL. In the LPR-BMS group, the pepsin was undetected in both fasting and bedtime tests in 8 patients (16.3%). The accuracy of pepsin test for the detection of LPR in BMS patients was 83.7% at threshold ≥ 16 ng/mL. Pepsin test was 83.7% sensitive and 71.4% specific. The PPV and NPV were 87.2% and 65.2%, respectively. Accuracy, SE, SP, PPV and NPV of pepsin test at thresholds ≥ 36, ≥ 100 ng/m were reported in Table 3. The ROC analysis reported that a threshold ≥ 21.5 ng/mL was 81.6% sensitive and 81.0% specific (Fig. 1). The area under the curve was 0.866. Considering the 21.5 ng/mL cutoff, the PPV and NPV were 90.1%, and 65.4%, respectively (Table 3). There were significant consistencies between the HEMII-pH, the pepsin test (kappa = 0.596, $p = 0.001$), and the RSS > 13 (kappa = 0.934, $p = 0.001$). There were no significant consistencies between HEMII-pH results and RSA > 14 or RSS > 13 & RSA > 14.

Clinical associations

There were significant moderate associations between age and the following outcomes: burning mouth score ($r_s = 0.482$; $p = 0.001$), oral RSA ($r_s = 0.532$; $p = 0.002$), and pharyngeal RSA ($r_s = 0.493$; $p = 0.004$). Age was strongly correlated with laryngeal RSA ($r_s = 0.680$; $p = 0.001$) and RSA ($r_s = 0.603$; $p = 0.001$). The score of burning mouth symptom was significantly associated with the saliva pepsin concentration ($r_s = 0.263$; $p = 0.029$), oral RSA ($r_s = 0.474$; $p = 0.007$), pharyngeal RSA ($r_s = 0.451$; $p = 0.010$), laryngeal RSA ($r_s = 0.747$; $p = 0.001$) and RSA ($r_s = 0.639$; $p = 0.001$). The pepsin saliva concentration was positively associated with pharyngeal RSA ($r_s = 0.371$; $p = 0.034$), laryngeal RSA ($r_s = 0.507$; $p = 0.003$), and RSA ($r_s = 0.471$; $p = 0.007$).

Discussion

The potential role of reflux disease in BMS was suspected for a long time but only a few clinical or epidemiological studies investigated the association between both conditions [5, 12–17]. One of the reasons of the lack of investigation is the difficulty to make the LPR diagnosis. Indeed, LPR is

Table 1 Patient features

Characteristics	LPR-BMS	Asymptomatic
Age (range, years)	31–85	18–53
BMI (range)	18.0–40.9	19.4–38.3
Male (*N*, %)	9 (18.4)	14 (66.7)
Female (*N*, %)	40 (81.6)	7 (33.3)
Gastrointestinal endoscopy (*N* = 39)		
Normal	13 (33.3)	–
Esophagitis	6 (15.4)	–
Hiatal hernia	10 (25.6)	–
LES insufficiency	17 (43.6)	–
Gastritis	4 (10.3)	–
HEMII-pH (mean, SD)		
Pharyngeal acid events	12.3 ± 16.8	–
Pharyngeal nonacid events	20.9 ± 51.0	–
Pharyngeal events (total number)	33.4 ± 50.9	–
GERD (*N*, %)	10 (25.6)	–
Clinical data (mean, SD)		
Reflux Symptom Score	128.2 ± 78.8	5.3 ± 4.3
Oral and laryngopharyngeal symptom score	62.1 ± 42.2	2.7 ± 3.2
Digestive symptom score	48.0 ± 35.9	2.1 ± 2.6
Respiratory symptom score	20.3 ± 22.4	0.5 ± 1.0
Reflux sign assessment		
Oral score	5.5 ± 2.5	2.6 ± 2.0
Pharyngeal score	9.5 ± 4.0	5.2 ± 3.0
Laryngeal score	10.7 ± 7.3	3.9 ± 2.2
Reflux sign assessment	21.5 ± 11.9	11.7 ± 5.2

BMI body mass index, *GERD* gastroesophageal reflux disease, *HEMII-pH* hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring, *LES* lower esophageal sphincter, *LPR* laryngopharyngeal reflux

known to be a different condition from GERD, with most patients without GERD-related symptom and lesion (e.g. esophagitis, esophageal stricture) [4]. In the same vein, most GERD patients do not have pharyngeal reflux events, and related upper aerodigestive tract symptoms and findings [4]. The current gold standard of the LPR diagnostic is the 24-h HEMII-pH, which is the only tool able to demonstrate the occurrence of esophago-pharyngeal reflux events [9, 18]. HEMII-pH is however a costly approach in some countries, inconvenience and its availability is limited, especially in dentistry or maxillofacial consultation. [4]

The primary finding of the present study was the high prevalence of pharyngeal reflux events and LPR disease in patients with primary BMS, which corroborates findings of previous studies [5, 13]. To date, only two studies investigated the association between BMS and LPR through pH-impedance monitoring. Becker et al. observed that 50% of patients BMS reported pharyngeal reflux events at the oropharyngeal pH measurement [13]. In a preliminary study, our group reported that 93% of patients with BMS had more than one pharyngeal reflux events at the HEMII-pH [5], which supports the findings of the present study. The association between reflux disease and primary BMS was indirectly supported in other studies, where authors focused on GERD diagnostic, and not LPR, through analyses of GI endoscopy, GERD-symptoms or single-probe pH monitoring data in BMS patients [12, 16]. In these studies, reflux disease was found in less than 50% of patients, which is a lower prevalence compared with our preliminary data. However, it is conceivable that the prevalence of LPR was previously misestimated regarding methodological discrepancies. Indeed, GERD findings, e.g. esophagitis or stricture, are commonly found in less than 50% of LPR cases, whereas GERD patients have LPR symptoms in approximately 30% of cases [4, 19]. Regarding the study of Becker et al., the comparison of results of the oropharyngeal pH monitoring and HEMII-pH does not make sense regarding variability between both devices in terms of detection of pharyngeal events. [20]

The data of the present study support the usefulness of pepsin test in the detection of LPR in BMS patients. The ROC analysis suggested a cutoff of 21.5 ng/mL, which is

Table 2 Symptom prevalence

Symptoms	Prevalence	
	N	%
Throat clearing	38	77.6
Heartburn	37	75.5
Abdominal distension/flatus	36	73.5
Excess throat mucus	35	71.4
Throat pain	35	71.4
Globus sensation	33	67.3
Cough	33	67.3
Ear pressure/pain	29	59.2
Dysphagia	27	55.1
Abdominal pain	27	55.1
Breathing difficulties	26	53.1
Voice disorder	26	53.1
Cough after eating/lying down	26	53.1
Regurgitations or burps	25	51.2
Odynophagia	25	51.0
Constipation	25	51.0
Indigestion	23	46.9
Nausea	23	46.9
Halitosis	22	44.9
Diarrheas	17	34.7
Chest pain	12	24.5

Symptoms prevalence was evaluated using full version of reflux symptom score

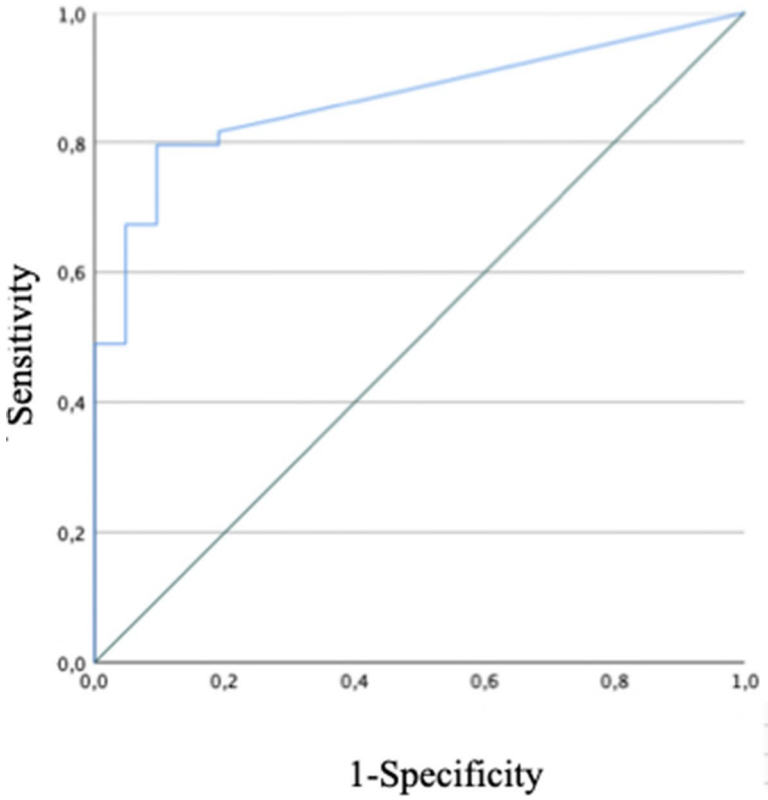
associated with SE and SP of 81.6% and 81.0%, respectively. To the best of our knowledge, this is the first study assessing SE, SP and predictive values of pepsin test in BMS patients, which limits our comparison with the literature. However, several studies have been conducted to evaluate the SE, SP, and predictive values of pepsin test in LPR at the HEMII-pH [7, 21–24]. Zhang et al. reported SE, SP, NPV of 76.9%, 25.0% and 14.3% in LPR patients at the 16 ng/mL cutoff considering the highest pepsin test of the testing day [23]. In a study using several saliva pepsin measurements throughout the day, Wang et al. reported that pepsin saliva measurement was 86.6% sensitive and 80.8% specific, while authors found a NPV of 58.3% at cutoff 45 ng/mL [21]. Zelenik et al. did not corroborate these results because they reported SE, SP, and NPV of 48.0%, 27.0%, and 40.0% [22]. The highest results found in the present study may be explained by two important points. First, contrarily to all of these studies [21–23], we included a control group. The assessment of SE, SP, and predictive values in a homogeneous population (all reflux patients at the HEMII-pH) may undoubtedly lead to inaccuracy of specificity and NPV assessments [21]. The importance of the control group was furthermore supported by the results of Hayat et al., who evaluated pepsin test accuracy in 111 GERD patients and 100 asymptomatic individuals [24]. Interestingly, these authors found higher SP (63.2%) and NPV (80.4%) compared to studies where there was no control group [21–23]. Second, the development of cell injuries and related upper aerodigestive tract symptoms and findings of LPR patient was related to the toxicity of pepsin [6]. In acidic or weakly acidic environment, pepsin may reduce the defense mechanisms of mucosa (e.g. activity of type III carbonic anhydrase, mucin expression) [25] and promote cell apoptosis through mitochondria injuries [26]. In addition to the diagnostic interest of pepsin test, the detection of pepsin in saliva of most BMS patients may support a potential role of pepsin in the development of primary BMS. The significant association between burning mouth severity score and the concentration of pepsin into the saliva of patients may support this assumption.

The originality of the present study and its application in daily maxillofacial or dentistry practice are its main strengths. The use of ROC curve to determine the best threshold of pepsin test in BMS patients is an additional strength of the study, as well as the consideration of a control group. Indeed, in the previous studies, authors used several thresholds, i.e. 16, 36, 45, 75 or 100 ng/mL, for the detection of LPR but none have carried out a ROC analysis. The low number of patients and asymptomatic individuals, and the lack of HEMII-pH in asymptomatic individuals are the main limitations of the study. These limitations are related to the cost and the inconvenience associated with the use of HEMII-pH in patients and controls. The lack of investigation of both other gastroduodenal enzymes and oral microbiome is an additional weakness. Indeed, bacteria are known to influence the oral

Table 3 Sensitivity, specificity and predictive values of pepsin test

Thresholds	Pepsin test				+Pepsin	
	SE	SP	PPV	NPV	*N* = 49	%
≥ 16 ng/mL	83.7	71.4	87.2	65.2	41	83.7
≥ 21.5 ng/mL	81.6	81.0	90.1	65.4	40	81.6
≥ 36 ng/mL	79.6	85.7	92.9	64.3	39	79.6
≥ 100 ng/mL	71.4	90.5	94.6	57.6	35	71.4

SE sensitivity, *SP* specificity, *PPV* positive predictive value, *NPV* negative predictive value



Pepsin concentration
Reference line

Peptest	SE	1-SP
-1,000	1,000	1,000
8,000	,837	,286
21,500	,816	,190
29,600	,796	,190
54,150	,796	,143
78,050	,796	,095
85,000	,755	,095
94,500	,735	,095
100,500	,714	,095
107,000	,694	,095
112,900	,673	,095
117,400	,673	,048
127,500	,653	,048
135,500	,633	,048
145,500	,612	,048
154,500	,571	,048
156,000	,551	,048
159,500	,531	,048
162,500	,510	,048
163,450	,490	,048
164,950	,490	,000

Fig. 1 Receiver operating characteristic curve. The ROC analysis reported that a threshold ≥ 21.5 ng/mL was 81.6% sensitive and 81.0% specific. The area under the curve was 0.866

health and the refluxate of proteolytic enzymes, such as pepsin, elastase, or trypsin, should theoretically influence the bacteria populations and their related roles in homeostasis of tissues.

Conclusion

Pepsin test is a valuable diagnostic approach for detecting LPR in patients with BMS. Patients with high level of saliva pepsin reported severe burning mouth symptoms. Future studies are needed to confirm the role of LPR in the primary BMS.

Author contributions Study concept and design: JRL, LAV, FB. Acquisition, analysis, or interpretation of data: JRL, FB. Drafting of the manuscript: JRL. Critical revision of the manuscript for important intellectual content: LAV, FB.

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Data availability Data are available on request.

Declarations

Conflict of interest Authors have no conflict of interest.

Informed consent Patients consented to the study.

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