

## PEPTEST AND INJURIES TO THE HARD TISSUES OF THE ORAL CAVITY: A PROSPECTIVE STUDY

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### ABSTRACT

**Introduction:** The aim of the study is to evaluate the correlation between the presence of pepsin in saliva and dental erosion in patients with GERD.

**Materials and methods:** 100 adult patients with typical GERD symptoms have been tested with the salivary pepsin test (PEPTEST) which was used to assess the presence of pepsin in saliva and, therefore, for the diagnosis of GERD. The presence and the localization of dental erosion was evaluated through a dental examination.

**Results:** In 52% of the patients the PEP test was positive. It was shown that out of 52 patients with gastroesophageal reflux disease, 16 (30%) had dental erosions, while in the remaining 48 healthy subjects only 4 patients (8%) showed dental erosions.

**Conclusions:** The results showed a positive correlation between the presence of pepsin and dental erosion. A multidisciplinary approach between the gastroenterologist and the dentist is very important in order to plan and implement the most suitable therapeutic strategy that aims to restore a state of health of all the anatomical districts concerned.

**Keywords:** Gastroesophageal reflux disease, GERD, Pepsin, Oral lesions, Palate.

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### Introduction

Dental erosion is defined as a progressive and irreversible loss of the hard tissues of the tooth, due to a chemical process that does not involve bacteria<sup>(1)</sup>. Both endogenous (intrinsic) and exogenous (extrinsic) acid are responsible for the increased incidence and high prevalence of dental erosion, and dental sensitivity observed in many countries, in both children and adults. Not only dental erosion from endogenous acid is more severe than that from exogenous acids, but gastric reflux, regurgitation and microaspiration can have significant negative repercussions on the esophagus and oropharynx mucosa

and respiratory system<sup>(2,3)</sup>. Numerous clinical conditions can cause erosive lesions of the dental tissues, including gastroesophageal reflux disease (GERD), characterized by the ascent of gastric juices from the stomach into the oral cavity.

Other GERD-related symptoms could include dysphonia or a sense of foreign body, frequently leading to considering different comorbidities, including tumors, in the differential diagnosis<sup>(4,5)</sup>.

Schroeder et al. in 1995 demonstrated through the measurement of PH in the proximal and distal esophagus, the direct connection between (GERD) and dental erosion<sup>(6)</sup>. However, there are wide divergences in the literature regarding the prevalence of these

dental lesions in patients with (GERD). In fact, in some studies it was found that, compared to the control group, the percentage of dental erosion was significantly higher in the gastroesophageal reflux disease group (12.5 vs 47.5%,  $p < 0.001$ , chi2 test), thus such as the number and severity of dental erosions<sup>(7)</sup>. On the other hand, Ranjitkar et al., do not show significant associations between (GERD) and dental erosion<sup>(8)</sup>. To reduce the effect of this phenomenon on dental tissues, primary prevention protocols are implemented: educational, such as lifestyle changes, dietary changes; secondary prevention: pharmacological (gastric acid buffering agents, and gastric anti-secretory agents), use of topical fluoride, restorative treatments in order to decrease dental sensitivity, and restore dental anatomy<sup>(9)</sup>.

Primary extraoral pathologies can secondarily involve the dental tissues, and therefore clinicians must observe the lesions of the oral cavity to early intercept systemic pathologies, such as dental erosions associated with gastroesophageal reflux. This allows to improve the prognosis of dental treatment, through a multidisciplinary approach starting from a careful medical history and an accurate objective examination<sup>(10-13)</sup>. In the current context in which none of the diagnostic tests in use prove to be a safe tool in the recognition of gastroesophageal reflux disease<sup>(14)</sup>, the search for pepsin inside the saliva may constitute a possible method of effective diagnosis. The aim of this work is to first identify the diagnostic value of salivary pepsin in the diagnosis of GERD, and subsequently to determine the correlation between test positive patients and oral lesions.

## Material and methods

We conducted a prospective study in the ENT section of the University Catania Hospital, between January 1, 2019 and February 1, 2020. GERD evaluation was performed through a specific tool: Pepsin salivary test<sup>(15)</sup> (PEPTEST, RDBiomed Limited). The test evaluates the presence of pepsin in saliva, commonly not present in oral secretions but increased in patients suffering from GERD. Pepsin is a protein degrading enzyme present in the stomach and small intestine in the form of pepsinogen and activated by hydrochloric acid into pepsin. The enzyme's identification in the oral cavity expresses the presence of stomach gastric contents, thus allowing diagnosing GERD. We enrolled 100 adult patients suffering from retrosternal burning, aging from aging from 18 to 70 years old, and subjected to pepsin

salivary test fasting and after normal oral hygiene practice at morning). Test results were achieved about 15 minutes after the execution. Subsequently, a dental examination was administered by the same dentist to evaluate hard and soft tissues of the oral cavity and correlate the data with PEP test outcomes.

## Results

Through PEP test we differentiated 52 subjects with GERD while 48 negative healthy ones. Based on the preliminary objective examination, 16/52 (30%) patients with GERD presented dental erosions, 10 (20%) to soft tissues lesions (periodontitis, gingivitis, erythema of the palate, and glossitis), 10 (20%) dental erosions and soft tissue lesions while 16 (30%) no lesions. In contrast, among healthy subjects 4/48 (8%) reported dental erosions, 2 (4%) soft tissue lesions while 42 (88%) no lesions.

## Discussion

Oral lesions's diagnosis could be very difficult both in adults than children<sup>(16-19)</sup>. Differential diagnosis should consider several different disorders, from infection-induced lesions to neoplasms<sup>(20-22)</sup>. A recent systematic review on GERD and dental erosion found a strong association between the two conditions<sup>(23)</sup>. The median prevalence of dental erosion in GERD patients was 24%, and the median prevalence of GERD in adults and children with dental erosion was 32.5% and 17%, respectively. Moreover, strong associations between oral and palatal surgery were found in hard tissues lesions development<sup>(24-26)</sup>.

Several authors reported in literature a higher prevalence of dental erosion, asthma, pneumonia and sinusitis in children with GERD compared to healthy controls<sup>(16,26)</sup>. However, a large case-control study reported no significant associations between GERD and dental erosion or tooth sensitivity, but significant associations between GERD and xerostomia, oral acid / burning sensation, subjective halitosis, and erythema of the palatal mucosa and uvula<sup>(27)</sup>. Additionally, a randomized clinical trial showed quantitatively short-term suppression of active dental erosion following treatment of medically confirmed GERD with a proton pump inhibitor (PPI)<sup>(17)</sup>. Intraesophageal refluxes contain a mixed composition of gas and liquid associated with GERD symptoms could led to endogenous tooth erosion<sup>(28,29)</sup>.

A recent clinical study including 88 subjects with GERD reported significantly higher dental ero-

sions and respiratory symptoms compared to healthy subjects. Palatal erosion of the maxillary incisors was found in 80% of patients with frequent respiratory symptoms such as chronic cough, laryngitis and asthma, comporting significantly high orotracheal risk intubation<sup>(30-32)</sup>. Strong associations have been reported between GERD and asthma<sup>(32)</sup>, and between asthma and dental erosion<sup>(33)</sup>.

The different ages and exposure's time to acids among the subjects could explain the variability of the oral pathologies found. Dental erosion is a multifactorial pathology that occurs more frequently in elderly subjects, but also associated with frequent food use, drink, and acid drugs, but above all with exposure to acid agents of endogenous origin. Our study demonstrated a considerably lower number of lesions in healthy subjects than GERD. Furthermore, the different lesions location could be due to different etiological causes. GERD subjects presented lesions mainly in the lingual and palatal areas, while healthy subjects present heterogeneous localization. Localized lesions are noted on the labial surfaces of the anterior teeth, the buccal surfaces of the posterior teeth and the occlusal surfaces of the molars.

## Conclusion

Our study suggests a strong correlation between gastroesophageal reflux disease and lesions of the hard and soft tissues of the oral cavity. The dentist plays a very important role in identifying early this type of oral lesions, giving the signs of a systemic pathology. A careful and scrupulous localization of the lesions, therefore, helps us to be able to distinguish the causes.

It is clear that a multidisciplinary approach between dentistry, gastroenterologist and otolaryngologist is considered desirable to plan and implement the most suitable therapeutic strategy that aims to restore a state of health of all the anatomical districts concerned.

## References

- 1) Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *American Journal of Gastroenterology*. 2006; 101(8): 1900-20.
- 2) Scalia G, Palermo CI, Maiolino L, et al. Detection of serum IgA to HSV1 and its diagnostic role in sudden hearing loss. *New Microbiol*. 2013; 36(1): 41-47.
- 3) Boeckstaens G, El-Serag HB, Smout AJ, Kahrilas PJ. Republished: Symptomatic reflux disease: the present, the past and the future. *Postgraduate medical journal*. 2015; 91(1071): 46-54.
- 4) Galletti B, Sireci F, Mollica R, Iacona E, Freni F, Martines F, Scherdel EP, Bruno R, Longo P, Galletti F. Vocal Tract Discomfort Scale (VTDS) and Voice Symptom Scale (VoiSS) in the Early Identification of Italian Teachers with Voice Disorders. *Int Arch Otorhinolaryngol*. 2020 Jul; 24(3): e323-e329.
- 5) La Mantia I, Ciprandi G, Varricchio A, Cupido F, Andaloro C. Salso-bromo-iodine thermal water: a nonpharmacological alternative treatment for postnasal drip-related cough in children with upper respiratory tract infections. *J Biol Regul Homeost Agents*. 2018; 32(1 Suppl. 2):41-47.
- 6) Li T, Guo H, Li H, Jiang Y, Zhuang K, Lei C, et al. MicroRNA-92a-1-5p increases CDX2 by targeting FOXD1 in bile acids-induced gastric intestinal metaplasia. *Gut*. 2019; 68(10): 1751-63.
- 7) Grassia V, Lombardi A, Kawasaki H, Ferri C, Perillo L, Mosca L, et al. Salivary microRNAs as new molecular markers in cleft lip and palate: a new frontier in molecular medicine. *Oncotarget*. 2018; 9(27): 18929.
- 8) Warsi I, Ahmed J, Younus A, Rasheed A, Akhtar TS, Ain QU, et al. Risk factors associated with oral manifestations and oral health impact of gastro-oesophageal reflux disease: a multicentre, cross-sectional study in Pakistan. *BMJ open*. 2019; 9(3): e021458.
- 9) Vinesh E, Masthan K, Kumar MS, Jeyapriya SM, Babu A, Thinakaran M. A clinicopathologic study of oral changes in gastroesophageal reflux disease, gastritis, and ulcerative colitis. *The journal of contemporary dental practice*. 2016;17(11):943-7.
- 10) Silva MAGS, Damante JH, Stipp ACM, Tolentino MM, Carlotto PR, Fleury RN. Gastroesophageal reflux disease: New oral findings. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2001; 91(3): 301-10.
- 11) Perillo L, d'Apuzzo F, Illario M, Laino L, Di Spigna G, Lepore M, et al. Monitoring Biochemical and Structural Changes in Human Periodontal Ligaments during Orthodontic Treatment by Means of Micro-Raman Spectroscopy. *Sensors*. 2020; 20(2): 497.
- 12) Grassia V, Gentile E, Di Stasio D, Jamilian A, Matarese G, D'Apuzzo F, et al. In vivo confocal microscopy analysis of enamel defects after orthodontic treatment: A preliminary study. *Ultrastructural pathology*. 2016;40(6):317-23.
- 13) Giudice AL, Leonardi R, Ronsivalle V, Allegrini S, Lagravère M, Marzo G, et al. Evaluation of pulp cavity/chamber changes after tooth-borne and bone-borne rapid maxillary expansions: a CBCT study using surface-based superimposition and deviation analysis. *Clinical oral investigations*. 2020:1-11.
- 14) Leonardi R, LGA, Ferronato M., Ronsivalle V., Musement G., Spampinato C.. Fully automatic segmentation of sino-nasal cavity and pharyngeal airway based on convolutional neural networks (CNNs). *American Journal of Orthodontics and Dentofacial Orthopaedics*. 2021.
- 15) Iannella G, Vicini C, Polimeni A, et al. Laryngopharyngeal Reflux Diagnosis in Obstructive Sleep Apnea Patients Using the Pepsin Salivary Test. *Int J Environ Res Public Health*. 2019; 16(11): 2056. doi:10.3390/

- ijerph16112056
- 16) Epstein JB, Silverman S Jr, Epstein JD, Lonky SA, Bride MA. Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue [published correction appears in Oral Oncol. 2008 Jun;44(6):615]. *Oral Oncol.* 2008;44(6):538-544. doi:10.1016/j.oraloncology.2007.08.011
  - 17) Ferlito S, Maniaci A, Di Luca M, et al. From Uncommon Infection to Multi-Cranial Palsy: Malignant External Otitis Insights.Dose Response. 2020;18(4):1559325820963910. Published 2020 Dec 17. doi:10.1177/1559325820963910
  - 18) Grillo C, La Mantia I, Zappala G, et al. Oral health in children with sleep-disordered breathing: a cross-sectional study. *Acta Biomed* 2019; 90(7-S): 52-59. doi: 10.23750/abm.v90i7-S.8661.
  - 19) Pennisi M, Di Bartolo G, Malaguarnera G, et al. Vitamin D Serum Levels in Patients with Statin-Induced Musculoskeletal Pain. *Dis Markers.* 2019;2019:3549402. doi:10.1155/2019/3549402
  - 20) Chen AA, Gheit T, Stellin M, et al. Oncogenic DNA viruses found in salivary gland tumors. *Oral Oncol.* 2017; b75:b106-110. doi:10.1016/j.oraloncology.2017.11.005
  - 21) Iannella G, Maniaci A, Magliulo G, et al. Current challenges in the diagnosis and treatment of obstructive sleep apnea syndrome in the elderly. *Pol Arch Intern Med.* 2020;130(7-8):649-654. doi:10.20452/pamw.1528322)
  - 22) Gelardi M, Silvestri M, Ciprandi G, et al. Relieving laryngopharyngeal reflux (RELIEF) survey in otolaryngology - the viewpoint of the otorhinolaryngologist. *J Biol Regul Homeost Agents.* 2018;b32(1 Suppl. 2): b9-19.
  - 23) Nucera R, Lo Giudice A, Bellocchio M, Spinuzza P, Caprioglio A, Cordasco G. Diagnostic concordance between skeletal cephalometrics, radiograph-based soft-tissue cephalometrics, and photograph-based soft-tissue cephalometrics. *European journal of orthodontics.* 2017;b39(4):b352-7.
  - 24) Schwendicke F, Frencken JE, Bjørndal L, et al. Managing Carious Lesions: Consensus Recommendations on Carious Tissue Removal. *Adv Dent Res.* 2016; 28(2): 58-67. doi:10.1177/0022034516639271
  - 25) Iannella G, Magliulo G, Di Luca M, et al. Lateral pharyngoplasty techniques for obstructive sleep apnea syndrome: a comparative experimental stress test of two different techniques. *Eur Arch Otorhinolaryngol.* 2020; 277(6): 1793-1800. doi:10.1007/s00405-020-05883-2
  - 26) Iannella G, Vallicelli B, Magliulo G, et al. Long-Term Subjective Outcomes of Barbed Reposition Pharyngoplasty for Obstructive Sleep Apnea Syndrome Treatment. *Int J Environ Res Public Health.* 2020; 17(5): 1542. Published 2020 Feb 27. doi:10.3390/ijerph17051542
  - 27) Di Luca M, Iannella G, Montevecchi F, et al. Use of the transoral robotic surgery to treat patients with recurrent lingual tonsillitis. *Int J Med Robot* 2020; 16(4): e2106. doi:10.1002/rcs.2106
  - 28) Du X, Wang F, Hu Z, Wu J, Wang Z, Yan C, et al. The diagnostic value of pepsin detection in saliva for gastro-esophageal reflux disease: a preliminary study from China. *BMC gastroenterology.* 2017; 17(1): 107.
  - 29) Wang Y-J, Lang X-Q, Wu D, He Y-Q, Lan C-H. Salivary Pepsin as an Intrinsic Marker for Diagnosis of Sub-types of Gastroesophageal Reflux Disease and Gastroesophageal Reflux Disease-related Disorders. *Journal of Neurogastroenterology and Motility.* 2020; 26(1): 74.
  - 30) Gelardi M, Silvestri M, Ciprandi G, et al. Correlation between the reflux finding score and the reflux symptom index in patients with laryngopharyngeal reflux. *J Biol Regul Homeost Agents.* 2018; 32(1 Suppl. 2): 29-31.
  - 31) Sireci F, Nicolotti M, Battaglia P, Sorrentino R, Castelnovo P, Canevari FR. Canine fossa puncture in endoscopic sinus surgery: report of two cases. *Braz J Otorhinolaryngol.* 2017 Sep-Oct; 83(5): 594-599
  - 32) Martines F, Salvago P, Ferrara S, Mucia M, Gambino A, Sireci F. Parietal subdural empyema as complication of acute odontogenic sinusitis: a case report. *J Med Case Rep.* 2014 Aug 21; 8: 282.
  - 33) Watanabe M, Nakatani E, Yoshikawa H, Kanno T, Nari-ai Y, Yoshino A, et al. Oral soft tissue disorders are associated with gastroesophageal reflux disease: retrospective study. *BMC gastroenterology.* 2017; 17(1): 92.

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