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Relationship Between Allergic Rhinitis Pathology And Gastro-Esophageal Reflux: A Simple Outpatient Method For Adults

Arturo Armone Caruso[1*] Salvatore Del Prete[2] Lydia Ferrara[3]
[1]**ENT Department, AIAS Structure Of Afragola, Contrada Leutrec Snc, 80021 Naples, Italy.*
[2] *Department Of Head And Neck. University Of Naples Federico II, Via Pansini 5, 80131 Naples, Italy*
[3] *Department Of Pharmacy,University Of Naples Federico II, Via Domenico Montesano 49, 80131 Naples, Italy*

Abstract:
Background*: The frequency of gastro-esophageal reflux disease is rising, and there has been a real spread of the disease as a consequence of modernity, lifestyle, dietary and behavioral norms, stress, work conditions and life in general. It is usually diagnosed with radiographic methods that employ contrast dyes, endoscopes, catheters and capsules to measure the intra-esophageal pH, impedance measurement.The purpose of our study was to highlight the relationship between gastro-esophageal reflux disease and chronic rhinitis using salivary pH measurement with indicator strips.*
Methods: *All patients underwent rhino-fiberoscopy, and anatomical elements of GERD (gastro-esophageal reflux disease) were identified. The nasal pH was determined by inserting an indicator paper moistened with distilled water into the patient's nostrils; the nasal mucosa cells were then withdrawn using nasal scraping and stained according to the Pappenheim method. To determine the saliva pH,2.5 ml of saliva was collected from each patient into a beaker, a Macherey-Nagel pH strip with a range of 1-14 was dipped into the saliva, and the strip's coloration was examined to determine the pH value.*
Results: *This method has provided excellent results, with no differences between the measured values and the results of tradition al instrumental measurement. Using these measurements, we detected an average nasal pH of 9 and an average salivary pH of 4.9 in the patients in group A who were affected by GERD; furthermore, the nasal cytology showed an abundant presence of mucous-like cells, and an absence of bacteria and fungi.*
Conclusion: *Salivary diagnostics could play a key role in routine health monitoring in the near future,*
Keywords: *Allergic rhinitis**,** GERD, Nasal cytology, pH determination*

I. Introduction

Esophageal diseases and rhinitis are among the main factors that contribute to chronic cough, and their role has been discussed in several studies. Studies in animal models and in humans show that afferent activators known as *C-fibers,* located on the esophageal and nasal mucosa, do not trigger a cough, but they contribute to cough when they encounter inhaled irritants.

These results are consistent with the hypothesis that activation of esophageal and nasal C-fibers contributes to the cough reflex and hypersensitivity observed in patients with chronic cough associated with gastro-esophageal reflux disease (GERD) and chronic rhinitis. The afferent nerves that cause coughing and esophageal activation are probably vagal fibers, specifically C-fibers arising from the jugular ganglion. In addition to their local response, which is activated at a pH<5, the esophageal C-fibers are also sensitive to bile acids. Regarding the neuro-sensory aspect of the nasal region, less information is available from current research. The increased sensitivity of the cough reflex has also been reported in several patients with GERD and in those with rhinitis who do not have GERD, indicating that other endogenous or exogenous factors could also contribute to the development of chronic cough. In addition, several epidemiological studies have reported an increased coexistence of gastro-esophageal reflux disease (GERD) and chronic rhino-sinusitis (CRS) [1-3]. It has been shown that the reflux is more often present in patients with CRS than in those without CRS [4]. A broader discussion addresses whether there might be an association between these two diseases and, if so, whether the association is causal. Gastro-esophageal reflux disease (GERD) is the most common digestive disease at present, and it has been associated with abnormalities of the larynx and pharynx [5]. Gastro-esophageal reflux is characterized by the spontaneous movement of gastric contents from the stomach into the esophagus, and it occurs daily in all human beings. When it is asymptomatic, it does no harm to the esophageal mucosa and is considered physiological; however, if it is characterized by inflammation of the larynx, cough, rhinitis, laryngeal tissue alterations, ulcers and other symptoms, it can cause severe injuries and illnesses, including epithelial neoplastic degeneration.

Saliva, with its organic and inorganic components, is responsible for the homeostasis of the oral and digestive tract mucous membrane. Saliva helps to protect the oral cavity, which is part of the digestive system, from physical and chemical aggression and maintain the integrity of its mucosa. Many studies have linked abnormalities in salivary pH and salivary volume with symptoms of GERD and LPH [6].GERD can also be caused by other factors, including the release of histamine from mast cells [7-9], which may promote the onset of this disease by means of lower esophageal sphincter contraction (SLEc). Many studies in the literature indicate the role of esophageal pH variation in the onset of GERD through the use of a 24-hour pH meter. Some authors argue that there is a relationship between the pH and volume of saliva and the esophageal pH [10] and have directly measured the hypo-pharyngeal pH in the clinic for patients with hoarseness [11].

The tentative diagnosis in the clinic, usually through the patient's medical history, is of crucial importance when there is no documentation of GERD. The diagnosis of reflux disease must be absolutely interdisciplinary and integrate different specialists because of the multiplicity of organs involved. The first assessment should aim to identify all aspects of reflux disease, and the physician must identify the most relevant symptoms, identify symptoms mistakenly attributed to other causes, and rule out that the possibility that the reported symptoms are secondary to other diseases. The patient may already be aware of the existence of reflux and may thereby assist the physician with the diagnosis; in other cases, the disease may be asymptomatic and thus more difficult to identify. In the absence of specific or typical symptoms, there may be recurrent and / or persistent breathing problems that tend to become chronic through the hypertrophy of the mucous lining of the airways. It is not uncommon for the diagnosis of reflux to be suspected by an otolaryngologist according to symptoms and to be reflected in examinations that reveal typical signs of chronic inflammation of the oro-pharynx, naso-pharynx and larynx. The typical symptoms of GERD are largely gastrointestinal; however, atypical symptoms that are of interest to oto-rhino-laryngologists may also be present. These symptoms occur via two different routes: vagal stimulation of the esophageal wall, characterized by persistent cough, ear pain, pharyngeal-laryngeal paresthesia, and pain on swallowing, and direct injury to the pharyngeal-laryngeal mucosa as a result of acid reflux, which is characterized by dysphagia, pain on swallowing, the sensation of a pharyngeal foreign body, drooling, sore throat, laryngospasm, episodes of sleep apnea, and oto-pathiccatarrh. There is a significant correlation between atypical manifestations of GERD and oto-rhino-laryngology-related aspects of gastro-nasal, gastro-esophageal and laryngo-tracheal reflux, and all of these phenomena can be studied by pH-meter using detectors placed in areas of the esophagus proximal and distal to the pharynx .Our study proposes a simple, accurate and non-invasive method for identifying possible GERD in subjects with allergic rhinopathy and selecting them for further investigation.

II. Gastro-Esophageal Junction

At the level of the esophagus-stomach junction, a functional area of great importance is represented by the lower esophageal sphincter (LES). The LES consists of fibers that are smooth and tonically contracted with respect to the middle portion of the esophagus, which remains released, creating a high-pressure area. The LES pressure is influenced by several factors: it increases considerably in response to a protein meal and in the presence of various hormones (gastrin, motilin, substance P) and certain drugs (metoclopramide, domperidone) and decreases in response to a purely lipid meal, the consumption of chocolate and alcohol, and the presence of certain hormones (cholecystokinin, glucagon, progesterone) and different drugs (diazepam, morphine, calcium channel blockers, nitrates).The most common cause of gastro-esophageal reflux disease is the altered functionality of the sphincter, the tone of which is conditioned by a number of factors with the main task of allowing relaxation after the start of swallowing and post-swallowing contraction to prevent the reflux of food.[12]. During swallowing, a peristaltic wave moves down the esophagus; there is a "receptive relaxation" of the LES in advance of this peristaltic wave, which allows the easy propulsion of the bolus from the mouth into the stomach. The vagus nerve is principally involved in the reflexive control of contraction or relaxation of the LES; the pre-ganglion neurons begin in the dorsal motor nucleus of the vagus and arrive at the LES. These cholinergic neurons are excitatory and stimulate excitatory muscarinic neurons or noradrenergic non-cholinergic (NANC) inhibitors [13] that control the tone of the LES. These NANC neurons release nitric oxide, which causes relaxation of the LES. These relaxations may be transient and independent of swallowing and generally last longer than post-swallowing relaxations. Transient relaxations facilitate the retrograde passage of intra-gastric air and cause belching, especially after the relaxation of the gastric fundus. The failure or incomplete operation of such a valve causes the gastric contents, acid, and sometimes pancreatic and bile juices to flow back into the esophagus and to come into contact for a relatively short time with the esophageal mucosa. The longer the stomach acid remains in contact with the mucous lining of the esophagus, the more severe the lesions that this contact will produce on the lining of the esophagus, causing different degrees of esophagitis. Since the 1960s, methods have been tested to determine the intra-esophageal acidity and duration of the esophageal mucosa's exposure to acidity to evaluate the relationship between symptoms and acid reflux. Esophageal pH monitoring is a minimally invasive technique that many researchers have considered the preferred method for diagnosing GER, which has been associated with a sudden decrease in the intra-esophageal pH to below 4 during monitoring. Johnson and De Meester in 1970 [14] proposed a range of normal pH values in various situations and performed measurements for periods as long as 24 hours to distinguish between normal and pathological esophageal acidity. Esophageal pH monitoring was also used to assess the effects of treatment with acid suppressive drugs (ASDs) and to compare different agents. The use of ASDs, however, has had abnormal results because of a lack of sensitivity and specificity of this method that, while being valid in the diagnosis of GER was flanked impedance measurement intraluminal that exploits differences in electrical conductivity between the esophageal wall and the intraluminal content and is independent of the pH. The coupling between impedance measurement and pH monitoring appears to be the most commonly used investigation that is not influenced by ASD therapy drugs, which are frequently used by GERD patients..Recently, many researchers and doctors have found an association between gastro esophageal reflux disease and chronic laryngitis [15,16], which represents the clinical form of the disease called *laryngo-pharyngeal reflux.* This disease is characterized according to the severity of the laryngeal inflammation, which can include small ulcers, larynx lining alterations, subglottic stenosis, and even epithelial neoplastic degeneration. This serious damage to the laryngeal epithelium is caused by substances such as hydrochloric acid and pepsin that are present in the reflux, but there are also defenses in these organic systems against daily mechanical and chemical aggressions, and saliva plays a fundamental role in these defenses. Saliva contains many organic and inorganic substances that contribute to the protection against physical and chemical aggression to maintain the integrity of the mucosa of the oral cavity and the entire digestive tract.

III. Saliva: Features And Activities

Saliva is a fluid with unique characteristics that influence oral health through specific and non-specific physical and chemical properties. It is produced by and secreted from the salivary glands, which are clusters of cells called acini. Saliva contains a wide range of organic substances, electrolytes and hormones that come from multiple locations in the oral cavity (local) and the rest of the body (systemic) [17]. The organic compounds consist mainly of proteins, glycoproteins and enzymes: amylase (ptyalin), pepsin, kallikrein, lactoperoxidase and lactoferrin. A small amount of protein is synthesized, stored, and secreted by the cells in the ducts, including the neural growth factor, epidermal growth factor, lysozyme and ribonuclease. Amylase and glycoproteins constitute the majority of the organic secretions of the terminal segments; the parotid gland secretes a rich glycoprotein that binds calcium and is made of six oligosaccharides with three mannose residues linked to asparagine for N-glycosylation. Mucin, a glycoprotein secreted by specialized sublingual glands, is a protein O-glycosylated with many oligosaccharides linked by covalent bonds to serine or threonin [18].

Saliva also contains a certain amount of albumin, immunoglobulin, thiocyanate and other substances that have bacteriostatic or even bactericidal activity, such as sialo-peroxidase and lysozyme. These substances are capable of counteracting the proliferation of bacteria, a very important action because the oral cavity is the food entry point and represents the first contact between the external and internal environment; as such, it is easily exposed to infections and is home to abundant bacterial flora [19]. Under conditions of reduced saliva secretion, the oral cavity is highly susceptible to pathological phenomena, such as inflammation, septic conditions and the easy onset of caries. The chemical protective action of saliva is associated with the physical containment of bacterial growth through the continuous washing provided by the coupling of salivation-swallowing, in which the gastric pH almost completely eliminates bacteria in the food bolus. Under normal conditions, in fact, the duodenum contains minimum values of bacterial content, and high bacterial values resume only in the large intestine, where the content remains longer (for approximately 24 hours) than in the small intestine.

The action of ptyalin, which cleaves carbohydrates into smaller fragments, is essentially limited to only one substrate: cooked starch (the human body has no enzyme to digest raw starch and cellulose). The action time of ptyalin is reduced but exceeds the stay of the bolus in the oral cavity as it continues to the stomach, where it is denaturized for inactivation by hydrochloric acid. The stomach is devoid of digestive enzymes for carbohydrates, and its low pH value would prevent the action of amylase, which requires a neutral or slightly alkaline pH. The stomach fills in concentric layers because the food falls from the esophagus into the center of the stomach and is subsequently scrambled by the movements of the gastric wall: it takes approximately 15 to 30 minutes, depending on the stomach content, for a complete remixing that completes the action of salivary amylase.

Another important component is the salivary secretion mucin, a compact, filamentous, viscous substance secreted by the buccal glands that acts as a lubricant. Mucin is strongly adhesive; by mixing with and coating the food bolus, mucin allows an easier and less traumatic passage through the isthmus of the mouth and esophagus. The parotid glands secrete saliva almost entirely of the serous type, while the sub-mandibles and sublingual glands secrete a mixed mucous-serous type.

Salivary changes have been used since ancient times to diagnose many diseases, especially in traditional Chinese medicine. It is believed that changes in saliva are indicative of the patient's well-being: the thickness and the smell of saliva and the patients taste sensations are all symptoms of specific states of the body and of disease, and interest in saliva as a diagnostic material has grown exponentially in the last 10 years [20,21].

Saliva has a pH between 6.0 and 7.0, a range necessary for the digestive action of ptyalin; variation in the pH of saliva is an important parameter for the diagnosis of certain pathologies [22].The capacities to evaluate physiological states, to detect the onset and the path of a disease and to monitor therapeutic effects through a non-invasive approach are among the most important objectives for scientific research. Saliva has proven to be suitable for the early detection of diseases as a result of new technologies that have allowed us to identify salivary biomarkers at very low concentrations, thus encouraging the development of salivary diagnostics [23].

IV. Experiment: Materials And Methods

In this study, we assessed the relationship between GERD in patients with allergic rhinitis and chronic variations determined using salivary pH indicator papers, a method that is commonly used in outpatient settings to conduct quick, non-invasive and accurate surveys.

The subjects were selected from among the users of the ENT Diagnostics and Nasal Cytology clinic of the AIAS (Italian Autism Association) Afragola (Naples). They included 20 adult subjects (10 males and 10 females) aged between 18 and 50 years with an average age of 35.3 years (GROUP A). As controls, a homogeneous group of 20 patients without GERD or any type of allergies (GROUP B) was enlisted. The criteria for inclusion and exclusion are reported in Table 1.

After completing privacy and informed consent forms, all patients underwent a physical examination that included rhino-fiberscope with a rhino-fiberscope (Xion Amplaid, Milan, Italy) 4 mm in diameter using disposable sheaths for protection. Anatomical elements of GERD were identified, including the presence of generalized mucositis along an oro-pharynx shaped map, especially at the level of the vocal folds, and hyperemia of the inter-arytenoids region. The patients returned the next day after outpatient fasting (including drinking and dental hygiene activities) to undergo the salivary examination.

Before the salivary pH was determined, the nasal pH was measured by inserting an indicator paper moistened with distilled water directly into one of the patient's nostrils and then with drawing nasal mucosa cells from the median part of the bilateral lower turbinate using nasal scraping®. The nasal mucosal cells were placed on an electrostatically charged cytology slide (Super Frost Plus Menzel – Gläser, Thermo Scientific, Milan, Italy). The cells were then stained according to the panoptic Pappenheim method (3 min in pure May-Grunwald dye [Carlo Erba, Milan, Italy],6 min. in 50% May-Grunwald dye; 1 min. in bidistilled water [Carlo Erba, Milan, Italy]; and 30 min. in Giemsa solution [Carlo Erba, Milan, Italy] diluted 1:10 v/v). The slide was then covered with a # 1 cover glass with dimensions of 24 x 50 mm and observed under an optical microscope (Nikon Eclipse 200) at 100 x enlargement in oil-immersion. For the acquisition of microscopy images, a NIKON DS FI1 tele-camera with the NIS - Elements D Version 2.30 image acquisition program was used. Although the numbers were small, possible changes in pH of the two districts were statistically evaluated using Student's t-test. The significance reference was $p < 0.05$.

To determine the saliva pH, 2.5 ml of saliva was collected from each patient into a beaker. No stimulation was used, and the mouth was rinse with water prior to collection to avoid contaminants. A Macherey-Nagel strip (Duren, Germany) with a pH range of 1-14 was dipped into the saliva and removed after a few seconds, and its coloration was observed to determine the pH value.

V. Results And Discussion

The results obtained show significant statistical variation (the greatest amount possible) between the two groups ($p < 0.05$). In particular, we detected an average pH of between 9 for the nasal district and 4.9 in the saliva for the patients in group A; furthermore, we detected abundant basophilic mucus that was proportional to the pH of the oral cavity.

The nasal cytology of this group was characterized by a minimum level of persistent inflammation and a reduction in negative ciliated cells, or cells that are above the core; a hyper-chromatic strip that we called the stria hyper-chromatic over-nuclear, which was selectively present in cells that were not affected by cell changes; an abundant presence of mucous-like cells; and an absence of bacteria and fungi. In only one case did we find eosinophilic and mast cell degranulation with super-imposed NARESMA (n*on-allergic rhinitis with eosinophils and mast cells)*, shown in the Figure 1. There were no differences between the two nostrils.

In group B, there were no interesting pathologies of the mucosa, and basophilic mucus was absent. The nasal pH ranges between pH 9 and pH 7, with an average of 7.85; the pH of the saliva ranged between pH 5 and pH 7, with an average of 6.5. There were no differences between the two nostrils examined (Figure 2).

Regarding the relationship between sinusitis and GERD [24,25], studies are conflicting, similar to those reporting the relationship between the nasal and pharyngeal pH [26]. Recent studies, however, seem to confirm the relationship between GERD and diseases of the upper airways, especially in terms of the nasal [27] and laryngeal [28] concentrations of pepsin.

Our study followed an approach based primarily on deductive clinical investigations because it is not always easy to obtain a deeper diagnosis via a pepsin test. The pH study mainly showed the net ratio of the nasal and oral pH. In fact, it was possible to note a tendency toward basicity in the nasal mucus and toward acidity in the saliva. This allows us to say that saliva, which normally has a pH between 7.0 and 7.2, is affected by acidic gastric juices in the presence of GERD. In terms of the basicity of the nose, which was documented inter alia in both the pH study and the nasal cytology, abundant mucus of the basic color (cyan) was detected in all patients. This difference between the pH values of the two areas is related to the fact that the nasal mucosa could function as a buffer after the acid stimulation of the esophagus, larynx, and pharynx districts. Regarding the allergy conditions, we detected abundant neutrophils, which protect against further damage to the epithelium of the nasal mucosa. In fact, neutrophils are known effects of the degradation of their factors, while the local immunological effects of NALT (nasal mucosa-associated lymphoid tissue immunology) and cytokines are little known. In the control group, a general hydrogenionic balance between the two districts was noted. The pH was likely to be physiological, which is associated with the absence of basophilic mucus (which we think may be an indicator of GERD at the microscopic level). In this group, a weekly acidic or basic pH can be linked to several factors that do not depend on reflux, such as the local anatomical variations.

These first results encourage further research on the relationship between pH changes in ENT and GERD areas, especially regarding the observation of cases with no history of allergy, GERD and borderline pH (pH 8 nasal and salivary 6) and the presence of mucus that tends toward the basic color. Periodic checks in these borderline cases will be needed to better assess the patient's clinical status.

VI. Conclusions

Our study allowed us to observe a strong correlation between the pH of saliva and the nasal cavities and the interaction between the two regions. This correlation could be the basis for a diagnosis of GERD, especially in primary health care clinics and in the initial stage of the disease. Based on our findings, a presumptive diagnosis of GERD requires a salivary pH less than or equal to 5, a nasal pH greater than or equal to 8 and the presence of basic nasal mucus. When the pH is borderline and the mucus tends toward a slight change in color from the baseline, the patient should be rechecked regularly, at least once a month, for further evaluation. The comparison of salivary pH with the nasal pH could be used as an additional element for recommending patients for pepsin and pH monitoring, thereby reducing costs for the NHS (National Health Service). The value of salivary analysis has long been ignored but is recently being recognized as a valid tool with diagnostic capabilities that allow doctors to frequently monitor patients and easily diagnose many diseases; consequently, this method will likely have a strong impact on future research and treatment. At present, we have promising preliminary results that show that saliva can be used to detect lung cancer, pancreatic cancer, breast cancer, and type II diabetes; however, each disease requires further scientific validation that compares the diagnostic capacity of saliva to other body fluids as references. Salivary diagnostics could play a key role in routine health monitoring in the near future and enable the early detection of diseases in a simple and effective manner.

VII. Tables And Figures

TABLE 1 : Criteria For Patient Recruitment (Left) And Exclusion (Right)

Patient inclusion criteria	**Patient exclusion criteria**
Medical history and positive diagnosis of GERD	The presence of oncological diseases
A history of rhinitis related to allergies to house dust mites, grasses and pellitory plants	Pharmacological treatment with antibiotics, steroids, proton pump inhibitors, antihistamines, cromolyn, anti-reflux medications, and prokinetics
Absence of significant abnormalities of the nasal cavity	Significant abnormalities of the nasal cavity
The absence of dental diseases	Improper dental hygiene
The exclusion of bacterial, fungal and viral infectious diseases of the upper airway	The presence of bacterial, fungal and viral infectious diseases of the upper airway
Non-smoking	The presence of dental disease
No pharmacological treatment with antibiotics, steroids, proton pump inhibitors, antihistamines, cromones , anti-reflux medications, or prokinetics	Smoking Pregnancy

FIG. 1 MMG . In 100x oil i FIG. 1 MMG . In 100x oil immersion.
Eosinophilic (RED ARROW) and mast cell degranulation (GREEN ARROW). (NARESMA superimposed).
The high content of basophilic (CYAN) cells found in patients with GERD can be observed

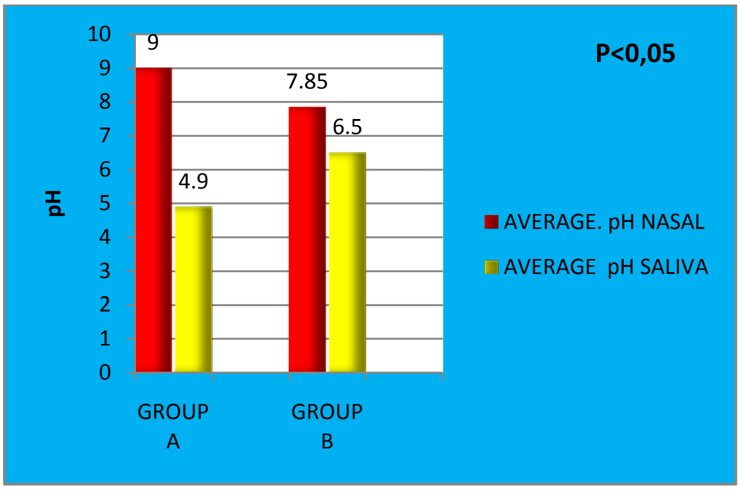

FIG.2 Variation in the average pH values of the examined districts. Right, GROUP A; left, GROUP B (control)

References

[1]. Garcia-Compean D., Gonzalez M.V., Galindo G., Mar D.A., Treviño J.L., Martinez R., Bosques F., Maldonado H. Prevalence of gastroesophageal reflux disease in patients with extraesophageal symptoms referred from otolaryngology, allergy, and cardiology practices: a prospective study Dig Dis 18(3), 2000,178-182

[2]. KatleE.J., Hatlebakk.J.G.,Steinsvag S. Gastroesophageal reflux and rhinosinusitis. Curr Allergy Asthma Rep 13 (2), 2013, 218-23

[3]. Hanna B.C., Wormald.P.J..Gastroesophageal reflux and chronic rhinosinusitis Curr Opin Otoryngol testacollo Surg 20 (1),2012, 15-8.

[4]. Lin Y.H. , Chang T.S., Yao Y.C., Li Y.C. Increased risk of chronic sinusitis in adults with gastroesophgeal reflux disease: a nationwide population-based cohort study. Medicine (Baltimore). 94(39) 2015,e1642.

[5]. Kahrilas.P.J., Lee T.J..Pathophysiology of gastroesophageal reflux disease Thorac Surg Clin 15,2015,323-333

[6]. Eckley C.A. ,Costa H.O. Comparative study of salivary pH and volume in adults with chronic laryngopharyngitis by gastroesophageal reflux disease before and after treatment Braz J Otorhinolaryngol.72(1),2006, 55-60

[7]. Skoner D.P., Gentile D.A., Fireman P., Cordoro K., GoyleW.J. Urinary histamine metabolite elevations during experimental influence infection. Ann Allergy Asthma Immunol 87(4),2001,303-306

[8]. Bechi P., Romagnoli P., Panula P., Dei R., Bacci.S,.Amorosi A, Masini E .Gastric mucosal histamine storing cells. Evidence for different roles of mast cells and enterochromaffin-li.ke cells in humans Dig Dis Sci . 40(10),1995,2207-2213

[9]. CarnevI.K., Gibson P.G.,Murree-Allen K.,Saltos.N.,.Olson.L.G.,Henslev M.J. A systematic evaluation of mechanisms in chronic cough. Am J Respir Crit Care Med 156(1),1997,211-216.

[10]. Costa H.O.,Neto O.M., Eckley C.A. Is there a relationship between the pH and volume of saliva and esophageal pH- metry results? Dysphagia 20,2005,175-181

[11]. Katz P.O. Ambulatory esophageal and hypopharyngeal pH monitoring in patients with hoarseness J Gastroenterol 85 **(1)**,1995, 38-40

[12]. Radu T. Update in the Diagnosis of Gastroesophageal Reflux disease J.Gastrointestin Liver Dis 15(3),2006, 243-247

[13]. Benett M.R.Non-adrenergic non-cholinergic (NANC) transmission to smooth muscle: 35 years on Prog Neurobiol. 52 (3**)**,1997, 159-195

[14]. Johnson L.F., Demeester T.R. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol. 62,1974,325-332

[15]. Hanson D.G., Jiang J.J. Diagnosis and management of chronic laryngitis associated with reflux. Am J Med 108 (4A),2000,112S-19S

[16]. Fraser A.G. Review article:gastro-oesophageal reflux and laryngeal symptoms Aliment Pharmacol Ther 8,1994, 265-72

[17]. Edgar W.M. Saliva: its secretion, composition and functions. Br Dent J 172,1992,305-312.

[18]. Kaufman E, Lamster I.B. The diagnostic applications of saliva: a review. Crit Rev Oral Biol Med 13,2002, 197-212.

[19]. Veerman E,C,, Valentijn-Benz M,, NieuwAmerongen A,V. Viscosity of human salivary mucins: effect of pH and ionic strength and role of sialic acid. J Biol Buccale 17,1989, 297-306.

[20]. Greabu M., Battino M., Mohora M., Totan A., Didilescu A., Spinu T., et al. Saliva-a diagnostic window to the body, both in health and in disease. J Med Life. 2, 2009,1 24–32.

[21]. Iorgulescu G. Saliva between normal and pathological. Important factors in determining systemic and oral health. J Med Life. 2, 2009, 303–7

[22]. Manjul T. Science behind human saliva J.Nat:Sc.Biol.Med. 2,2011,53-8

[23]. LeeY.H.,Wong D.T. Saliva: An emerging biofluid for early detection of diseases. Am J Dent. 22(4),2009, 241–248.

[24]. Satvinder Singh Bakshi, Chronic rhinosinusitis in gastroesophageal reflux disease, Am J Rhinology & Allergy 29 (6), 2015e225

[25]. Bohnhorst I., Jawa.D.S.,LangeB.,Kjeldsen.J., Hansen.J.M., Kjeldsen A.D. Prevalence of chronic rhinosinusitis in a population of patients with gastroesophageal reflux disease. Am J Rhinol Allergy29(3),2015,e70-4. doi: 10.2500/ajra.2015.29.4167

[26]. Subbotina M .V.,Temnikova I.V.,Onuchina E.V. pH values in the pharynx of the patients presenting with compromised nasal breathing of inflammatory and non-inflammatory genesis concomitant with gastroesophageal reflux disease Vestn Otorhinolaryngol 80(3),2015,35-39

[27]. Southwood J.E., Hoekzema C.R., Samuels T.L., Wells C., Poetker D.M., Johnston N., Loehrl T.A. The Impact of Pepsin on Human Nasal Epithelial Cells In Vitro: A Potential Mechanism for Extraesophageal Reflux Induced Chronic Rhinosinusitis, Ann OtolRhinolLaryngol. 124 (12),2015, 957-964. doi: 10.1177/0003489415593556

[28]. Johnston N ,Wells C.W.,Blumin J.H.,Toonill R.J.,Merati A.L. Receptor-mediated uptake of pepsin by laryngeal epithelial cells Ann Otol Rhin Laryngol 116 (12),2007,934-938