PROFESSOR JEROME RENE LECHIEN (Orcid ID : 0000-0002-0845-0845)

Article type : Our Experience

Alkaline, protein, low-fat and low-acid diet in laryngopharyngeal reflux disease: Our experience on 65 patients.

Jérôme R. Lechien, MD, PhD, MS[1-4], Kathy Huet, PhD[2], Mohamad Khalife, MD[3], Lisa G. De Marrez, MD[1], Camille Finck, MD, PhD[2,5], Bernard Harmegnies, PhD[2#], Sven Saussez, MD, PhD[1,3,4#]

Institutions:

1. Laboratory of Anatomy and Cell Biology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium.
2. Laboratory of Phonetics, Faculty of Psychology, Research Institute for Language sciences and Technology, University of Mons (UMons), Mons, Belgium.
3. Department of Otorhinolaryngology and Head and Neck Surgery, RHMS Baudour, EpiCURA Hospital, Baudour, Belgium.
4. Department of Otorhinolaryngology and Head and Neck Surgery, CHU Saint-Pierre, Faculté de medicine, Université Libre de Bruxelles, Bruxelles, Belgium.
5. Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Liege, Liege, Belgium.

# Contributed equally to this work and should be regarded as *joint last authors*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/coa.13269

Correspondence to:
Jay R. Lechien, M.D., M.S., Ph.D.,
Laboratory of Anatomy and Cell Biology, Faculty of Medicine, University of Mons (UMONS), Avenue du Champ de mars, 6, B7000 Mons, Belgium,
Email: jerome.lechien@umons.ac.be
Telephone fax: +32 65 37 35 84

Conflict of interest: none

Financial disclosure: none

Funding : This research has been subsidized by the ARC N°AUWB-2012-12/17-UMONS convention from Communauté Française de Belgique.

Key points:

-The respect of diet and lifestyle modifications could be associated with better improvement of laryngopharyngeal symptoms, perceptual dysphonia, and acoustic measurements.

-The potential positive impact of alkaline, protein, low-fat, low-acid diet could be explained by many physiological effects on esophageal sphincter tonicity, acid and pepsin productions, and gastric emptying time.

-Future controlled prospective studies are needed to confirm the potential key role of alkaline, protein, low-fat, low-acid diet and lifestyle modifications in the clinical improvement of patients with suspected LPR disease.

Keywords: laryngopharyngeal; reflux; laryngitis; voice; diet.

INTRODUCTION

Laryngopharyngeal reflux (LPR) is the back flow of gastric or duodenal contents into the laryngopharynx where it comes in contact with the tissues of the upper aerodigestive tract.[1] Approximately 10% of patients visiting Otolaryngology – Head and Neck Surgery departments would be concerned and LPR is involved in up to 75% of patients with refractory ear, nose, and throat

symptoms.[2,3] Many factors are involved in the development of LPR including anatomical (gastroeosophageal sphincter incompetence, hiatus hernia), histological (ectopic gastric mucosa in esophagus), and environmental (stress, diet, and lifestyle habits) considerations.[4] It has recently been suggested that diet and lifestyle habits could play a key role in the disease development.[5] Nowadays, LPR treatment is based on proton pump inhibitors (PPIs), diet and lifestyle modifications during a period of 3 to 6 months. Despite efficient treatment, the long-term control of LPR symptoms and signs still remains difficult with 25 to 50% of patients with chronic course.[1] To date, a very few number of studies interested to the impact of diet and lifestyle modifications on the improvement of symptoms, signs, and voice quality in LPR disease.[5-7] However, with regard to the significant risk of adverse effects and the increasing cost of long-term PPI prescription,[5,6,8] diet and lifestyle modifications remain an interesting way for short and long-term control of LPR, especially in patients with chronic course.

The aim of this study is to determine how a treatment based on PPIs, alkaline, protein, low-fat and low-acid diet improves LPR symptoms, findings, and voice quality in comparison with a PPI treatment without respect of diet.

MATERIALS AND METHODS

Ethical considerations

The ethical committee of EpiCURA Hospitals approved this retrospective study (reference: B707201524621).

Study design and patients

A retrospective medical chart review of patients who were diagnosed with LPR in three Hospitals (CHU Liege, EpiCURA Hospitals, Belgium) from 2013 to 2016 was performed. LPR diagnosis was based on positive pH impedance metry or the use of Reflux symptom score (RSI>13) and reflux finding score (RFS>7); which were associated with positive pH impedance metry result.[9] As described in a previous clinical study,[2] patients with cofactors able to bias the LPR clinical and voice quality evaluations were rigorously excluded.

According to a clinically validated protocol for the LPR management,[10] patients were treated by a 3 to 6 months course of pantoprazole (20mg twice daily), diet and lifestyle modifications. Precisely, patients received diet and behavioral recommendations in the form of a recommendation grid (Table 1). The diet was developed by a multi-disciplinary team composed of otolaryngologists, gastroenterologists, and nutritionists. Experts conducted a careful review of the composition (i.e. carbohydrates, lipids, proteins, pH) of the commonly consumed foods in Western Europe. According

to these compositions, experts analyzed the impact of foods on gastroeosophageal physiology to identify those that lead to gastroeosophageal dysfunction (i.e. increased pepsin and acid secretion; slowing digestion; and esophageal sphincter dysfunction). Adherence to diet recommendations was weekly assessed by the patient throughout the therapeutic course using a point scale ranging from 0 (non-adherent) to 10 (fully adherent). At the end of the treatment, physician and patient reviewed the adherence to PPIs and diet. Patients who did not have to respect the PPI intake were excluded. According to the median calculating, two groups were isolated from the respect of diet and lifestyle modifications (group 1: full respect; group 2: non-compliance of diet and lifestyle modifications).

Clinical and voice quality outcomes

The tools used to assess symptoms and signs of reflux were RSI and RFS.[9] Patients fulfilled RSI at baseline and 3 months after the start of treatment. An experienced laryngologist (MK) rated RFS using videolaryngostroboscopy in a blind manner in regard to the patient complaints (RSI). Patients completed the Voice Handicap Index (VHI) throughout therapeutic course. The perceptual voice quality (grade of dysphonia, roughness, and breathiness, (GRB scale)) was performed by 3 experienced speech therapists (with previously described good interrater reliability).[2] Judges were blinded in regard to the time of the recording (baseline *versus* posttreatment). At baseline and posttreatment, patients produced 3 sustained /a/ to measure acoustic parameters using MDVP software (KayPentax®, NJ, USA). We collected acoustic data to compare the evolution of percent jitter, percent shimmer, and noise-to-harmonic ratio according to the respect of diet.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS version 22.0; IBM Corp. Armonk, NY). To assess changes in RSI, RFS, VHI, perceptual voice assessments, and acoustic measurements (within-subject factors) between the two groups of patients (between-subjects factor), mixed ANOVAs were performed. A level of significance of 0.05 was adopted. When the Sphericity condition has not been met (significant Mauchly's test), the Greenhouse-Geisser correction was used.

RESULTS

A total of 65 patients were included in this retrospective study. There were 26 patients in group 1 (16 females) and 39 in group 2 (18 females). The mean age of patients in each group was 50.3±15.4 and

52.4±17.6 years old respectively. At baseline, the characteristics of both groups were similar according to age, gender, RSI, RFS, VHI, GRB, and acoustic measurements ($p>0.05$).

At the end of the treatment, RSI, and RFS significantly improved in both groups (Tables 2 and 3). However, according to our mixed statistical design, the improvement of RSI was significantly better in patients who respected diet (group 1) in comparison with patients who did not respect diet (group 2) with $p=0.001$. Excess throat mucus and postnasal drip ($p=0.003$), coughing after eating or after lying down ($p=0.015$), and troublesome cough ($p=0.013$) better improved in group 1 in comparison with group 2. About LPR findings, we found a trend improvement of the scores of ventricular obliteration ($p=0.05$) and posterior commissure hypertrophy ($p=0.06$) in group 1 in comparison with group 2.

With regard to the evolution of subjective voice quality; VHI total score, grade of dysphonia, roughness, and breathiness significantly improved in both groups (Table 2). The improvement of grade of dysphonia ($p=0.010$) was better in group 1 than group 2. The mean values of acoustic measurements (i.e. percent jitter and percent shimmer) significantly improved in group 1. We did not find statistical acoustic improvement in group 2. The pattern of evolution of acoustic parameters according to the group, and the posttreatment comparison of RSI total and item scores between groups are described in Figure 1.

DISCUSSION

Our results demonstrate that treatment with PPI therapy, alkaline, protein, low-acid and low-fat diet is significantly more effective than PPI therapy alone on laryngopharyngeal symptoms and voice quality. These observations can be explained by the multi-tiered impact of foods composing our diet on gastroeosophageal physiology.

First, some studies have found an association between LPR and abnormalities of the tonicity of lower (LES) and/or upper esophageal sphincter (UES).[8,11] Precisely, the occurrence of transient LES and UES relaxations may be an important causative factor of reflux in a large number of LPR patients.[8,11] The consumption of high protein foods improves the tonicity of both LES and UES while carbonated beverages, caffeine, alcohol, fat, and tobacco are known to decrease the sphincter tonicity that promotes LPR and GERD.[8] Second, it has been demonstrated that the development of LPR signs and symptoms is due to the presence of tissue-bound pepsin in the upper aerodigestive tract mucosa that causes depletion of protective cell proteins or mucus, microtraumatisms of the epithelium, and local inflammatory reaction.[5,12] Pepsin has a maximal activity at pH 2.0.[5] Based on these findings summarized in recent reports,[5,12] we have postulated that the intake of acidic foods significantly contributes to the reduction of gastric pH and the occurrence of related reflux episodes. Thus, the reduction of consumption of some acidic foods (i.e. spicy, caffeine, beer, chocolate, etc.), the intake

of alkaline water, as well as the modifications of some lifestyle habits (tobacco, stress) may significantly increase the pH of refluxed episodes and the related pepsin activity. Third, it has long been recognized that fatty foods and some uncooked vegetables take longer to digest and the delayed gastric emptying time inevitably increases both number and duration of reflux episodes.[8] The digestion process also depends of cooking food. With regard to the pH modification of some acidic foods cooked with water (pH increase), it could be useful to cook acidic vegetables (i.e. onions, beans, lentils) than to consume them raw. Fourth, esophageal motility is another important defensive mechanism against reflux since it allows, in a first phase, rapid elimination of refluxed gastroduodenal contents of the esophagus, and, in a second phase, the neutralization of residual refluxed content by bicarbonate in saliva.[8] In that respect, the acidification or the lack of saliva may favor the LPR development. Whenever possible, we carefully excluded drugs associated with modification of the saliva production. Figure 2 summarizes the impact of diet on gastroeosophageal physiology.

The main limitation of this retrospective study is the low number of patients that limits us in the highlighting of additional significant clinical and voice quality differences between groups. Moreover, it would have been interesting to have a control group of LPR patients treated with diet without PPIs.
It is important to bear in mind that our diet recommendations were established on Western European dietary and lifestyle habits and we did not include many foods usually consumed in other regions of the world. The establishment of adapted recommendations taking into account the local characteristics of diet makes sense by region. Thus, we could expect to treat some mild and moderate LPR with diet and lifestyle modifications; making substantial drugs economy.

CONCLUSION

Many physicians only prescribe PPIs without consideration for diet and lifestyle changes. The results of this retrospective study support that the addition of diet and lifestyle modifications significantly improves the curative effect of PPIs, especially on laryngeal symptoms, roughness, and acoustic measurements. Further prospective studies are needed to better identify the pathophysiological mechanisms underlying the development of LPR according to the diet.

References:

1. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991; 101(4 Pt 2 Suppl 53):1-78.
2. Lechien JR, Finck C, Khalife M, Huet K, Delvaux V, Picalugga M, Harmegnies B, Saussez S. Change of signs, symptoms and voice quality evaluations throughout a 3- to 6-month empirical treatment for laryngopharyngeal reflux disease. *Clin Otolaryngol*. 2018.
3. Sen P, Georgalas C, Bhattacharyya AK. A systematic review of the role of proton pump inhibitors for symptoms of laryngopharyngeal reflux. *Clin Otolaryngol*. 2006; 31(1):20-4; discussion 24.
4. Saruç M, Aksoy EA, Vardereli E, Karaaslan M, Ciçek B, Ince U, Oz F, Tözün N. Risk factors for laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol*. 2012; 269(4):1189-94.
5. Koufman JA. Low-acid diet for recalcitrant laryngopharyngeal reflux: therapeutic benefits and their implications. *Ann Otol Rhinol Laryngol*. 2011; 120(5):281-7.
6. Yang J, Dehom S, Sanders S, Murry T, Krishna P, Crawley BK. Treating laryngopharyngeal reflux: Evaluation of an anti-reflux program with comparison to medications. *Am J Otolaryngol*. 2018; 39(1):50-55.
7. Zalvan CH, Hu S, Greenberg B, Geliebter J. A Comparison of Alkaline Water and Mediterranean Diet vs Proton Pump Inhibition for Treatment of Laryngopharyngeal Reflux. *JAMA Otolaryngol Head Neck Surg*. 2017; 143(10):1023-1029.
8. Ducrotté P, Chaput U. Pathophysiology of gastro-œsophageal reflux. *EMC-Hepato-gastroenterol*. 2005 ; 362-369.
9. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice*. 2002; 16(2):274-7.
10. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA*. 2005; 294(12):1534-40.
11. Benjamin T, Zackria S, Lopez R, Richter J, Thota PN. Upper esophageal sphincter abnormalities and high-resolution esophageal manometry findings in patients with laryngopharyngeal reflux. *Scand J Gastroenterol*. 2017; 52(8):816-821.
12. Lechien JR, Saussez S, Harmegnies B, Finck C, Burns JA. Laryngopharyngeal Reflux and Voice Disorders: A Multifactorial Model of Etiology and Pathophysiology. *J Voice*. 2017; 31(6):733-752.

Figure 1: Clinical and acoustical differences in LPR patients according to the respect of diet.

Figure 1 footnotes: At 3 months posttreatment, patients who respected diet and lifestyle modifications (Group 1) had less laryngopharyngeal symptoms (RSI), especially throat clearing, heartburn, and globus sensation than patients who did not respect diet and lifestyle modifications (Group 2). From baseline to posttreatment time, patients of group 1 had significant improvement of both percent jitter and percent shimmer. Acoustic measurements did not change in patients of group 2.

Figure 2: Summarize of the diet effect on gastroeosophageal functioning.

Figure 2 footnotes: Foods that contribute to the effective gastroeosophageal functioning are marked in green. Foods that alter the effective gastroeosophageal functioning are marked in red.

Table 1: Recommendation grid (diet and lifestyle modifications).

Lifestyle habits	**Foods to favor**	**Foods to avoid**
1. Stress control 2. Tobacco & other addiction(s) reduction 3. Reduction of size of meals 4. Hot lunch in place of hot diner 5. Eat slowly 6. Do not talk while eating 7. Avoid tight clothing 8. If possible avoid the following drugs: *Non steroidal anti-inflammatory drugs* *Corticosteroids, aspirin, theophylline,* *Progesterone, iron supplementation,* *Calcium channel blockers*	1. Meat, fish, chicken, eggs Fresh & thin fish Shrimps, lobster, shellfishs Chicken fillet (without skin) Turkey (without skin & fat) Duck (without skin & fat) Low fat meat* *-Veal cutlet, pork tenderloin,* *-Rindless, fatless, cooked ham* *-Steak, fillet, striploin* *-Roast veal, veal chop, horse* *Remove fat from meat Egg white Other:……..	1. Meat, fish, chicken, eggs Fat fish, fish oil (sardines, cods, herrings) Fat chicken High-fat meat* *-kidneys, bacon, ground meat,* *-Pâté, tripes, lamb* *-Lamb chops, shoulder or legs of lamb* *-Ribs, rib steak* *-Pork chops, roast, and shoulder* *-Foie gras* Delis, sausage, salami Other:……..
If heartburn 1. Reduction of overweight 2. Elevating the head of the bed	2. Dairy products Low-fat cheese Skim milk Other:……..	2. Dairy products Chocolate, ice cream, whole milk Hard cheese, full-fat cheese *-Goat cheese, cheddar, Roquefort,* *-Fontina, gruyere, parmesan, munster, etc.* Other:……..
Laryngopharyngeal reflux treatment Drug: …… To take: before - during - after Meals (circle the adequate response): -Breakfast	3. Cereals & Starches Oat, wheat, cracker, pasta, Wholemeal bread, brown bread, Boaled potatoes, rice, brown rice Other:…….. 4. Fruit & vegetables Agave, asparagus, Banana, melon Broccoli, celery, fennel Cooked mushrooms	3. Cereals & Starches Chocolate cookies, peanut, white bread, French fries & frying Nut, cashew, hazelnut Other:…….. 4. Fruit & vegetables Shallot Spicy Onion Chilli

-Lunch -Diner	Cauliflower, green beans, ginger Turnip, parsley, tofu Other:…….. Preparation: Cooked by steaming or boiling in water	Tomato (sauce or raw tomato) Other:……..
Drug: …… To take: before - during - after Meals (circle the adequate response): -Breakfast -Lunch -Diner	5. Beverage Chamomile Water, alkaline water Appel/pear juices (no sugar added) Melon/banana juices (no sugar added) Other:…….. 6. Greasy substances Olive oil Other:…….. 7. Sugar Honey	5. Beverage Strong alcoho, red & rosé wines Sparkling beverage (water, soda, beer, etc.) Coffee, tea Citrus juices (orange, lemon, grapefruit) Other:…….. 6. Greasy substances Butter, spicy oils Sauces (mayonnaise, mustard, ketchup, etc.) Other:…….. 7. Sugar Sweets

Table 1 footnotes: Diet and lifestyle modifications.

Table 2: Reflux symptom index; reflux finding score; subjective and objective voice quality evolutions in patients treated by proton pump inhibitors and diet (mean values ± standard deviation).

	Group 1: PPIs + Diet			Group 2: PPIs		
Scales	Pretreatment	Posttreatment	p-value	Pretreatment	Posttreatment	p-value
Reflux Symptom Index	23.50 ± 6.95	5.73 ± 3.94	0.001	21.38 ± 6.15	11.23 ± 6.58	0.001
Voice problem	3.19 ± 1.88	1.12 ± 1.24	0.001	2.59 ± 1.55	1.56 ± 1.39	0.011
Throat clearing	3.35 ± 2.10	1.16 ± 1.43	0.001	3.67 ± 1.56	2.26 ± 1.46	0.001
Postnasal drip	3.19 ± 1.79	0.88 ± 1.20	0.001	2.23 ± 1.95	1.44 ± 1.59	0.024
Dysphagia	1.42 ± 1.70	0.40 ± 1.08	0.009	1.51 ± 1.60	0.41 ± 1.02	0.001
Coughing post-eating & lying down	2.50 ± 2.18	0.48 ± 0.92	0.001	1.51 ± 1.75	0.74 ± 1.43	0.014
Breathing difficulties	1.50 ± 1.77	0.40 ± 0.91	0.001	1.62 ± 1.76	0.87 ± 1.40	0.017
Troublesome cough	2.85 ± 1.99	0.36 ± 0.75	0.001	2.13 ± 1.82	0.95 ± 1.21	0.001
Globus pharyngeus	2.46 ± 1.99	0.44 ± 0.92	0.001	2.87 ± 1.81	1.46 ± 1.58	0.001
Pyrosis, heartburn & chest pain	2.88 ± 1.95	0.52 ± 0.92	0.001	3.28 ± 1.73	1.46 ± 1.62	0.001
Reflux Finding Score	11.42 ± 3.16	4.85 ± 3.80	0.001	10.38 ± 1.78	5.15 ± 2.99	0.001
Subglottic edema	0.15 ± 0.54	0.01 ± 0.01	0.157	0.06 ± 0.13	0.01 ± 0.01	0.317
Ventricular obliteration	1.46 ± 1.66	0.56 ± 1.28	0.012	0.92 ± 1.20	0.67 ± 1.16	0.197
Arytenoid/diffuse redness	3.15 ± 1.01	1.60 ± 1.29	0.001	2.97 ± 1.11	1.38 ± 1.23	0.001
Vocal folds edema	1.42 ± 0.90	0.32 ± 0.48	0.001	1.21 ± 0.77	0.54 ± 0.64	0.001
Diffuse laryngeal edema	1.27 ± 0.96	0.28 ± 0.68	0.001	1.10 ± 0.97	0.54 ± 0.76	0.004
Posterior commissure hypertrophy	2.15 ± 0.78	1.44 ± 0.92	0.002	2.21 ± 0.66	1.05 ± 0.76	0.001
Granuloma/Granulation	0.58 ± 0.90	0.24 ± 0.66	0.086	0.51 ± 0.89	0.31 ± 0.73	0.206
Endolaryngeal mucous	1.23 ± 0.99	0.48 ± 0.87	0.008	1.44 ± 0.91	0.67 ± 0.96	0.001
Subjective voice quality						
Voice Handicap Index	19.15 ± 17.13	9.46 ± 11.20	0.001	17.11 ± 11.95	10.84 ± 8.86	0.001
Grade of dysphonia	1.54 ± 0.58	0.58 ± 0.50	0.001	1.44 ± 0.55	0.90 ± 0.72	0.001
Roughness	1.23 ± 0.71	0.42 ± 0.58	0.001	1.33 ± 0.70	0.90 ± 0.75	0.001
Breathiness	0.96 ± 0.66	0.38 ± 0.57	0.001	0.77 ± 0.74	0.44 ± 0.72	0.007
Acoustic parameters						
Percent jitter	2.61 ± 1.43	2.11 ± 1.25	0.028	2.54 ± 1.45	2.55 ± 2.88	0.141
Percent shimmer	7.30 ± 3.27	5.99 ± 2.31	0.014	6.82 ± 2.47	6.85 ± 3.87	0.538
Noise-to-harmonic ratio	0.19 ± 0.06	0.17 ± 0.04	0.357	0.19 ± 0.07	0.19 ± 0.12	0.627

Table 2 footnotes: PPIs = proton pump inhibitors. The pre- to post- statistical analysis was performed using mixed ANOVAs.