Impact of Acid, Weakly Acid and Alkaline Laryngopharyngeal Reflux on Voice Quality

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Summary: Objectives. To analyze pre to posttreatment voice changes regarding the type of reflux in patients with acid, weakly acid or alkaline laryngopharyngeal reflux (LPR).

Methods. Patients with LPR, diagnosed using hypopharyngeal-esophageal multichannel intraluminal impedance pH-monitoring (HEMII-pH), were prospectively recruited from three University Hospitals. Patients were treated with a combination of diet, proton pump inhibitors, magaldrate and alginate for 3 months. The following clinical and voice quality outcomes were studied pre to posttreatment according to the type of reflux (acid, weakly acid, nonacid): HEMII-pH, gastrointestinal endoscopy features, reflux symptom score (RSS), reflux sign assessment (RSA), voice handicap index (VHI), perceptual voice assessment (grade of dysphonia and roughness), aerodynamic and acoustic measurements.

Results. From December 2018 to March 2021, 160 patients completed the evaluations, accounting for 60 acid, 52 weakly acid, and 48 alkaline cases of LPR. There were no baseline differences in clinical and voice quality outcomes between groups. RSS and RSA significantly improved from pre to posttreatment in the entire cohort and in all patient groups. VHI, dysphonia and roughness, maximum phonation time, Jitter, Shimmer and noise to harmonic ratio significantly improved from pre to posttreatment. Individuals with alkaline reflux reported better voice quality improvements as compared to acid and weakly acid reflux patients.

Conclusion. Patients with acid and alkaline reflux reported better posttreatment voice quality outcomes as compared to weakly acid reflux patients. Future basic science and clinical studies are needed to better understand the histological changes of the vocal folds due to reflux of varying pH types and gastroduodenal enzyme content.

Key Words: Reflux—Laryngopharyngeal—Gastroesophageal—Voice—Acoustic—Dysphonia.

INTRODUCTION

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effects of gastroduodenal contents suspended in liquid of variable pH. These enzymes and salts induce morphological changes in the upper aerodigestive tract.[1] LPR-related symptoms occurs in 10% to 30% of patients who visit otolaryngology clinics and up to 55% of patients with dysphonia.[1,2] The voice symptoms are various chronic or intermittent combinations of hoarseness, vocal breaks, vocal effort or vocal fatigue.

Pepsin, a proteolytic digestive enzyme, plays a key pathophysiologic role in the development of macroscopic and microscopic histological changes on the vocal folds.[3,4] In an acidic environment, pepsin is able to alter defense mechanisms of the vocal folds, including those of mucin production, type III anhydrase carbonic activity and growth factor secretion. These changes may favor the development of epithelial cell dehiscence, microtraumas, inflammatory infiltrate and macroscopic lesions.[3-5] Clinically, these pepsin-mediated histological changes are associated with perceptual, aerodynamic and acoustic voice quality impairments that have been identified in some clinical studies.[3,6-8]

The majority of basic science and clinical studies have previously focused on pepsin in acid-only reflux environments that was identified with pH-only (non-impedance) monitoring.[1] However, the recent development of hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) affords the identification of weakly acid and alkaline refluxate that make up more than 50% of cases of LPR.[9,10] The effects of acid, weakly acid and alkaline LPR, or the prevalence of gastroesophageal reflux disease as a comorbidity to LPR, may cause different physical laryngeal changes.[9,10] To date, no study has investigated the potential voice quality differences and

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outcomes, pre to posttreatment, between patients with acid, weakly acid or alkaline LPR using subjective and objective evaluations.

In this study, pre and posttreatment subjective and objective voice measures were evaluated in patients grouped according to the pH "type" of reflux (acid, weakly acid or alkaline) based on HEMII-pH testing. In addition, the usefulness of aerodynamic and acoustic measurements as outcomes of treatment efficacy in LPR patients was investigated.

METHODS

From December 2018 to March 2021, 198 patients with a positive diagnosis of LPR after 24-hour HEMII-pH testing were prospectively recruited from three University European hospitals (Foch Hospital, Paris, France; Cesar de Pape Hospital and CHU Saint-Pierre, Brussels, Belgium). The LPR diagnosis was based on prior studies evaluating LPR treatment outcomes and is defined as the presence of LPR-related symptoms[1] and ≥1 hypopharyngeal reflux events (HRE) seen on HEMII-pH testing while the patient was off acid suppressive medication.[11] Gastrointestinal (GI) endoscopy was performed on patients with gastroesophageal reflux disease (GERD)-related symptoms or older patients (>55 yo) at baseline. Patients were excluded if they were an active smoker, alcoholic, had a history of upper respiratory tract infection within the last month, comorbid neurologic or psychiatric illness, current or prior head and neck malignancy and/or head and neck radiotherapy, were using inhaled corticosteroids, or had active seasonal allergies or asthma. Patients who did not report significant medication adherence were excluded. Patients had to consent to participate to the study (IRB-CHU Saint-Pierre, Brussels, n° BE076201837630).

Hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing

The HEMII-pH catheter placement and composition are reported in previous studies.[10,12] Brieflly, the probe is composed of 8 impedance ring pairs and 2 pH electrodes (Versaflex Z, LPR ZNID22+8R FGS 9000-17; Digitrapper pH-Z testing System, Medtronic, Hauts-de-France, France). The catheter is introduced transnasally. Six impedance rings are placed below the upper esophagus sphincter (UES). Two additional impedance rings are placed 1 and 2 cm above the UES in the hypopharynx. Two pH electrodes were placed 2-5 cm above LES and 1-2 cm above UES. The HEMII-pH is started in the morning at rest (8:00 AM). A HRE was defined as an episode that reaches two hypopharyngeal impedance sensors. A LPR diagnosis is given if ≥1 acid or nonacid HRE are identified.

An acid LPR event was defined as a HRE having pH≤4.0. A nonacid LPR event was defined as a HRE being pH >4.0. The HEMII-pH tracing was electronically analyzed by the software and the result was verified or updated by two senior physicians (JRL and VM). As previously reported,[10] a patient was designated as having acid LPR when the ratio of number of acid HRE/number of nonacid HRE was >2. LPR was defined as nonacid or alkaline when the ratio of number of acid HRE/number of nonacid HRE was <0.5. A patient was categorized as having mixed or weakly acid reflux when the same ratio ranged from 0.51 to 2.0. A GERD diagnosis was based on a DeMeester score >14.72 or >4.0% of the 24-hour recording time spent below pH 4.0 in the lower pH sensor.[13]

Treatment

HEMII-pH findings were used to determine personalized treatments for each patient.[10] First line treatment included an anti-reflux diet, and a combination of proton pump inhibitors (PPIs, Pantoprazole 20 mg in the morning, fasting) and post meal alginate (Gaviscon Advance thrice daily, Reckitt Benckiser, Slough, UK) or magaldrate (Riopan thrice daily, Takeda, Zaventem, Belgium) for 3 months. This treatment regimen was based on a previous study demonstrating the effectiveness of personalized LPR treatment based on HEMII-pH findings.[10] A summary of therapeutic approach is available in Appendix 1.

The anti-reflux diet consisted of a validated European diet based on the consumption of high-protein, low-fat, alkaline, plant-based foods and beverages.[14] In addition, patients were instructed to avoid caffeine, sparkling beverages and alcohol, all of them being suspected to impair the LES tonicity.[14] This diet was also used in patients with alkaline LPR regarding the impact of low-fat and high-protein foods in esophageal motility and sphincter tonicity. Indeed, proteins are known to increase the LES and UES tonicity, while fats are associated with slower gastric emptying time and a related higher risk of both transient sphincter insufficiency and reflux events.[14] Specifically, subjects with acid LPR were treated with pantoprazole and post meal alginate. Nonacid LPR patients were given post meal magaldrate or alginate as a sole agent. Patients with weakly acid LPR received a combination of pantoprazole and post meal alginate or magaldrate if they did not respond to alginates alone. Patients with nighttime alkaline reflux identified on HEMII-pH testing received additional alginate or magaldrate at bedtime.

Clinical and voice quality evaluations

The pre to posttreatment symptom changes were assessed with the Reflux Symptom Score (RSS).[15] Findings were rated with the Reflux Sign Assessment (RSA) in a blind manner by two laryngologists using videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany).[16] Patient adherence to both diet and medication were assessed through a 10-point Likert scale, ranging from 0 (= no adherence) to 10 (= perfect adherence).

The subjective voice quality outcomes were obtained using the French versions of the voice handicap index (VHI)[17] and the GRBAS scale.[18] Aerodynamic and acoustic

measurements were measured on the production of the vowel /a/, twice, at a distance of 30 cm from the microphone in a sound-attenuated room. Maximum phonation time (MPT) consisted of the longest sustained vowel. Acoustic parameters were measured with MDVP software (KayPentax, NJ). The following acoustic measurements were obtained: jitter, shimmer and noise to harmonic ratio (NHR). The acoustic parameters were taken from the entire signal of the two sustained vowel productions with the exclusion of the first and the last second of the vowel due to expected instability.

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 27.0; IBM Corp, Armonk, NY). The statistical analyses were performed for the entire cohort and for the following patient groups: acid, weakly acid and non-acid LPR patients. Kruskal-Wallis and Mann-Whitney U tests were used for the group comparison, while Chi square was used to compare the dichotomic outcomes. The pre to posttreatment changes were assessed with the Wilcoxon signed-rank test. A level of significance of $P < 0.05$ was used.

RESULTS

A total of 160 patients completed the study. Thirty-eight patients were excluded because incomplete evaluations or lost to follow-up. There were 90 (56.3%) females. The mean age of patients was 50.2 ± 15.3 yo. The study included 60 (37.5%), 52 (32.5%), and 48 (30%) patients with acid, weakly acid and alkaline LPR. The epidemiological and clinical outcomes are described in Table 1. Hiatal hernia was significantly more prevalent in acid LPR. Groups were comparable in age, body mass index, stress level, baseline RSS sub- and total scores, RSA sub- and total scores, VHI, GR, MPT and acoustic measurements.

Otolaryngologic, digestive, respiratory and total RSS scores significantly improved from baseline to 3-month posttreatment in all patients (Table 2), as well as in patients with acid (Table 3), weakly acid (Table 4), and alkaline (Table 5) LPR. Similar findings were observed for pharyngeal, laryngeal and total RSA scores. The adherence to diet and medication was similar across groups, ranging from 6.75 to 8.19/10.

TABLE 1.
Epidemiological and Clinical Data of Patients Regarding Their Weight

Characteristics	Acid (N = 160)	Acid (N = 60)	Weakly acid (N = 52)	Alkaline (N = 48)	*P*-value
Age	50.2 ± 15.3	50.0 ± 13.8	49.8 ± 16.5	52.0 ± 16.1	NS
Gender					
Male	70 (47.3)	21 (35.0)	28 (53.8)	21 (43.8)	NS
Female	90 (56.3)	39 (65.0)	24 (46.2)	27 (56.2)	NS
Level of stress (Likert Scale/10)	7.5 ± 2.3	7.5 ± 2.3	6.2 ± 2.7	6.6 ± 2.7	NS
Gastrointestinal endoscopy	N = 108	N = 47	N = 38	N = 23	
Normal	17 (15.7)	6 (12.8)	4 (10.5)	7 (30.4)	NS
Esophagitis	42 (38.9)	21 (44.7)	15 (39.5)	6 (26.1)	NS
Hiatal hernia	27 (25.0)	16 (34.0)	9 (23.7)	2 (8.7)	0.041
LES insufficiency	39 (36.1)	21 (44.7)	13 (34.2)	5 (21.7)	NS
Gastritis	46 (42.6)	18 (38.3)	17 (44.7)	11 (47.8)	NS
Helicobacter Pylori	8 (7.4)	4 (8.5)	4 (10.5)	0 (0)	NS
HEMII-pH feature (m ± SD)					
Pharyngeal acid reflux episodes	18.0 ± 16.4	28.4 ± 17.2	19.2 ± 12.6	4.5 ± 6.5	0.001
Pharyngeal nonacid reflux episodes	12.9 ± 14.9	6.6 ± 5.6	16.7 ± 13.4	16.3 ± 20.8	0.004
Pharyngeal reflux episodes upright	30.1 ± 23.7	28.2 ± 19.5	28.6 ± 20.4	33.8 ± 30.3	NS
Pharyngeal reflux episodes supine	6.2 ± 10.0	7.3 ± 12.7	6.5 ± 8.4	4.5 ± 7.9	NS
Total number of pharyngeal reflux episodes	36.4 ± 25.6	36.0 ± 22.3	36.5 ± 23.5	36.9 ± 31.4	NS
GERD (N)	N = 66	N = 42 (70.0)	N = 17 (32.7)	N = 7 (14.6)	0.001
Percentage of time with distal pH<4	7.4 ± 13.0	14.9 ± 17.6	3.5 ± 5.2	1.4 ± 2.7	0.001
DeMeester score	26.8 ± 39.8	49.2 ± 52.2	14.0 ± 20.2	6.9 ± 12.2	0.001
Reflux symptom score	116.1 ± 70.6	126.9 ± 76.2	109.3 ± 73.0	110.5 ± 60.3	NS
Reflux sign assessment	28.1 ± 8.4	27.9 ± 7.9	28.0 ± 8.1	28.3 ± 9.5	NS

Statistics were performed with Mann-Whitney and Kruskal-Wallis tests.
Abbreviations: GERD, gastroesophageal reflux disease; HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing; LES, lower esophageal sphincter; LPR, laryngopharyngeal reflux; NS, non significant.

TABLE 2.
Pre to Posttreatment Clinical and Subjective and Objective Voice Quality Changes in the Entire Cohort

Outcomes	Pretreatment	Posttreatment	*P*-value
Reflux symptom score			
Otolaryngological score	58.5 ± 38.1	35.2 ± 36.7	0.001
Digestive score	39.9 ± 32.3	21.8 ± 27.5	0.001
Respiratory score	17.7 ± 20.8	9.4 ± 15.5	0.001
RSS - score total	116.1 ± 70.6	66.4 ± 67.4	0.001
Reflux sign assessment			
Oral score	5.5 ± 2.4	4.6 ± 2.3	0.010
Pharyngeal score	10.1 ± 4.4	7.4 ± 3.8	0.001
Laryngeal score	13.2 ± 5.2	7.2 ± 4.7	0.001
RSA - total score	28.1 ± 8.4	19.2 ± 7.4	0.001
Subjective voice quality			
Voice Handicap Index	15.5 ± 19.3	10.9 ± 17.6	0.001
Perceptual voice quality			
Grade of dysphonia	1.1 ± 0.5	0.9 ± 0.5	0.001
Roughness	0.9 ± 0.7	0.7 ± 0.7	0.002
Breathiness	0.5 ± 0.7	0.4 ± 0.7	NS
Aerodynamic: MPT	14.6 ± 7.0	16.4 ± 7.2	0.001
Acoustic measurements			
Jitter	2.3 ± 1.6	1.9 ± 1.2	0.006
Shimmer	6.6 ± 3.1	5.7 ± 2.3	0.002
NHR	0.2 ± 0.1	0.2 ± 0.1	NS

Abbreviations: MPT, maximum phonation time; NS, non significant; RSA, reflux sign assessment; RSS, reflux symptom score; VHI, voice handicap index.

VHI, grade of dysphonia and roughness significantly improved from baseline to 3-months posttreatment in the entire cohort (Table 2). Among subgroups, the improvement of VHI, grade of dysphonia and roughness depended on the type of LPR. VHI significantly improved in patients with acid and alkaline LPR but not in patients with weakly acid LPR (Tables 3, 4 and 5). Patients with acid LPR reported improvements of dysphonia scores (Table 2), while the dysphonia and the roughness scores significantly decreased in patients with alkaline LPR (Table 5).

TABLE 3.
Pre to Posttreatment Clinical and Subjective Voice Quality Changes in Patients With Acid Reflux

Outcomes	Pretreatment	Posttreatment	*P*-value
Reflux symptom score			
Otolaryngological score	62.6 ± 40.9	33.1 ± 38.6	0.001
Digestive score	47.1 ± 34.4	25.3 ± 31.1	0.001
Respiratory score	17.3 ± 20.6	9.8 ± 17.2	0.008
RSS - score total	126.9 ± 76.2	68.3 ± 78.9	0.001
Reflux sign assessment			
Oral score	5.8 ± 2.2	4.3 ± 1.9	0.027
Pharyngeal score	10.0 ± 4.5	7.0 ± 3.7	0.001
Laryngeal score	13.3 ± 5.2	6.7 ± 4.5	0.001
RSA - total score	27.9 ± 7.9	18.2 ± 7.4	0.001
Subjective voice quality			
Voice Handicap Index	19.0 ± 20.1	8.1 ± 13.8	0.005
Perceptual voice quality			
Grade of dysphonia	1.2 ± 0.5	0.9 ± 0.4	0.007
Roughness	0.9 ± 0.6	0.7 ± 0.6	NS
Breathiness	0.7 ± 0.8	0.4 ± 0.6	NS
Aerodynamic: MPT	13.6 ± 6.1	15.3 ± 6.2	0.020

Abbreviations: MPT, maximum phonation time; NS, non significant; RSA, reflux sign assessment; RSS, reflux symptom score; VHI, voice handicap index.

TABLE 4.
Pre to Posttreatment Clinical and Subjective Voice Quality Changes in Patients With Weakly Acid Reflux

Outcomes	Pretreatment	Posttreatment	*P*-value
Reflux symptom score			
Otolaryngological score	51.9 ± 36.2	39.3 ± 39.5	0.007
Digestive score	37.3 ± 33.6	22.0 ± 26.5	0.001
Respiratory score	20.3 ± 22.3	9.7 ± 14.2	0.001
RSS - score total	109.3 ± 73.0	71.0 ± 65.9	0.001
Reflux sign assessment			
Oral score	5.0 ± 2.6	4.8 ± 2.5	NS
Pharyngeal score	10.6 ± 4.2	8.5 ± 3.7	0.001
Laryngeal score	13.1 ± 4.7	7.7 ± 5.3	0.001
RSA - total score	28.0 ± 8.1	20.8 ± 7.8	0.001
Subjective voice quality			
Voice Handicap Index	12.7 ± 17.1	14.1 ± 21.7	NS
Perceptual voice quality			
Grade of dysphonia	1.2 ± 0.5	1.0 ± 0.5	0.012
Roughness	1.0 ± 0.7	0.9 ± 0.8	NS
Breathiness	0.4 ± 0.6	0.4 ± 0.7	NS
Aerodynamic: MPT	16.8 ± 8.0	16.0 ± 7.7	NS

Abbreviations: MPT, maximum phonation time; NS, non significant; RSA, reflux sign assessment; RSS, reflux symptom score; VHI, voice handicap index.

Individuals with weakly acid LPR reported a significant reduction of dysphonia.

The objective voice quality evolution significantly varied between groups. In the entire cohort MPT, Jitter and Shimmer significantly improved from pre to posttreatment (Table 2). MPT significantly improved throughout treatment in acid and alkaline reflux patients. The pre to posttreatment changes of acoustic measurements are described in Table 6. Jitter, Shimmer and NHR significantly improved throughout treatment in patients with alkaline LPR. Pre to posttreatment acoustic parameters did not change overall in patients with weakly acid and acid LPR. At 3-month posttreatment, patients with alkaline reflux reported significant lower values of shimmer, and NHR

TABLE 5.
Pre to Posttreatment Clinical and Subjective Voice Quality Changes in Patients With Alkaline Reflux

Outcomes	Pretreatment	Posttreatment	*P*-value
Reflux symptom score			
Otolaryngological score	60.8 ± 36.4	31.9 ± 28.7	0.001
Digestive score	34.2 ± 26.8	16.0 ± 22.4	0.001
Respiratory score	15.5 ± 19.2	8.3 ± 15.5	0.002
RSS - score total	110.5 ± 60.3	56.2 ± 48.7	0.001
Reflux sign assessment			
Oral score	5.7 ± 2.4	4.3 ± 1.9	NS
Pharyngeal score	9.7 ± 4.7	7.0 ± 3.7	0.013
Laryngeal score	13.4 ± 5.9	6.7 ± 4.5	0.002
RSA - total score	28.3 ± 9.5	18.2 ± 7.4	0.005
Subjective voice quality			
Voice Handicap Index	14.2 ± 21.8	10.5 ± 15.9	0.038
Perceptual voice quality			
Grade of dysphonia	1.0 ± 0.5	0.8 ± 0.5	0.020
Roughness	0.7 ± 0.8	0.6 ± 0.6	0.020
Breathiness	0.4 ± 0.5	0.5 ± 0.6	NS
Aerodynamic: MPT	15.7 ± 7.9	17.1 ± 8.2	0.030

Abbreviations: MPT, maximum phonation time; NS, non significant; RSA, reflux sign assessment; RSS, reflux symptom score; VHI, voice handicap index.

TABLE 6.
Acoustic Measurements in Patients With Acid, Weakly Acid and Alkaline Reflux

Acoustic	Type of Reflux	Baseline	3-month	*P*-value	Among Group
F0 short-term perturbation					
	Acid reflux	2.5 ± 1.6	2.2 ± 1.3	NS	
Jitter	Weakly acid reflux	2.2 ± 1.6	2.0 ± 1.0	NS	0.055
	Alkaline reflux	2.2 ± 1.3	1.4 ± 0.5	0.039	
Intensity short-term perturbation					
	Acid reflux	6.3 ± 3.0	5.8 ± 2.3	NS	
Shimmer	Weakly acid reflux	6.9 ± 3.2	5.9 ± 2.6	0.012	0.035
	Alkaline reflux	6.4 ± 2.5	4.8 ± 1.3	0.015	
Noise-related measurements					
	Acid reflux	0.2 ± 0.1	0.2 ± 0.1	NS	
NHR	Weakly acid reflux	0.2 ± 0.1	0.2 ± 0.1	NS	0.030
	Alkaline reflux	0.2 ± 0.1	0.1 ± 0.1	0.026	

Abbreviation: NS, non significant.

compared with individuals with acid or weakly acid LPR (Table 6). The statistical analysis reported a trend of posttreatment differences between groups for percent jitter ($P = 0.055$).

The multivariate analysis reported significant positive association between the number of nonacid pharyngeal reflux events and the grades of dysphonia ($r_s = 0.243$; $P = 0.004$) and roughness ($r_s = 0.192$; $P = 0.023$). MPT was negatively associated with jitter ($r_s = -0.327$; $P = 0.001$) and VHI ($r_s = -0.196$; $P = 0.045$). The main acoustic measurements (jitter, shimmer and NHR) reported significant correlations with the following perceptual voice quality evaluations: grade of dysphonia (jitt: $r_s = 0.194$, $P = 0.019$; shimmer: $r_s = 0.257$; $P = 0.002$; NHR = rs = 0.258, $P = 0.001$), roughness (jitt: $r_s = 0.226$, $P = 0.001$; shimmer: $r_s = 0.324$, $P = 0.001$; NHR: $r_s = 0.319$, $P = 0.001$), and breathiness (jitt: $r_s = 0.451$, $P = 0.001$; shimmer: $r_s = 0.355$, $P = 0.001$; NHR: $r_s = 0.279$, $P = 0.001$). In addition, the shimmer values were significantly associated with the laryngeal RSA score ($r_s = 0.166$; $P = 0.046$) and the RSA total score ($r_s = 0.203$; $P = 0.015$). Note that there was no significant association between diet or medication adherence and the posttreatment outcomes.

DISCUSSION

The association between reflux and laryngeal disorders was originally identified at the end of the 1960s by Cherry and Marguelies.[19] Since then, many clinical and basic science studies have supported the association between acid LPR, chronic laryngitis and dysphonia, yielding the voice quality measurements useful as therapeutic outcomes.[6,20] More than 50% of outpatients consulting in laryngology office have reflux symptoms or findings,[2] but, to date, the role of LPR in the pathophysiology of dysphonia is not clearly elucidated.

The findings of the present study support the usefulness of voice quality evaluations as LPR therapeutic outcomes. The results are consistent with previous studies where authors identified significant improvement of VHI,[21] perceptual evaluations,[21] aerodynamic[21,22] and acoustic outcomes[6,21,22] throughout treatment. The degree of severity of dysphonia in LPR may however vary between patients. Some patients may present perceptual dysphonia, while others reported subtle voice changes, which appear undetectable with perceptual evaluations but that may be highlighted with aerodynamic or acoustic measurements. In this study, significant voice quality differences between LPR patients according to the type of LPR were investigated. At baseline, there were no voice quality differences between patients with acid, weakly acid or alkaline reflux but from pre to posttreatment, patients with acid and alkaline LPR reported significant better improvements of voice quality outcomes compared with patients with weakly acid LPR. To the best of our knowledge, there has never been a similar study investigating voice quality outcomes according to the type of reflux. However, some recent studies reported clinical differences between acid, weakly acid and alkaline reflux patients, especially on laryngeal findings. Lee et al reported that patients with alkaline reflux had fewer GERD, pharyngeal reflux events and more severe laryngeal findings, including subglottic edema, posterior commissure hypertrophy and ventricular obliteration.[9,23] Similarly, in the present study, it was observed that patients with alkaline reflux had fewer GERD and pharyngeal reflux events while having similar symptom and sign score severity than those with acid or weakly acid reflux.[24] Both experimental[25] and clinical studies,[9,23,24] suggest some different pathophysiological mechanisms in the development of mucosal lesions between acid, weakly acid and alkaline reflux. In that context, the better improvement of acoustic parameters in individuals with alkaline reflux may be a further argument for the existence of potential differences in the pathophysiology.

From a biomolecular standpoint, pepsin has a key role in the development of vocal fold microtraumas and lesions, but there is limited data available in the literature on the potential role of other gastroduodenal enzymes that are activated in weakly acid or alkaline pH. Interestingly, two recent studies supported the presence of bile salts in the saliva of patients with LPR,[26,27] and the laryngopharyngeal mucosa toxicity of bile salts was demonstrated in some basic science studies.[25,28] Pepsin and conjugated bile salts remains more active in acidic pH,[5] while non-conjugated bile salts and trypsin are effective in pH above 6.0.[29] Thus, the baseline voice quality impairments may not only be related to pepsin activity but may also involve a mosaic of gastroduodenal enzymes, eg pepsin, bile salts, elastase or lipase, that are more or less active in different pH environments and may lead to vocal fold lesions. This hypothesis may be supported by the similarities in symptoms, signs, and voice quality evaluations between patients with acid, weakly acid and nonacid reflux, the latter being characterized by an alkaline environment and, therefore, a reduced pepsin activity. In other words, patients with alkaline reflux may develop similar vocal fold lesions as patients with acid LPR througother pathophysiologic mechanisms involving non-conjugated bile salts or trypsin.

Considering the existence of a mosaic of gastroduodenal enzymes in the mucosa of LPR patients, the better voice quality improvement of alkaline reflux patients may be explained by two hypotheses.The first hypothesis is that patients with acid or weakly acid LPR require more time to cure. The acidic environment and the activated pepsin are known to be associated with more important impairments of defense mechanisms of the vocal folds, including mucus secretion, mucin production, type III carbonic anhydrase activity, and the overall healing process as compared with a more alkaline environment where pepsin is less active.[4,5] Thus, patients with acid LPR and activated pepsin could have more difficulties healing the vocal fold mucosa in comparison with alkaline reflux patients.

The second hypothesis is thats more effective treatments exist for alkaline reflux patients. In the present study, patients with alkaline reflux more frequently received magaldrate in place of alginate, which is able to absorb and eliminate conjugated and non-conjugated bile salts.[29] Thus, magaldrate may be better than classical alginate for patients with alkaline reflux. Interestingly, in practice, LPR patients are often seen who do not respond to classical alginate (Gaviscon) and who later experienced symptom relief with magaldrate. Although it remains a clinical observation and hypothesis, there could be different LPR-types based on the proportions of the various refluxate enzymes; therefore, different therapeutic responses would be seen based on the medications offered. All of these explanations are based on suppositions and hypotheses and may not be directly confirmed through the findings of the present study. However, these potential explanations are added to the discussion because they support the need to conduct future basic science (saliva enzyme concentration), clinical and voice quality studies to better understand the potential pathophysiological differences between acid, weakly acid, and alkaline reflux in the development and the relief of LPR-related dysphonia. A particular focus could be on the dynamic alterations in the mucosal barrier as they may be potential therapeutic targets for LPR.[30]

The primary limitations of the present study are the design (uncontrolled study) and the lack of saliva analyses to identify gastroduodenal enzymes. However, the only available enzyme test is that of salivary pepsin through the Peptest device To the best of the knowledge of the authors, there does not exist a similar device for other gastroduodenal enzymes. In the present study, the definitions of acid, weakly acid and alkaline reflux are based on the ratio of acid to nonacid pharyngeal reflux events. It is important to keep in mind that there are no agreed upon guidelines for the definition of acid, weakly acid and alkaline LPR, yielding the comparison with future studies difficult. It would be beneficial to adopt the current, presented definitions for other future studies to afford uniformity to future analyses . Moreover, other, useful voice quality outcomes such as phonatory quotient, Cepstral analysis or estimated subglottic pressure were not used and could provide additional information to better understand the pathophysiological effects on voice change. Another limitation remains the administration of the same diet for different LPR diseases (acid, weakly acid and alkaline). The alkaline part of the diet may be more useful for acid and weakly acid LPR in comparison with alkaline LPR, which is already alkaline. The rest of the antireflux diet recommendations (low-fat, high-protein foods, no caffeine, alcohol or sparkling beverages) may be effective on alkaline LPR.

CONCLUSION

Patients with acid and alkaline reflux may report better posttreatment voice quality outcomes compared with patients with weakly acid reflux. Future basic science and clinical studies are needed to better understand the vocal fold histological changes related to the different pH types of LPR and their potentially variable gastroduodenal enzyme patterns.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.jvoice.2021.09.023.

APPENDIX 1. REFLUX MANAGEMENT ALGORITHM

Abbreviations: GERD, gastroesophageal reflux disease; GI, gastrointestinal; LPR, laryngopharyngeal reflux; PPI, proton pump inhibitor; RSS, reflux symptom score.

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