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Proton pump inhibitors as treatment of laryngeal disorders among patients with gastroesophageal reflux disease: a single-arm (pre and post) quasi-experimental study

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Abstract

Background Laryngopharyngeal reflux is a silent cause of laryngeal disorders which was documented in the last decade by many studies. This study aimed to evaluate the prevalence of laryngeal reflux in GERD cases and to evaluate the effect of GERD treatment on these laryngeal disorders.

Methodology In this single-arm (pre and post) quasi-experimental study, eighty patients with GERD were examined for laryngeal disorders by rigid laryngoscopy and assessed by the Reflux Finding Score (RFS). Complaints of patients were evaluated using the 9-item Reflux Symptom Index (RSI) questionnaire. Patients received medical treatment of GERD in the form of proton pump inhibitors (PPIs) only, and they were reassessed after 3 months for improvement in their symptoms and signs using RSI and RFS systems to compare patient complaints and findings in the laryngeal endoscopy pre- and post-treatment.

Results Among 80 confirmed GERD cases, 70 (87.5%) suffered from laryngeal disorders. Throat clearing and postnasal drip were the most prevalent symptoms, and ventricular obliteration and erythema, vocal fold and diffuse laryngeal edema, and posterior commissure hypertrophy were the most detected signs. Significant improvement in both symptoms and signs after 3 months of PPI therapy was clearly observed. The resistance rate among our studied patients was reported to be 22.4%.

Conclusion GERD can be considered as an inducer or cause of laryngeal disorders, with a significant direct proportional relationship between the severity of GERD and both the RSI and RFS. PPI greatly improves laryngeal disorders among GERD patients with a high response rate (77.6%).

Keywords Laryngeal disorders, Gastroesophageal reflux, Proton pump inhibitors, GERD, Laryngopharyngeal reflux

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Background

Gastric reflux disease is defined as a GIT motility disorder that results from the reflux of gastric juice into the esophagus or oral cavity, causing symptoms or complications. Gastric juice reflux can affect organs other than the esophagus as far as they ascend, so GERD can be divided into extraesophageal reflux, atypical reflux,

laryngopharyngeal reflux (LPR), and reflux laryngitis. Laryngopharyngeal reflux disease (LPRD) is caused by the backflow of stomach contents and/or gastric acid into the laryngopharynx [1].

Extraesophageal manifestations of GERD recently started to have an important role in causing respiratory tract diseases. Clinically, LPR is known as "silent reflux" with rarely associated gastric symptoms, and treatment is usually delayed because of inadequate diagnostic and therapeutical protocols. Laryngeal symptoms are the most common complaints as the first organ to be exposed to the refluxed gastric juice, so patients are usually treated by otolaryngologists. Otolaryngologists developed Reflux Symptom Index (RSI), as a diagnostic tool, according to the importance of certain disease symptoms which uses a 0–5 rating scale (with 0 = no problem and 5 = severe) [2].

Laryngopharyngeal reflux (LPR) is characterized by dysphonia, globus pharyngeus (lump sensation in the throat), hoarseness, recurrent throat clearing, and chronic cough. LPR represents about 10% of all ENT clinic patients and half of voice complaint patients. But, due to the lack of a good diagnostic test, the prevalence of LPR may be overestimated. A meta-analysis reviewed that 10 to 60% of normal subjects demonstrated reflux from pH probe reading reporting [3].

Laryngoscopy is used to discover laryngeal pathological changes described as hyperemia or erythema of the vocal folds and laryngeal edges, edema, granulation, presence of dense endolaryngeal secretion ventricular obliteration, and hypertrophy of the posterior commissure [4]. The Reflux Finding Score (RFS) based on these laryngoscopic signs is used by some studies to evaluate the effect of LPR on the larynx.

Jamie Koufman published one of the first studies in 1991 investigating the estimated LPR incidence in outpatients presenting to otolaryngology clinics with extraesophageal manifestations of GERD. Patients with otolaryngologic disorders having suspected GERD were evaluated, and after 6 months of treatment with antireflux therapy, 85% of patients resolved [5].

Connor et al. aimed to determine the prevalence of extraesophageal reflux disease (EERD) and the effect on health-related quality of life in adults within a large community-based sample. They found that about 66% of subjects reported either laryngeal symptoms or GERD and 26% reported both laryngeal symptoms and GERD (reflects symptoms commonly reported for LPR) and 39% of patients had medicine for heartburn. Forty-four percent of patients with both laryngeal disorders and GERD had breathing difficulties, and 38% had voice changes. Significant reductions in voice-related quality of life, digestive health, and general health were found in patients with both laryngeal disorders and GERD, in comparison to patients manifesting each symptom alone, or in asymptomatic patients [6].

A study by Habermann et al. aimed to evaluate if patients over a period of 20 months with abnormal RSI and Reflux Finding Score (RFS) benefit from proton pump inhibitor (PPI) therapy. The estimated treatment effect by doctors and patients was 50% excellent. Patients with positive results of RSI and RFS had excellent improvements after 8–12 weeks of PPI treatment [7].

A study by Chen et al. aimed to assess the prevalence of laryngopharyngeal reflux disease (LPRD) in the Fuzhou region in China on subjects aged from 10 to 70 years. Subjects with a total RSI score of more than 13 were defined as having LPRD. The author found that the prevalence of LPRD was 5.0% and the prevalence in subjects of 30–39 years old was significantly more than that in subjects of 10–19 years old and in men was higher than in women [8].

Gao et al. found that there was a significant difference in the RFS cutoff between the genders. For male subjects, the author recommends a cutoff of 9.0 for diagnosing LPRD, and for female subjects, he recommends a cutoff of 6.0 [9].

Finally, a prospective study evaluated the prevalence of laryngeal reflux symptoms in cases of GERD in 200 Egyptian patients by applying RFS and RSI. The patients were divided into two groups, patients with and without laryngeal reflux symptoms. The author reported that for group I, GERD was found in all 100% of patients, and all patients had symptoms and signs of laryngeal reflux, and for group II, 92% of patients were found to be free of laryngeal reflux signs and 8% of patients were found to have signs of laryngeal reflux (silent laryngeal reflux) [10].

The aim of this study was to study the prevalence of laryngeal disorders among GERD patients and to determine the effect of GERD treatment on these laryngeal disorders without any treatment to laryngeal disorders.

Methods

Patients

This study is considered a single-arm (pre-post) quasi-experimental study and was conducted between the otorhinolaryngology department and gastroenterology department, Faculty of Medicine, Assiut University Hospital, Egypt, from January 2020 to October 2021 on patients diagnosed to have GERD by either gastroscopy or 24-h PH-esophageal monitoring at GIT and tropical medicine department. All patients diagnosed in the Gastroenterology Department to have gastroesophageal reflux were examined in the ENT Department by laryngoscopy during the study period.

Using G*Power 3 software, a calculated minimum sample of 80 patients were needed to detect an effect size of 0.3 in the mean of RFS and RSI on two repeated occasions, with an error probability of 0.05 and 80% power on a two-tailed test.

Inclusion criteria are as follows:

1. Sex: male and females
2. Age: adult persons from 18 years old up to 60 years old
3. Diagnosed to have gastric reflux before the start of treatment

Exclusion criteria are as follows:

1. Patients below 18 years
2. Voice abusers as singers, teachers, and readers
3. Patients refused to participate in our study
4. Pregnant females

Methodology

Eligible patients were subjected to the following preliminary evaluation

A. Name, age, sex, residence, occupation, marital status, and special habits.
B. Full history to assess the general condition of the patient.
C. Complaints of patients who were diagnosed with GERD were evaluated with the 9-item Reflux Symptom Index (RSI) questionnaire, including symptoms of hoarseness, postnasal discharge, throat clearing, difficulty of swallowing, cough after eating, breathing difficulties, annoying cough, globus sensation, and heartburn. Patients rated their severity from 0 to 5 as 0: no and 5: severe (difficult to tolerate, preventing daily activities) with RSI greater than or equal to 13 being clinically significant and indicative of significant reflux disease [2].
D. The laryngeal findings were evaluated by using a rigid laryngoscope at the outpatient clinic. The findings were evaluated by a Reflux Finding Score (RFS) based on 8 laryngoscopic findings (subglottic edema, diffuse laryngeal edema, ventricular edema, vocal cord edema, erythema, thick endolaryngeal mucus, hypertrophy of the posterior commissure and granuloma, or granulation tissue) which scored ranging from 0 (best) to 26 (worst); scores greater than or equal 7 were positive [11].
E. Strategy that was put for treatment only for GERD:

- Proton pump inhibitors in the form of omeprazole 40mg once daily 1h before breakfast without any treatment to laryngeal symptoms and follow-up after 3 months
- Lifestyle modifications as avoiding reflux-enhancing foods, using high pillows while sleeping, and taking dinner 4 h before sleep were made.
- Reflux Symptom Index and laryngeal findings as Reflux Finding Score were evaluated again with the same methods after treatment.
- Data before and after treatment were compared statistically.

Operational design

The researcher introduced himself to the patients included in this study and illustrated to them the goal of the study. All participants received comprehensive information regarding the objectives and the expected benefits of the study. All ethical considerations were taken throughout the whole work.

Statistical analysis

All statistical calculations were done using SPSS version 22. Data were expressed as mean ± standard deviation, or median and range when not normally distributed, number of cases and percentages when appropriate. A comparison of quantitative paired variables was done using a paired sample *t* test for normally distributed data. The chi-square (χ^2) test was performed for comparing categorical data. An exact test was used instead when the expected frequency is less than 5. The *P*-value is always 2-tailed set significant if ≤ 0.05 level.

Results

A total of 80 patients who presented to our outpatient clinic after being referred from the Gastroenterology Department diagnosed with GERD were included in our study. The mean age of enrolled patients was 37.56 ± 9.51 years with a range between 18 and 60 years. Out of 80 studied GERD cases, 38 (47.5%) were males and 42 (52.5%) were females (Table 1). Seventy (87.5%) patients had laryngeal disorders out of the eighty patients, while 10 (12.5%) patients had no laryngeal disorders as the Reflux Finding Score by laryngoscopic examination was below 7.

Our study included 70 patients who had laryngeal disorders, 3 of them were missed in the follow-up, so sixty-seven patients were included in our study. All patients at baseline had throat clearing and postnasal drip. Other frequent symptoms at baseline were coughing after eating or lying down (98.5%), sensation of something

Table 1 Demographic distribution of patients

Personal data	No. (80)	%
Age (years)		
< 40	45	56.3%
≥ 40	35	43.8%
Mean ± SD (range)	37.56 ± 9.51 (18.0–60.0)	
Sex		
Male	38	47.5%
Female	42	52.5%

sticking in the throat (97.0%), and heartburn, chest pain, indigestion, or stomach acid coming up (83.6%). At baseline, all patients had reflux symptoms more than 13 while after therapy 52 (77.6%) patients had an index < 13 and 15 (22.4%) patients had an index ≥ 13 (Table 2).

During follow-up, after 3 months of gastric reflux treatment, there was a significant improvement in all laryngopharyngeal reflux symptoms according to the number of patients except hoarseness and breathing difficulty and to the severity of all laryngopharyngeal reflux symptoms except breathing difficulty according to the Reflux Symptom Index score (Table 2).

At baseline, all studied participants suffered from ventricular obliteration, erythema or hyperemia, vocal fold edema, diffuse laryngeal edema, and posterior commissure hypertrophy. 61.2% suffered from subglottic edema, 44.8% suffered from granuloma or granulation, and 73.1% suffered from thick endolaryngeal mucus (Table 3). During follow-up, there was a significant improvement in the number of patients having subglottic edema, ventricular obliteration, granuloma, or granulations and thick endolaryngeal mucus (P<0.001 for all) but not for

Table 2 Comparison between laryngeal symptoms among studied patients and the mean of each symptom in RSI score before and after treatment

Reflux symptoms and patient number	Baseline ($n = 67$)	Follow-up ($n = 67$)	P-value
Hoarseness: no.	56 (83%)	55 (82.1%)	0.819
Mean ± SD	2.16 ± 1.33	1.45 ± 1.08	
Median (range)	3.0 (0.0–4.0)	1.0 (0.0–4.0)	0.000*
Clearing your throat: no.	67 (100%)	58 (86.6%)	0.003*
Mean ± SD	3.00 ± 0.65	1.69 ± 1.52	
Median (range)	3.0 (2.0–4.0)	1.0 (0.0–5.0)	0.000*
Postnasal drip: no.	67 (100%)	51(76.1%)	0.000*
Mean ± SD	2.91 ± 0.73	1.55 ± 1.48	
Median (range)	3.0 (2.0–5.0)	1.0 (0.0–5.0)	0.000*
Difficulty swallowing food, liquid, and pills: no.	36 (53.7%)	17 (25.4%)	0.001*
Mean ± SD	0.45 ± 0.88	1.03 ± 1.37	
Median (range)	0.0 (0.0–3.0)	1.0 (0.0–5.0)	0.007*
Coughing after you eat or lying down: no.	66 (98.5%)	35 (52.2%)	0.000*
Mean ± SD	2.45 ± 0.80	1.36 ± 1.73	
Median (range)	3.0 (0.0–4.0)	1.0 (0.0–5.0)	0.000*
Breathing difficulties or choking episodes: no.	33 (49.4%)	30 (44.8%)	0.604
Mean ± SD	0.94 ± 1.11	0.76 ± 0.92	
Median (range)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.319
Troublesome or annoying cough: no.	50 (74.6%)	35 (52.2%)	0.007*
Mean ± SD	2.01 ± 1.64	1.16 ± 1.25	
Median (range)	2.0 (0.0–5.0)	1.0 (0.0–4.0)	0.000*
Sensation of something sticking in your throat: no.	65 (97%)	45 (67.2%)	0.000*
Mean ± SD	3.22 ± 1.20	1.39 ± 1.45	
Median (range)	3.0 (0.0–5.0)	1.0 (0.0–5.0)	0.000*
Heartburn chest pain indigestion or stomach acid coming up: no.	56 (83.6%)	41 (61.2%)	0.004*
Mean ± SD	2.69 ± 1.55	1.21 ± 1.30	
Median (range)	3.0 (0.0–5.0)	1.0 (0.0–5.0)	0.000*
Reflux Symptom Index			
Mean ± SD	19.84 ± 4.96	11.94 ± 10.61	
Median (range)	19.0 (14.0–32.0)	7.0 (4.0–36.0)	0.000*

Table 3 Reflux finding scores among studied patients and reflux finding score severity at baseline and follow-up

Reflux finding score and patient number	Baseline (n= 67)	Follow-up (n= 67)	*P*-value
Subglottic edema: no.	41 (61.2%)	13 (19.4%)	0.000*
Mean ± SD	1.22 ± 0.98	0.39 ± 0.80	
Median (range)	2.0 (0.0–2.0)	0.0 (0.0–2.0)	0.000*
Ventricular obliteration: no.	67 (100%)	15 (22.4%)	0.000*
Mean ± SD	2.06 ± 0.34	0.48 ± 0.93	
Median (range)	2.0 (2.0–4.0)	0.0 (0.0–4.0)	0.000*
Erythema or hyperemia: no.	67 (100%)	67 (100%)	--
Mean ± SD	3.91 ± 0.42	2.45 ± 0.84	
Median (range)	4.0 (2.0–4.0)	2.0 (2.0–4.0)	0.000*
Vocal fold edema: no.	67 (100%)	67 (100%)	--
Mean ± SD	1.70 ± 0.70	1.25 ± 0.53	
Median (range)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	0.000*
Diffuse laryngeal edema: no.	67 (100%)	67 (100%)	--
Mean ± SD	1.39 ± 0.70	1.22 ± 0.42	
Median (range)	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.001*
Posterior commissure hypertrophy: no.	67 (100%)	67 (100%)	--
Mean ± SD	1.51 ± 0.80	1.25 ± 0.50	
Median (range)	1.0 (1.0–3.0)	1.0 (1.0–3.0)	0.000*
Granuloma or granulation: no.	30 (44.8%)	3 (4.5%)	0.000*
Mean ± SD	0.87 ± 0.98	0.09 ± 0.42	
Median (range)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.000*
Thick endolaryngeal mucus: no.	49 (73.1%)	12 (17.9%)	0.000*
Mean ± SD	1.46 ± 0.89	0.36 ± 0.77	
Median (range)	2.0 (0.0–2.0)	0.0 (0.0–2.0)	0.000*
Reflux Finding Score			
Mean ± SD	14.12 ± 2.87	7.49 ± 4.80	
Median (range)	14.0 (10.0–21.0)	5.0 (5.0–20.0)	0.000*

ventricular obliteration, erythema or hyperemia, vocal fold edema, diffuse laryngeal edema, and posterior commissure hypertrophy as 100% of the studied participants still suffered from it. There was a significant improvement in the severity of all laryngeal signs according to the Reflux Finding Score (Table 3) and in reflux findings during follow-up. At baseline, all patients (100.0%) had a Reflux Finding Score > 7 while during follow-up the majority (77.6%) of patients had a Reflux Finding Score < 7.

It was found that gastroesophageal reflux therapy was effective in 52 (77.6%) patients while 15 (22.4%) patients had no improvement as the RSI was still more than 13 and RFS more than 7.

There was a positive correlation between RSI and RFS as the greater the RSI, the greater the RFS (Fig. 1).

Discussion

The retrograde movement of stomach contents into the esophagus, larynx, and pharynx, known as laryngopharyngeal reflux (LPR), is thought to be an extraesophageal symptom of gastroesophageal reflux disease (GERD), causing tissue damage in these regions and symptomatizing as odynophagia, pharyngeal globus, throat clearing, dysphonia, dry cough, and laryngospasm crisis [12]. It became to be significant and increasingly common disease seen by an otolaryngologist, with an estimated range from 18 to 80% [13].

The mean age of the studied participants was 37.56 ± 9.51 years and ranged from 18 up to 60 years. In agreement with our study, Gaber et al. [10], Patigaroo et al. [14], Mosli et al. [15] found that the mean age of the LPR cases was 38, 40.1 ± 11.8 and 43 ±16 years, respectively.

It is well known that advancing age has been inconsistently associated with an increased risk for GERD symptoms. In a meta-analysis, the summary odds ratio for 50 years or more versus less than 50 years of age was 1.32 [16]. In our study, we only included GERD cases who attended our clinic before starting any treatment; this explains the younger age at the time of GERD diagnosis among our studied participants.

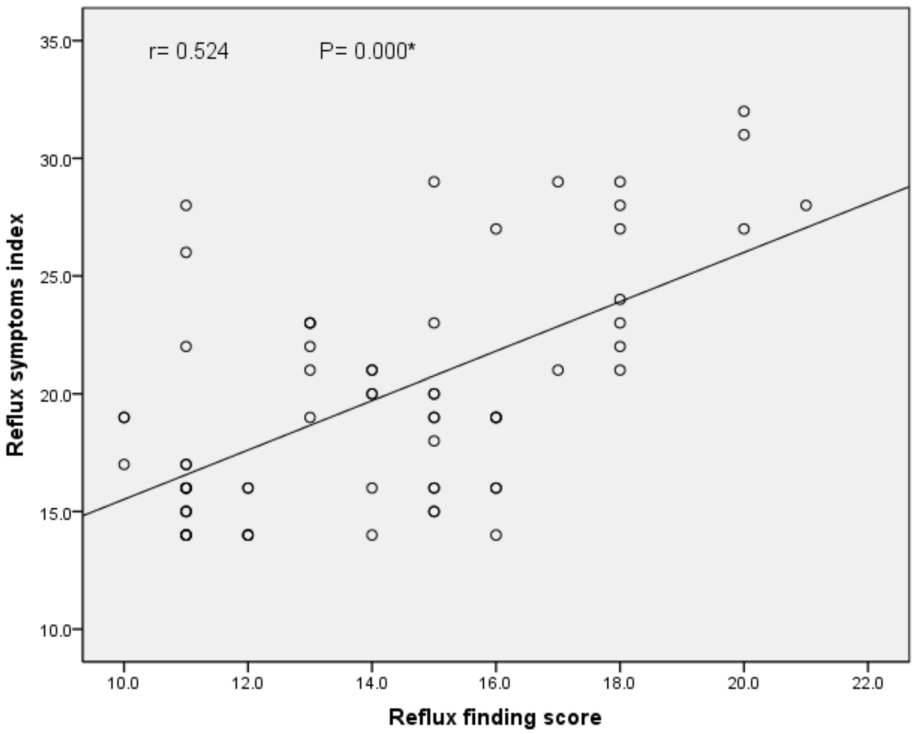

Fig. 1 Scatter plot graph showing the correlation between Reflux Finding Score and Reflux Symptom Index

No sex predilection was found in our study among studied GERD cases, as 38 (47.5%) were males and 42 (52.5%) were females out of 80 studied GERD cases. In line with our research, Gaber et al. reported that 50% of the studied cases were males with a male to female ratio of 1:1 [10]. Also, in line with our study, GERD symptoms are not associated with sex in North America or Europe, but in South America and the Middle East, women are almost 40% more likely to report GERD symptoms than males [16].

The manifestations of GERD were divided into esophageal and extraesophageal disorders, and the association between laryngopharyngeal reflux disease (LPR) and GERD has been established according to the Montreal Consensus Conference [17]. In this current study, in order to determine the prevalence of laryngeal reflux in GERD cases, all studied participants were evaluated by laryngoscopic examination using the Reflux Finding Score (RFS). RFS is an 8-item clinical severity scale that depends on the fiberoptic laryngoscopy findings. The scale ranges from 0 which means no abnormal findings to 26 which is the worst possible score.

Also, complaints of GERD patients were evaluated with Reflux Symptom Index (RSI), first described by Belafsky et al., as a self-administered and validated 9-item scoring system designed to assess the symptoms related to LPR (throat clearing, excess throat mucus or postnasal drip, hoarseness, breathing difficulties, dysphagia, globus pharyngeus, coughing after eating or lying down, troublesome or annoying cough, and heartburn) [2]. An RSI score quantifies the severity of LPR symptoms on a scale of 0–5, with a total score of 45 indicating the most severe form. RSI levels above 13 are considered abnormal and suggest LPR, which is used as the diagnostic cutoff point. Farahat et al. developed an Arabic version of the RSI which was used in the current study [18].

In this study, 80 patients with confirmed GERD were examined and 70 patients (87.5%) of them were diagnosed with LPR. In line with our study, many previous studies reported a strong correlation between the two conditions (laryngopharyngeal disorders and GERD). Tauber et al. reported 69% of patients with GERD had laryngitis confirmed by inter-arytenoid edema and erythema diagnosed by laryngoscopic examination [19]. Also, a study by Vardar et al. had similar results as LPR was reported in 70% of patients diagnosed with GERD [20]; recently, Mosli et al. reported that 71% of confirmed GERD patients had LPR [15]; and lastly, Silva et al. reported that 82.8% of confirmed GERD cases had LP [12].

According to RFS, all studied participants at the baseline examination were suffering from ventricular obliteration, erythema or hyperemia, diffuse laryngeal edema,

vocal fold edema, and posterior commissure hypertrophy. 61.2% suffered from subglottic edema, 44.8% suffered from granuloma or granulation, and 73.1% suffered from thick mucus endolaryngealy, and the mean RFS was about 14.12 ± 2.87 and ranged from 1 up to 21.

Other studies have also found that the most common laryngeal finding "as assessed by RFS" was found to be erythema/hyperemia like studies of Book et al., Mesallam et al., Karkos et al., Toros et al., Patigaroo et al., and Osman et al. [13, 14, 21–24]. Also, other authors have noted that the most common laryngoscopic signs are posterior commissure hypertrophy as by Belafsky et al. and partial ventricular obliteration as by Tezer et al. [11, 25].

After 3 months of gastric reflux treatment with PPIs, significant improvement was noticed in all abovementioned findings (P<0.001 for all) except for ventricular obliteration, erythema or hyperemia, vocal fold edema, diffuse laryngeal edema, and posterior commissure hypertrophy as 100% of the studied participants still suffered from it. However, there was a significant decrease in the mean values of the used RFS for all these items from before to after treatment (P<0.001), and the mean RFS was significantly decreased from 14.12 ± 2.87 to 7.49 ± 4.80, P<0.001.

Our study showed similar results to other studies done for the response of RFS to PPI like studies of Belafsky et al., who reported that the mean of RFS at entry was 11.5 (± 5.2 SD) and improved to 9.3 (± 4.7 SD) at 2 months, 7.3 (± 5.5 SD) at 4 months, and 6.1 (± 5.2 SD) at 6 months of treatment with PPIs [11]. Bilgen et al. reported that the RFS before the start of the therapy was 14.8±3.8 and improved significantly to 7.7±3.8 at the second month, to 4.5±2.3 at the fourth month, and to 1.4±0.9 at the sixth month of treatment with proton pump inhibitors [26]. Also, our study was supported by the recent study of Silva et al., who reported that the RFS assessment showed a reduction in the values when compared with the pre- and post-treatment with 90 days with PPI [12].

According to RSI, at baseline, the most common symptom in the study was found to be clearing throat and postnasal drip in 100% of the study population, followed by coughing after eating or lying down documented in 98.5%, sensation of something sticking in throat 97.0%, then chest pain, heartburn, stomach acid coming up, or indigestion documented in 83.6%; the mean RSI was 19.84 ± 4.96 and ranged from 14 up to 32.

In line with our results, Toros et al. found frequent clearing of the throat as the most common symptom [24], while some studies have found other most common symptoms of LPR like the study of Patigaroo et al. who found the most common symptom to be globus sensation in 74% of patients followed by the frequent clearing of the throat in 64% of patients and annoying coughing in 56% of the study population and the least common symptom was breathing difficulties [14]. Studies of Issing et al., Mesallam et al., Karkos et al., and Osman et al. also found that the most common symptom like our study was globus pharyngeus [13, 22, 23, 27].

After 3 months of gastric reflux treatment with PPIs, we observed significant improvement in all laryngopharyngeal reflux symptoms "as assessed by RSI" except hoarseness of voice and breathing difficulty. However, there was a significant decrease in the mean values of the used RSI for hoarseness of voice, but not for breathing difficulty, which was still a problem facing our patients, from before to after treatment (P<0.001), and the mean RSI was significantly decreased from 19.84 ± 4.96 to 11.94 ± 10.61, P<0.001.

Similar results were obtained in other studies like the study by Belafsky et al. who reported that the mean RSI of LPR patients improved from 21.2 ± 10.7 to 12.8 ± 10.0 after 6 months of treatment with PPI [2]. Also, the study of Patigaroo et al. reported that the mean of RSI before treatment for all patients was 24.75, and after 8 weeks of treatment with PPI, it decreased to 13.5 and after 16 weeks dropped to 13.25 [14]. Osman et al. reported reflux symptoms markedly improved at the end of 2 months and 6 months of PPI therapy with significant [13]. Also, our study was supported by the recent study of Silva et al. who reported that the RSI assessment showed a decrease in the values when compared to the pre- and post-treatment values with PPI for 3 months (p <0.001) [12].

We reported a 22.4% resistance rate among our studied participants. Some studied patients still have persistent signs, as 100.0% still have erythema or hyperemia, vocal fold edema, diffuse laryngeal edema, and posterior commissure hypertrophy; 22.4% still have ventricular obliteration; 19.4% still have subglottic edema; 17.9% still have thick mucus endolaryngealy; and three cases (4.5%) still have granuloma. Persistent symptoms such as throat cleaning in 86.6%, 82.1% still suffering from hoarseness of voice, 67.1% from postnasal drip, 67.2% from globus pharyngeus, 61.2% from heartburn, 53.7% from difficult swallowing, 52.2% from coughing post-prandial or on lying down or annoying cough, and 49.3% still suffering from breathing difficulties were still detected 3 months post-PPI therapy.

Osman et al.'s study detected the persistence of some of the presenting signs after still 6 months post-therapy: partial ventricular obliteration was still detected in 8 (13.1%) of included patients, mild vocal fold edema in 10 (16.4%) of patients, mild laryngeal edema in 7 (11.5%) of patients, and granuloma in 6 (9.8%) of them [13].

On the other hand, other studies show higher response rates like studies of Jaspersen et al. and

Patigaroo et al. which demonstrated completely (100%) symptom-free patients after treatment with 40 mg omeprazole per day, and Kamel et al. found the response rate was 92% [14, 28, 29].

The difference between this study and the previously mentioned studies leads us to question the duration of treatment, which in the present study led to a discrete reduction in the overall sum of the RFS from 14.12 to 7.49 and RSI from 19.84 to 11.94. Perhaps a longer follow-up time could change the profile of these scores since our follow-up was of only 3 months. Also, it is well known that unlike GERD, response to PPI in patients with LPR has been described to be highly variable. This may be due to that LPR require prolonged and more aggressive therapy, which may last for several months, than GERD [30]. This finding was confirmed by Belafsky et al. in 2001 and 2002 who found a more improvement in the scores of individuals treated with PPIs for 6 months, double the time used in our study [2, 11].

One of the limitations of our study was the small sample size, so larger prospective studies are needed to confirm the role of PPI in controlling the laryngeal disorders associated with GERD disease and evaluate its long-term side effects. Another limitation of our study may be the subjectivity of RFS, as these signs can be present in up to 86% of asymptomatic subjects, because both the interobserver and interobserver reproducibility of laryngeal signs due to LPR is poor, which may lead to overdiagnosis of laryngopharyngeal reflux; evaluation of the patients by two examiners is needed. There is a vital need for the implementation of RSI and RFS in daily use to decrease time consumption and expensive examinations for patients and to help in early diagnosis of LPR with a subsequent decrease in serious complications such as laryngeal granuloma, subglottic stenosis, and laryngeal cancer.

Conclusion

From this study, it was concluded that laryngopharyngeal reflux disease (LPRD) is becoming a commonly diagnosed condition among pharyngeal and voice disorders and the diagnosis depends on full history and clinical examination followed by laryngeal endoscopy. A large percentage (87.5%) of GERD patients had laryngeal disorders. The main complaint was throat clearing and postnasal drip, i.e., 100% each, while ventricular obliteration, erythema or hyperemia, vocal fold edema, diffuse laryngeal edema, and posterior commissure hypertrophy were the most obvious signs, i.e., 100% each. There was a significant direct proportional relationship between the severity of GERD and both the RSI and RFS. PPI greatly improves laryngeal disorders among GERD patients with a high response rate (77.6%).

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Authors' contributions
MAR: Conception and design, acquisition of data, analysis and interpretation of data and critical revision of the submitted protocol for important intellectual content. SSS: Data collection. EEM: Examination of patients at gastroenterology department and diagnosis and treatment of GERD. HAMA: Patient examination in phoniatric unit. MMR: Analysis and interpretation of data and supervision. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The protocol of the study had been approved by Assiut Medical Ethical Review Board under IRB no:17101130 clinical trials approval (NCT04231344). All studied patients who participate in this study had received their medical care free of charge. For patients who refused to participate in the study, it did not affect the quality of care they had received. An informed written consent from all participants was taken and confidentiality of information was ensured all through the study.

Consent for publication
Not applicable.

Competing interests
No conflict of interest exists.

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