Clinical Presentation of GERD:
A Prospective Study on Symptom Diversity and Modification of Questionnaire Application

Ryan Broderick MD[1], Karl-Hermann Fuchs MD[1], Wolfram Breithaupt MD[2], Gabor Varga MD[2] , Thomas Schulz MD[2] , Benjamin Babic MD[3], Arielle Lee MD[1], Frauke Musial PhD[4] , Santiago Horgan, MD[1]

1- University of California San Diego, Dept. of Surgery, Center for the Future of Surgery, La Jolla, CA, USA
2- AGAPLESION Markus Krankenhaus, Dept. of General- and Viszeral-Surgery, Frankfurt am Main, Germany
3- University of Mainz, Department of Surgery, Mainz, Germany
4- NAFKAM Department of Community Medicine Uit, The Artic University of Norway, Tromso; Norway

Address of Correspondence:

Karl-Hermann Fuchs, MD
Visiting Associate Professor
University of California San Diego, Dept. of Surgery,
Center for the Future of Surgery
9500 Gilman Drive, MC:0740
La Jolla, CA, 92093, USA
Karl-Hermann.Fuchs@gmx.de

Conflicts of interest: The authors have no conflicts of interest to declare.

Abstract:

Introduction: Symptoms occuring in GERD such as heartburn, regurgitation, thoracic pain, epigastric pain, respiratory symptoms and others can show a broad overlap with symptoms from other forgut disorders. The goal of this study is the accurate assessment of symptom presentation in GERD.
Methods: Patients with foregut symptoms were investigated for symptoms as well as endoscopy and GI-functional studies for presence of GERD and symptom-evaluation by standardized questionnaire. Questionnaire included a graded evaluation of foregut symptoms documenting severity and frequency of each symptom. Questionnaires by study nurse solicitated, self-reported, free-form self reported by the patient.
Results: For this analysis 1031 GERD patients(572males and 459females) were enrolled. Heartburn was the most frequent chief complaint, seen in 61% of patients. Heartburn and regurgitation are the most common (82.4%/58.8%, respectively) in overall symptom prevalence. With regard to modification in questionnaire technique, if patients fill in responses without prompting, there is a trend towards more frequent documentation of respiratory symptoms (up to 54,5% ($p<0,01$), fullness (up to 93,9% and gas-related symptoms($P<0.001$). Self-reported symptoms are more diverse (e.g. throat-burning(12%), mouth-burning(9%), globus(6%), dyspnea(9%), and fatigue(7%)).
Conclusions: GERD symptoms are commonly heartburn and regurgitation, but overall symptom profile for patients may change depending on questionnaire technique.

Key words: GERD, GERD-symptoms, heartburn, regurgitation, GERD-diagnosis

Introduction:

Since Gastroesophageal Reflux Disease (GERD) has a prevalence of 20% in industrialized countries, symptoms associated with the disease are common in these populations (1,2). In order to define GERD, the authors of the Montreal classification relied heavily on symptoms and their effect on patients: “GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications“(1). These symptoms can reduce patient`s well-being and have a negative influence on quality of life (3,4).

In many studies, GERD symptoms are used to define the study populations (5-13). Other studies, however, have some evidence that symptoms are not always reliable as a guide to the diagnosis of GERD (14-17). GERD symptoms such as heartburn, regurgitation, thoracic pain, epigastric pain, respiratory symptoms, globus, and others show a broad overlap with symptoms from other esophageal and gastric disorders such as dyspepsia, esophageal motility disorders, functional heartburn, hypersensitive esophagus, irritable stomach and bowel, and somatoform disorders (1,14-17). The wide array of symtpoms and potential diagnoses makes one consider if there is a specific questioning technique or symptom profile that is more highly suggestive of GERD. Klauser et al. have stated that heartburn and regurgitation are the most typical symptoms characterizing GERD, but in clinical practice a large variety of esophageal and extraesophgeal symptoms can be reported (18).

Over the last 3 decades, our team had documented symptoms of GERD patients in a large data bank. Initially, the evaluations were standardized and leaned heavily on the early DeMeester symptom score and GIQLI (19-22). Several years later these questions were validated within the project of creating a symptom questionnaire featuring 53 items to determine somatoform tendencies (17). With the exception of respiratory symptoms, all items in this current questionnaire differentiated significantly between healthy volunteers and patients with foregut symptoms (17).

The goals of this study are to determine the diversity and most common symptoms of GERD in large patient populations over time. Additoinally, we aim to determine if method of questioning is significant in altering the symptom profile of GERD patietns.

Methods:

Study design:

Over the course of more than 2 decades, our working group had the opportunity to investigate a large population of patients with GERD in a specalized center for benign esophageal and gastric disorders. All patients with foregut symptoms referred for further exploration of esophageal and/or gastric disease underwent a history and physical examination. The symptoms of the patients were evaluated by a standardized questionnaire over the complete time period from 1995-2017. Only the method of application for the questionaires was changed over time, as described in detail below. All patients received an upper GI endoscopy and esophageal manometry. In more recent years, a high resolution manometry was performed (23). The presence of pathologic reflux was evaluated by 24 hour pH monitoring, later by impedance-pH-monitoring.

Varying methods of questionnaire administration were used over the years in different time segments to evaluate the patient's symptoms, as indicated below:

Group 1: (Study period 1995-1999) The study nurse used the standard questionaire to ask the patients for the symptoms and marked the answers of the patients regarding presence and severity of the symptoms herself .

Group 2: (Study period 2005-2009) Study nurse handed the questionaire over to the patients and the patients were left alone to fill in the presence and the severity of the symptoms. The patients could ask for assistance to the nurse, if needed.

Group 3a: (study period 2015-2017) Study nurse handed the questionaire over to the patients and the patients were left alone to fill in the presence and the severity of the symptoms in the document.

Group 3b: (study period 2015-2017) patients (same patients of group 3a) were asked to document in a free text version the 3 most important symptoms that limit or reduce the patient‘s quality of life. Patients were instructed by the study nurse to document their most relevant symptoms as precisely as possible. Additionally, the study nurse also handed the standard questionaire over to the patients and the patients were left alone to fill in the presence and the severity of the symptoms. It is important to notice, that the free formulated description of the symptoms by the patient themselves was always conducted ***before*** the patients filled in the standardized questionnaire. This order was kept with the aim to avoid influences of the standard questionnaire to the patient formulated free text.

The groups were chosen for different time periods, in which changes of the symptom evaluation was established (solicited, self-reported, and free-form self reported). The standard symptom questionaire remained the same over the study duration.

Patient selection and inclusion/exclusion criteria:
The patients were recruited in a tertiary referral center for Foregut Disorders and its diagnostic functional laborartory and surgery unit. The management of the patients was performed by the same team (same study nurse) over the complete period 1995-2017. The patients were asked to give informed consent to the study evaluation and the diagnostic work-up. The study was approved by our Institutional Review Board.

The data were reviewed in a prospectively maintained databank. Inclusion criteria for this analysis were patients with documented GERD which required either the presence of esophagitis (esophagitis grading according to Savary-Miller 1-4), pathologic esophageal acid exposure on pH testing, and/or a hiatal hernia with heartburn and/or regurgitation. The hiatal hernia was documented during endoscopy by measuring the vertical extent of the distance between the cardia (begin of the gastric folds) and the waist of the crurae, best assessed during inspiration (distance > 1cm). Care was taken to measure this length in the beginning of the endoscopy without major air-insufflation of the stomach to avoid hernia reduction.

Exclusion from this analysis was performed in some time periods (2000-2004 and 2010-2014), in which the documentation of symptoms was not rigorously followed due to shortage in personnel for administering the questionnaire. In addition, other exclusion criteria were if patients had other diseases such as cancer, inflammatory bowel disease, esophageal spasm, achalasia, or if they had prior operations for GERD.

The questionnaire:

For symptom evaluation, a standardized questionaire was established and used over 25 years. The questionaire included a graded evaluation of foregut symptoms: heartburn, regurgitation, retrosternal/thoracic pain, respiratory symptoms (cough/hoarseness), dysphagia, epigastric pain (pain/cramps/burning), nausea/vomiting, fullness (unpleasant fullness,early satiety), and gas-related symptoms (belching/bloating/flatulence). Patients had to document the severity and frequency of each symptom by grading according to the following system: 0= no symptoms; 1= symptom ocurring rarely; 2= symptom occuring occasionally; 3=symptom occuring monthly and or with mild intensity; 4= symptom occuring weekly and/or with moderate intensity; 5=symptoms occuring daily and/or with severe intensity.

Statistical methods:

Symptom results were analyzed according to their documented overall presence in these patients, independent of their severity, as well as by the reported most-significant/chief complaints. The mean intensity of the presented symptoms were analyzed. Statistical comparison with a t-test for unpaired samples was used for the comparison of data from the different samples. A Chi-square test was used for comparison of group data.

Results:

From 1995-2017, over 2000 patients with symptoms indicative of GERD were seen by our team. Patients with other gastrointestinal diseases that could influence foregut symptoms were excluded from this study. 1031 met all inclusion criteria as GERD patients and were enrolled from 3 different time segments.. Group 1 (1995-1999)

included 481 patients, Group 2 (2005-2009) had 333 patients and in Group 3a/3b (2015-2017) were 217 patients. There were 572 males and 459 females. Table 1 demonstrates the characteristics of patients in the different groups. Presence of esophagitis, evidence of LES incompetence, esophageal acid exposure, and the level of quality of life showed severity of GERD among the patients in different groups over the years.

Frequency of chief complaints and overall presence of symptoms:

Heartburn (retrosternal burning rising from the epigastrium to the chest) was the most frequent chief symptom (intensity: 5), independent of exam technique (Table 2:: Group 1: 60%; Group 2: 61%; Group 3a: 61.6%, Group 3b: 48.5%). Table 2 shows the frequency of chief complaints in the different groups. When the questionaire is filled in by the study nurse (Group 1) the most common symptoms are heartburn and regurgitation (60%, 17%,). Additionally in Group 1, other symptoms such as epigastric pain, dysphagia, or gas-related symptoms such as bloating, belching, and flatulence are not often experienced as the primary symptom (frequencies<15%). When comparing between groups, there is significant differences between symptoms reported (Group1 versus Group 2/Group 3a). More often patients self-report respiratory symptoms (1.6% versus 21.3%/20.2%)($p<0,001$), epigastric pain (13.1 % versus 24.7%/12.1%) and gas-related problems (2.6% versus 27.2%/22.0%) ($p< 0.01$) .

Table 3 provides the overview on the overall presence of symptoms as evaluated in the various time periods. Heartburn and regurgitation are most frequent in Group 1 (82.4% and 58.8%, respectively). If patients fill in the questionaire themselves, there are significant differences between groups in the presence of documentation of respiratory symptoms (Group 1:11.8% Group 2: 24.9%; Group 3a: 54.5%) ($p<0.01$), fullness (1: 11%; 2: 72.7%; 3: 93.9%) ($P<0,001$), and gas-related symptoms (1: 34%; 2: 72.7%; 3: 93.9%). These differences are even more pronounced in recent years.

Administration of free-text form of symptom evaluation:

When patients report their symptoms in their own words prior to completing the standard questionnaire (Group 3b), the documented variety of symptoms increases compared to the structured questionnaire alone (Table 4). In group 3b, heartburn remains the most frequent reported symptom both as chief complaint (31%), as well as in the overall presence (48.5%). Reported symptoms are much more diversified: burning in the throat (12%), burning in the mouth (9%), globus (6%), headache (1%), dyspnea (9 %), and fatigue (7%) (Table 4).

Intensity of symptoms and their relation to objective functional data:
Data on the intensity of symptoms are summarized in Table 5. The intensity of heartburn is highest in all groups (Group 1: 3.61; Group 2: 3.88; Group 3a: 3.39). The nurse documented the intensity of the symptoms such as regurgitation, retrosternal pain, epigastric pain, and respiratory symptoms higher (Group 1) than the patients themselves (Groups 2 and 3).

The relationship between symptom intensity and the esophageal functional status show only for heartburn a significant rise in intensity for patients with and without LES-incompetence. These differences were for group1: 3,1 versus 3,9; for group 2: 3,2 versus 3,9; for group 3: 1,8 versus 3,4 (all $p< 0,005$). The differences in symptom intensity are also significant for some comparisons with regurgitation, however all other symptoms have no remarkable differences detected for changes in objective functional status.

Discussion:
We show that despite altering modality of questioning and symptom assessment in GERD patients, heartburn is the most reported symptom. The severity and intensity of heartburn was documented highest among all other symptoms through all years of investigation. The reported intensity of heartburn is significantly increased when the functional status of the antireflux barrier deteriorates. On the other hand, the presence/absence and intensity of other symptoms (e.g. regurgitation, respiratory symptoms, bloating, etc) can depend on the concept and details of questioning. Allowing the patients to report free-form selection of symptoms shows a larger variety

of documented chief complaints and other gas-related symptoms that may not be appreciated on standardized questioning.

Similar to our study, literature review shows that heartburn is reported to be present in patients with pathologic esophageal acid exposure in 72 -99% (1,3,14,17,18). Regurgitation is another important symptom in GERD, with a prevalence of 33 - 86% (1,14,17,29,30). According to some studies, epigastric pain is present in patients with foregut symptoms in 70% and in those with documented pathologic acid reflux in 12 - 67 % (1,3,14,17). Our study confirms the importance of heartburn as the classic symptom with the highest intensity and the highest frequency as a chief complaint throughout the study. In Group 3b (free-text format), the symptom of heartburn was further delineated as “burning in the throat“ or “burning in the mouth“ in up to 14%.

Results of the present study show that the documented presence of symptoms can depend on the method of questioning (e.g. whether the symptoms are asked by a study nurse or if the patients are documenting without solicitation). The more the patient is free in her/his answering the questionaire, symptom variability increases, especially with increased incidence of gas-related and atypical symptoms. The overall presence of heartburn remains independent of questionnaire administration around 80%. Notably, a statistically significant finding of respiratory symptom presence increases from 11% to 50% and the gas-related symptoms from 30% to 90% depending on questionnaire modality of application. All other symptoms have a much lower incidence in our GERD patients, and therefore functional investigations are helpful to confirm the disease if esophagitis is absent.

There has been a controversial discussion about symptoms as a diagnostic tool for the presence of GERD, initiated by the Montreal definition (1,14,18,19,20). Our study confirms that there is a significant diversity of foregut symptoms present in GERD patients, as well as numerous extra-esophageal complaints such as cough, hoarseness, burning sensation in pharynx, mouth and tongue patients(1,14-17). Extra-esophageal symptoms can be respiratory symptoms such as chronic cough, hoarsness, and shortness of breath. There may also be symptoms at the level of the head and neck such as globus or burning in the mouth or throat. Recent studies

show a limitations of measuring acid reflux in the pharynx with current technology (37,39,40). It remains difficult to correlate these symptoms with reflux episodes, even with objective testing (31-38).

We show that our validated questionnaire provides adequate assessment of patient symtpoms. Allowing free-form reporting of symtpoms in addition to a structured questionnaire may provide a more robust symptom profile in reflux disease. There is evidence in literature that structured questionaires are very helpful and effective for symptom evaluation, and this is confirmed by our study (41-46). Several instruments have been published, validated and successfully used in clinical practice (41-46). Various questionnaires published include the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM), the Gastrointestinal Rating Scale (GSRS), the Chinese GERD Questionnaire, the GERD-Health Related Quality of Life Instrument (GERD-HRQL), the Esophageal Symptoms Questionnaire (ESQ), and the Reflux Disease Questionnaire (RDQ) (41,42,43,47-50). A systematic review of all the avialable questionnaires for assessment of GERD showed that many differ in design, validation, and translations (43). One should be aware of the strength and shortcomings of each before selecting one for use (43). All instruments have a self-assment or self-administered mode of application, usually evaluating severity and/or frequency of GERD-symptoms with a median of 15 items (6-30 items) (41-43,47-50). The most useful instruments allowed for self-assessment by the patients (43). However, none of these surveys allow for a free-text version of symptom documentation such as the one tested in this study.

When using the questionnaire over the years we noticed that many patients added remarks in the margin, indicating a possible lack of options or inadequate description. The umprompted free form clarification of symptoms stimulated the impetus for providing patients more space to document symptoms in this way. None of the available validated questionnaires leaves room for the patient's free text. Variations in patient symptoms such as burning in the mouth, burning at the tongue and in the throat may be important features to document. In the past, one could only speculate that these symptoms were superficially classified as heartburn or odynophagia. Most of the available structured and validated questionnaires focus on heartburn,

epigastric pain, fullness, bloating, regurgitation and dysphagia. Therefore, it may be reasonable to add a free-text section to GERD-questionnaires for detection of rare but important symptoms restricting the patient‘s quality of life.

While expanding structured questionnaires to integrate all possible symptoms would be able to register all symptom variations, the more items to be answered lengthens and complicates the questionnaire process, potentially reducing applicability. Recently developed technologies allow patients to record symptoms in an electronic diary using a mobile electronic device. These technologies may be able to integrate self-administered and free-text from evaluations to receive a more realistic and clinically valuable assessment.

Limitations of this study include the retrospective character of the analysis and the long duration of data sampling. Additionally, there were periods of time during the study period where documentation was not able to be rigorously completed due to nursing shortage (2000-2004, 2010-2014), so data from these periods were excluded and sample size reduced as a result. Overall, the size of the patient data sampling performed by one team and one study nurse provides a dependable performance of data sampling and robust data for comparison of the changing techniques of administrating the assessment of GERD-symptoms.

GERD remains a disease with a wide variety of symptoms experienced by patients. While heartburn and regurgitation remain mainstays of symptom reporting, there may be a range of symptoms and intensities of symptoms that go unreported if not elicited in a free-text format. The variety of symptoms experienced also shows the importance of a full correlating objective workup with EGD, high resolution manometry, and impedance pH testing to assist with accurate diagnosis of patients who may need surgical correction of their disease.

Conclusion:

GERD symptoms are commonly heartburn, regurgitation, fullness, respiratory, and gas/bloat-related. The most important and frequent symptom is heartburn and its intensity parallels objective functional parameters of the esophagus. The overall

symptom profile of patients may vary depending on the modality of questioning: practitioner directed, patient questionnaire, or free-form patient reporting of symptoms. Objective studies should be a key component in determining treatment for GERD due to the wide disparity in presenting symptoms.

References:

1. Vakil N, van Zanten SV, Kahrilas PJ, Dent J, Jones R, and the global consensus Group. The Montreal Definition and Classification of GERD: a global Evidence-based Consensus. Am J Gastro, 2006; 101:1900-1920.
2. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of GERD: a systematic review. Gut, 2014, 63:871-880.
3. Wiklund I, Carlsson J, Vakil N. Gastroesophageal Reflux symptoms and Well-Being in a Random Sample of the General Population of a Swedish Community. Am J Gastroenterol 2006, 101: 18-28.
4. Kamolz T, Granderath, Pointner R. Laparoscopic antirefluxsurgery: disease-related quality of life assessment before and after surgery in GERD patients with and without Barrett´s esophagus. Surg Endosc 2003;17:880-885.
5. Rydberg L, Ruth M, Abrahamsson H, Lundell L: Tailoring antireflux surgery: a randomized clinical trial. World J Surg 1999, 23: 612-618.
6. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001 121:5-14.
7. Dallemagne B, Weertz J, Markiewicz S, Dewandre JM, Wahlen C, Monami B, Jehaes C. Clinical results of laparoscopic fundoplication ten years after surgery. Surg Endosc 2006; 20: 159 – 165.
8. Metha S, Bennett J, Mahon D, Rhodes M,. Prospective Trial of Laparoscopic Nissen Fundoplication Versus Proton Pump Inhibitor Therapy für Gastroesophageal Reflux disease: Seven-Year Follow up. J Gastrointest Surg, 2006; 10, (9):1312-1317.

9. Fein M, Bueter M, Thalheimer A, Pachmayer V, Heimbucher J, Freys SM, Fuchs KH. Ten year outcome of laparoscopic antireflux procedures. J Gastrointest Surg, 2008; 12: 1893-1899.
10. Strate U, Emmermann A, Fibbe, Layer, P, Zornig C. Laparoscopic fundoplication: Nissen versus Toupet two-year outcome of prospective randomized study of 200 patients regarding preoperative esophaegal motility. Surg Endosc 2008;22:21-30.
11. Anvari M, Allen C, Marshall J, Armstrong D, Goree R, Ungar W, Goldsmith C. A randomized controlles trial of laparoscopic Nissen fundoplication versus proton pump inhibitors fort he treatment pof patients with chronic gastrooesophageal reflux disease (GERD): 3 year outcomes. Surg Endosc. 2011;25 (8):2547-54.
12. Frazzoni M, Piccoli M, Conigliaro R, Manta R, Frazzoni L, Melotti G. Refractory gastroesophageal reflux disease as diagnosed by impedance-pH monitoring can be cured by laparoscopic fundoplication. Surg Endosc. 2013; 27(8): 2940-2946.
13. Fuchs KH, DeMeester TR, Albertucci M. Specificity and sensitivity of objective diagnosis of GERD. Surgery, 1987; 102(4):575-580.
14. Costantini M, Crookes PF, Bremner RM, Hoeft SF, Ehsan A, Peters JH, Bremner CG, DeMeester TR: Value of physiologic assessment of foregut symptoms in a surgical practice. Surgery 1993, 114, (4): 780-786.
15. Tack J, Caenepeel P, Arts J, Lee KJ, Sifrim D, Janssens J: Prevalence of acid reflux functional dyspepsia and its association with symptom profile. Gut. 2005; 54 (10): 1370-6.
16. Savarino E, Pohl D, Zentilin P, Dulbecco P, Sammito G, Sconfienza L, Vigneri S, Camerini G, Tutuian R, Savarino V. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. Gut 2009; 58(9):1185-1191.
17. Fuchs KH, Musial F, Ulbricht F, Breithaupt W, Reinisch A, Schulz T, Babic B, Fuchs HF, Varga G. Foregut symptoms, somatoform tendencies, and the selection of patients for antireflux surgery. Dis Esophagus 2017; 30: 1-10.
18. Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-esophageal reflux disease. Lancet 1990; 335: 205-208.
19. DeMeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. Patterns of gastroesophageal reflux in health and disease. Ann Surg. 1976 Oct;184(4):459-70.

20. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmülling C, Neugebauer E, Troidl H. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg. 1995 Feb;82(2):216-22.
21. Fuchs KH, Thiede A, Engemann R, Deltz E, Stremme O, Hamelmann H. Reconstruction of the food passage after total gastrectomy: randomized trial. World J Surg. 1995 Sep-Oct;19(5):698-705; discussion 705-6.
22. Fein M, Fuchs KH, Thalheimer A, Freys SM, Heimbucher J, Thiede A. Long-term benefits of Roux-en-Y pouch reconstruction after total gastrectomy: a randomized trial. Ann Surg. 2008 May;247(5):759-65. doi: 10.1097/SLA.0b013e318167748c.
23. DeMeester TR. Etiology and Natural History of Gastroesophageal Reflux Disease and Predictors of progressive Disease. in Shackelford`s Surgery of the Alimentary Tract, eds CJ Yeo, SR DeMeester, DW Mc Fadden, 8th edition, Elsevier Philadelphia, 2019, 204-220.
24. Kavitt RT, Higginbotham T, Slaughter JC et al. Symptom reports are not reliable during ambulatory reflux monitoring. Am J Gastroenterol 2012; 107: 1826-1832.
25. Bradley LA, Richter JE,Pulliam TJ et al. The relationship between stress and symptoms of gastroesophageal reflux: the influence of psychological factors. Am J Gastroenterol. 1993; 88(1):11-19.
26. Johnston BT, Lewis SA, Love AH: Stress, personality and social support in gastro-oesophageal reflux disease. J Psychosom Res. 1995; 39(2):221-6.
27. Oustamanolakis P, Tack J. (2012), Dyspepsia – organ versus functional. J Clin Gastroenterol 46: 175-190.
28. Lei WY, Chang WC, Wen SH, Wong MW, Hung JS, Yi CH, Liu TT, Hsu CS, Orr WC, Vaezi MF, Pace F, Hsieh TC, Chen CL. Impact of concomitant dyspepsia and irritable bowel syndrome on symptom burden in patients with gastroesophageal reflux disease. J Formos Med Assoc. 2019 Apr;118(4):797-806. doi: 10.1016/j.jfma.2018.12.002.
29. Kahrilas PJ, Jonsson A, Denison H, Wernerson B, Hughes N, Howden CW. Concomitant symptoms itemized in the Reflux Disease Questionaire are associated with attenuated heartburn response to acid suppression. Am J Gastroenterol, 2012; 107(9): 1354-60.
30. Kahrilas PJ, Jonsson A, Denison H, Wernersson B, Hughes N, Howden CW: Regurgitation is less responsive to acid suppression than heartburn in patients

with gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2012; 10 (6): 612-9.

31. Kiljander TO, Salomaa ERM, Hietanen EK, et al. Chronic cough and gastro-esophageal reflux: A double-blind placebo-controlled study with omeprazole. Eur Respir J 2000;16:633–8.
32. Allen CJ, Anvari M. Gastro-esophageal reflux related cough and its response to laparoscopic fundoplication. Thorax 1998; 53:963–968.
33. Smith JA, Decalmer S, Kelsall A et al. Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. Gastroenterology 2010; 139:754-762.
34. Pacheco-Galvan A, Hart SP, Morice AH Relationship between gastro-oesophageal reflux and airway diseases: the airway reflux paradigm. Arch Broncopneumol. 2011; 47:195-203.
35. Kahrilas PJ, Altman KW, Chang AB et al. Chronic cough due to gastroesophageal reflux in adults: Chest guideline and expert panel report. Chest 2016; 150: 1341-1360.
36. Ayazi S, Lipham JC, Hagen JA et al. A New Technique for Measurement of Pharyngeal pH: Normal Values and Discriminating pH Threshold. Journal of Gastrointestinal Surgery 2009; 13: 1422-1429.
37. Fuchs HF, Muller DT, Berlth F et al. Simultaneous laryngopharyngeal pH monitoring (Restech) and conventional esophageal pH monitoring-correlation using a large patient cohort of more than 100 patients with suspected gastroesophageal reflux disease. Dis Esophagus 2018, DOI: 10.1093/dote/doy018
38. Fuchs KH, Babic B, Breithaupt W, Dallemagne B, Fingerhut A, Furnee E, Granderath F, Horvath OP, Kardos P, Pointner R, Savarino E, Van Herwarden-Lindeboom M, Zaninotto G. EAES recommendations for the management of Gastroesophageal reflux Disease, Surg Endosc, 2014; 28: 1753- 1773.
39. Wilhelm D, Jell A, Feussner H, Schmid RM, Bajbouj M, Becker V. Pharyngeal pH monitoring in gastrectomy patients - what do we really measure? United European Gastroenterol J. 2016 Aug;4(4):541-5. doi: 10.1177/2050640615617637.

40. Nennstiel S, Andrea M, Abdelhafez M, Haller B, Schmid RM, Bajbouj M, Becker V. pH/multichannel impedance monitoring in patients with laryngo-pharyngeal reflux symptoms - Prediction of therapy response in long-term follow-up. Arab J Gastroenterol. 2016 Sep;17(3):113-116. doi: 10.1016/j.ajg.2016.08.007.
41. Dent J, Vakil N, Jones R,Bytzer P; Schöning U, Halling K, Junghard O Lind T. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of PPI treatment: the Diamond Study. Gut, 2010; 59: 714-721.
42. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, Lind T. Development of the GERDQ, a tool for the diagnosis and management of gastroesophageal reflux disease in primary care; Aliment Pharmacol Ther, 2009; 30: 1030-8.
43. Bolier EA, Kessing BF, Smout AJ, Bredenoord AJ. Systematic review: questinonaires for assessment of GERD, Dis Esophagus, 2015; 28: 105-120.
44. Koloski NA, Jones M, Hammer J, von Wulffen M, Shah A, Hoelz H, Kutyla M, Burger D, Martin N, Gurusamy SR, Talley NJ, Holtmann G. The validity of a new structured assessment of Gastrointestinal Symptoms scale (SAGIS) for eevaluating symptoms in the clinical setting. Dig Dis Sci, 2017; 62: 1913-1922.
45. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 years later: Past,Present and Future developments. J pain Symptom Manage, 2017; 53: 630-643.
46. Monroy M, Ruiz MA, Rejas J, Soto J. Mapping of the Gastrointestinal Short Form Questionnaire (GSF-Q) into EQ-5D-3L and SF-6D in patients with GERD. Health Qual Life Outcomes. 2018; 16.177; doi 10.1186/s12955-018-1003-y.
47. Wong WM, Lam KF, Lai KC, Hui WM, Hu WH, Lam CL, Wong NY, Xia HH, Huang JQ, Chan AO, Lam SK, Wong BC. A validated symptoms questionnaire (Chinese GERDQ) for the diagnosis of gastro-oesophageal reflux disease in the Chinese population. Aliment Pharmacol Ther. 2003 Jun 1;17(11):1407-13.
48. Rentz AM, Kahrilas P, Stanghellini V, Tack J, Talley NJ, de la Loge C, Trudeau E, Dubois D, Revicki DA. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. Qual Life Res. 2004 Dec;13(10):1737-49.

49. Velanovich V. The development of the GERD-HRQL symptom severity instrument. Dis Esophagus. 2007;20(2):130-4.
50. Kwiatek MA, Kiebles JL, Taft TH, Pandolfino JE, Bové MJ, Kahrilas PJ, Keefer L. Esophageal symptoms questionnaire for the assessment of dysphagia, globus, and reflux symptoms: initial development and validation. Dis Esophagus. 2011 Nov;24(8):550-9. doi: 10.1111/j.1442-2050.2011.01202.x.

Table 1: patients characteristics for each group

	Group 1 1995-1999	Group 2 2005-2009	Group 3a and 3b 2015-2017	Statistics p
n	481	333	217	
Sex (male / female)	275 / 206	180 / 115	123 / 94	ns
age (years) Mean median	 48.7 50	 51.9 53	 52.6 55	Group 1vs2 p<0.0014 1vs3 p<0.0009 2vs3 ns
BMI mean	27.1	27.3	27.2	ns
Esophagitis % presence	76.2	55.1	55.6	Group 1vs2 p< 0.00001 1vs3 p<0.00001 2vs3 ns
Hiatal hernia % presence	94.5	86.3	78.8	Group 1vs2 p<0.0002 1vs3 p<0.00001 2vs3 p<0.032
GIQLI mean (normal: 121)	92.9	91.1	88.5	ns
LES incompetence % presence	89.4	78.0	85.0	Group 1vs2 p<0.0004 1vs3 ns 2vs3 ns
Esophageal acid exposure	53.9	39.0	56.2	Group 1vs2 p<0.001

Mean (normal:<14.7) % presence of pathologic acid exposure	85.5	70.6	87.0	1vs3 ns 2vs3 p<0.001

Table 2: Overview on the percentage of documented symptoms with intensity 5 (chief complaint) differentiated for each group

Symptom	Group1 %	p	Group2 %	p	Group3a %
Heartburn	60	Ns	61	Ns	61.6
Regurgitation	17	Ns	13.6	Group1: 0.03 Group2: 0.01	36.4
Retrosternal pain/ cramps	4.2	ns	6.3	Ns	4.0
Respiratory symptoms Cough, hoarseness	1.6	0.001	21.3	group2: ns group1: 0.001	20.3
Dysphagia	3.6	ns	3.2	Ns	2.0
Epigastric pain	13.1	0.01	24.7	Group2: 0.02 Group1: ns	12.1
Nausea, vomiting	6.6	Ns	9.7	Ns	2.0
Fullness	7.0	Ns	10.7	Ns	7.0
„gas“-related symptoms Belching, bloating, flatulence	3.3	0.01	27.2	Group2: ns Group1: 0.01	22.0

Table 3: Overview on the percentage of overall presence of documented symptoms differentiated for each group

Symptom	Group1 %	p	Group 2 %	p	Group 3a %
Heartburn	82.4	Ns	89.9	Group2: 0.007 Group1: ns	78.8
Regurgitation	58.8	Ns	54.6	Group2: 0.001 Group1: 0.01	73.7
Retrosternal pain/ cramps	16.7	ns	14.0	ns	14.1
Respiratory symptoms Cough, hoarseness	11.8	0.03	24.9	0.00001	54.5
Dysphagia	18.7	0.01	31.4	Group2: 0.04 Group1: ns	19.2
Epigastric pain	47.2	0.04	58.9	Group2: 0.0001 Group1: ns	32.3
Nausea, vomiting	23.6	Ns	39.2	ns	32.3
Fullness	11	0.00001	73.2	Group2: 0.00001 Group1: 0.00006	93.9
„gas“-related symptoms Belching, bloating, flatulence	34	0.00001	72.7	Group2: 0.0001 Group1:0.00001	93.9

Table 4: Overview on percentage of symptoms in a free text version self-assessed symptoms versus and documentation in a self-assessed structured questionnaire

Symptoms	Self-assessed chief complaints (intensity 5) in free text %	Self-assessed chief complaints (intensity 5) in a structured questionnaire %
heartburn	31	62
regurgitation	5	36
Retrosternal pain	8	4
Respiratory symptoms	9	20
dysphagia	1	2
Epigastric pain	9	12
Nausea / vomiting	5	2
fullness	1	7
Gas-related symptoms	4	22
Burning in throat	7	-
Burning in mouth	7	-
globus	2	-
dyspnea	3	-
headache	1	-

Table 5: Overview on the mean intensity of symptoms differentiated for each group

Symptom	Group1 %	p	Group2 %	p	Group 3a %
Heartburn	3.6	ns	3.88	0.03	3.4
Regurgitation	3.2	0.0001	1.7	0.001	2.6
Retrosternal pain/ cramps	3.3	0.0001	0.5	ns	0.5
Respiratory symptoms Cough, hoarseness	2.4	0.0001	0.99	0.00001	1.8
Dysphagia	2.6	0.0001	0.9	ns	0.5
Epigastric pain	3.2	0.0001	2.2	0.0001	1.1
Nausea, vomiting	1.9	ns	1.4	ns	1.1
Fullness	2.2	ns	2.3	ns	2.5
„gas“-related symptoms Belching, bloating, flatulence	2.5	ns	2.3	ns	2.4