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ORIGINAL ARTICLE

Ninety-Six Hour Wireless Esophageal pH Study in Patients with GERD Shows that Restrictive Diet Reduces Esophageal Acid Exposure

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Abstract

Background Prolonged (96 h) pH monitoring may explore the effect of diet on pH and symptoms in patients with GERD.

Aims To assess the usefulness of a 96 h esophageal pH study in patients with GER symptoms under different diets (pro- and anti-GER).

Methods Prospective study of 66 patients with GERD undergoing wireless 96 h pH monitoring. Two-day periods, one on liberal (pro-reflux) and another on restricted (anti-reflux) diet assessed esophageal acid exposure and symptoms. The *primary* end point was normalization of acid exposure time while on restricted diet. *Secondary* end point was a > 50% reduction in symptoms with restricted diet.

Results Normal (pH time < 4 of < 6%) was found in 34 patients (51.5%) while on the initial 48 h (liberal) diet [median % time < 4: 3.2 (95% CI, 1.9, 4.0)] and remained normal while on restricted diet [median % time < 4: 2.6 (95% CI, 0.8, 3.4)]. Abnormal acid exposure (% pH time < 4: > 6%) was found in 32 patients (48.5%) while on initial 48 h liberal diet [median % time < 4: 10.5, (95% CI 8.9, 12.6)], and decreased significantly with restricted diet [median % time < 4: 4.5 (95% CI 3.1, 7.3)] ($p = 0.001$), and normalized with anti-GERD diet in 21 patients (65.6%). Only 11/66 patients were candidates for proton pump inhibitor (PPI) use; 34 had either normal pH studies or normalized them with restricted diet ($n = 21$). Symptoms did not improve with restricted diet.

Conclusions The 96-h esophageal pH study tests for GERD under pro- and anti-GER diets and allows minimization of PPI therapy to only 16.6% of patients.

Keywords Gastroesophageal reflux disease (GERD) · Proton pump inhibitors (PPI) · High-resolution impedance manometry (HRM) · Esophageal ambulatory pH monitoring · Diet

Abbreviations

GERD	Gastroesophageal reflux disease
PPI	Proton pump inhibitors
HRM	High-resolution impedance manometry
AET	Acid exposure time

Introduction

Wireless ambulatory esophageal pH measurement provides an objective tool for the diagnosis of gastroesophageal reflux disease (GERD). The test is used to confirm pathological esophageal acid exposure in patients with reflux symptoms that fail to respond to acid suppressive therapy, to correlate reflux events and symptoms, and to validate the presence of GERD in patients considered for anti-reflux surgery [1]. The 48 h Bravo® wireless system has made pH studies more comfortable and acceptable to patients, with less impact on patient behavior and diet, although occasional foreign body sensation upon swallowing may be reported [2]. In clinical practice, 48 h Bravo pH measurements can be very useful in assessing all such patients and identifying who may truly benefit from long-term proton pump inhibitor (PPI) use. Performing the study "off" PPI therapy establishes the role

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of GERD in the induction of symptoms in patients who are either complete responders (diagnosis validation), partial responders (dosage validation), or non-responders to PPIs (diagnosis exclusion) [3]. Given emerging data regarding PPI adverse effects, increasing patient anxiety regarding treatment and financial implications, pH monitoring that objectively assesses reflux in lieu of empiric PPI therapy may be beneficial from both patient-oriented and societal standpoints. The Symptom Index (SI) and the Symptom Association Probability (SAP) can also be used to correlate the patient's symptoms with the timing and nature of reflux-ate [4]. According to some authors, more prolonged (96-h) recordings using the Bravo pH system may not be needed and potentially misleading [5]. There have been no studies exploring the role of pH monitoring in recognizing and validating GERD under different dietary conditions.

The aim of the present study was to assess the feasibility, tolerability, and practical value of 96 h wireless ambulatory esophageal pH study in patients presenting with GER symptoms under different dietary conditions that favor or impede GER. Such prolonged study would allow for 2x48 h wireless pH studies to be performed in tandem, first on liberal (pro-GER) diet, followed by restricted (anti-GER) diet. We hypothesized that in patients with normal acid exposure time (AET), defined as $\%pH < 4.0 < 6$, there would be no pH or symptom differences between pro-GER and anti-GER diets. In contrast, in those patients with pathologic AET, defined as $\%pH < 4.0 \geq 6$, the restricted diet would potentially reduce the magnitude of AET and GERD symptoms. If the 96-h study were normal, there would be no need for PPI and one could stop previously administered empiric PPI therapy. If pathologic AET was to occur only with pro-GER diet, restricted (anti-GER) diet could be the preferred long-term approach, again avoiding PPI. If pathologic AET was to occur even with the anti-GER diet, then PPI therapy (or endoscopic or surgical therapy) would be necessary. Further, if symptoms and AET were to match, the presence of GERD would be validated; if not, other therapies could be implemented for functional heartburn, using Rome IV criteria [6].

Patients and Methods

Patients

This prospective open study was approved by the Institutional Research Board of El Camino Hospital and was conducted at the Neuro-gastroenterology and Motility Center of Silicon Valley Gastroenterology, in Mountain View, CA. All studies were performed with the intention of acquiring 96-h pH and symptom data in patients referred for the investigation of symptoms suspected to be related to acid reflux. Acid suppressive treatments were stopped at least 10 days before the pH study, and all studies were performed entirely off acid suppressing medications. *Inclusion criteria*: We included all patients reporting heartburn and/or regurgitation in addition to other GERD symptoms, such as dysphagia, chest and epigastric pain, and/or belching. The patients' esophageal complaints were recorded both upon questioning as well as by formal questionnaire-based assessment. At baseline, all patients in the cohort also underwent a full structural (upper endoscopy with biopsies) and functional (high-resolution manometry and 96-h wireless ambulatory pH monitoring) evaluation. These studies were performed in order to phenotypically characterize the patients and it was based on our previous experience where significant overlap was noted among patients presenting with GERD symptoms [7]. A detailed review of patient's medical, endoscopic, manometric, pH, and histological records was then performed to ensure proper inclusion in the 2 groups, those with normal (defined as time with $\%pH < 4.0 > 6$) and those with abnormal AET (defined as time with $\%pH < 4.0 > 6$). *Exclusion criteria*: Patients < 16 years old, those with known obstructive esophageal disease by endoscopy (i.e., cancer, stricture), scleroderma, and those who had previously undergone esophago-gastric surgery (i.e., anti-reflux surgery or myotomy) or endoscopic intervention (i.e., transoral fundoplication) were excluded. Patients with atypical (ENT or respiratory) symptoms only and those with oropharyngeal dysphagia without associated esophageal symptoms were also excluded. End points: The *primary* end point was normalization of AET while on restricted (anti-GER) diet as compared to the AET while on liberal (pro-GER) diet. As such, this end point would potentially eliminate the need for PPI therapy. The *secondary* end point was a > 50% reduction in reflux symptoms as recorded by patients during the two study periods. Both the primary and secondary end points were analyzed separately in two groups (normal and abnormal AET) during the first 48 h on a liberal diet. Additional analyses of data from all patients were also made.

Questionnaires

To qualify for inclusion into the study, patients had to be symptomatic on a simple and previously extensively used questionnaire that was filled out upon initial presentation in the absence of treatment with acid blockers, prokinetics, or other drugs affecting gastrointestinal motility. In this questionnaire, the symptoms were graded with scores for dysphagia, heartburn, regurgitation, lower chest and epigastric pain, and belching (0 = no symptom, 1 = mild symptom, 2 = moderate symptom, and 3 = severe symptom, occurring at various frequencies [once a week = 0, 2 to 6 times a week = 1, 7 to 15 times a week = 2, and more than 15 times a week = 3]) [8]. Although not intended for the diagnosis of gastroesophageal reflux disease (GERD), this questionnaire is similar to

the 6-item GerdQ tool but incorporates additional ratings for dysphagia and belching [9].

Endoscopy and Biopsies

Upper endoscopy with random proximal and distal esophageal biopsies as well as targeted biopsies of esophageal lesions was performed as part of the structural assessment in all patients. Patients were classified in various disease categories as follows: Normal: Endoscopy-negative; Erosive esophagitis (EE): endoscopy-positive for any LA classification grades; Barrett's esophagus (BE): Endoscopically visible and histologically proven intestinal metaplasia. The diagnosis of eosinophilic esophagitis was based on the histological presence of > 15 eosinophils per high-power field. Sliding hiatal hernia was defined endoscopically and graded in cm length. Esophagitis and BE were also independently assessed histologically, using standard criteria [10].

Prolonged Esophageal Ambulatory pH Monitoring

In all patients, esophageal ambulatory pH monitoring was performed "off" PPI therapy for a minimum of 10 days before and 4 days during the study, using a wireless 96-h Bravo® pH system (Medtronic, Sunnyvale, CA) comprised of a delivery system, pH recording capsule with integrated radio transmitter, a radio receiver and recording device, and software for data analysis. After calibration, the capsule was positioned 6 cm above the Z line previously determined by direct endoscopic control. Data were transmitted to a receiver worn on a strap or belt. Subjects were instructed to document meal times, position change, and symptoms (heartburn, chest pain, regurgitation) on the receiver. Symptoms in patient diaries and symptom logs on the Bravo receiver were compared. Reflux event detection was set at a sampling frequency of every 6 s and defined as two consecutive measurements of pH < 4 (*i.e.*, 12-s acid exposure). These data were downloaded and analyzed by proprietary software (Medtronic, Sunnyvale, CA). Patients were instructed to carry out normal daily activities consuming liberal (pro-GER) diet during the first 48 h of the study, followed by a restricted (anti-GER) diet for the next 48 h and to record their symptoms using the recorder button and a diary. The percentages of upright, supine, and postprandial reflux during liberal and restricted diets were also assessed in both groups, as was the SAP that was used to correlate the patient's symptoms with the timing and nature of refluxate. The instructions and diet recommendations are shown in "Appendix" [11]. In order to preserve the practical, real-life, nature of the study, patients were not asked to record the specifics of the meals (nature, caloric content, or timing), but instead, they were only counselled on generalities of the 2 dietary regimens recommended.

Acid exposure time (AET) was defined as the percentage of total time the pH in the distal esophagus remained lower than 4.0, expressed as a percentage; values ≥ 6% per 24 h defined an abnormal AET. For each patient, the average from the first 2 days (on pro-GER diet) was considered as the baseline AET and was compared to the average from the latter 2 days on restrictive (anti-GER) diet. Depending on the baseline (first 48 h) AET, patients were divided into two groups, those with normal and those with abnormal AET. Total pH times < 4.0, as well as upright and supine times and the SAP scores were also recorded as percentages.

High-Resolution Impedance Manometry

To better clinically characterize the patients, solid state HRIM catheter with 4.2 mm outer diameter with 36 circumferential sensors located at 1 cm intervals incorporating impedance measurements to assess the success or failure of bolus movements through the esophagus was used (Manoscan Eso-Z module, Medtronic, Sunnyvale, CA). After at least a 6 h fast, the manometric protocol included 30 s without swallows to assess basal EGJ pressure and morphology followed by 10 5-ml swallows of 0.3% saline. The final diagnosis was made according to the Chicago Classification v.3 [12].

Statistics

Statistical analysis was performed using commercial statistical software (Minitab Express). The paired *t* test was used to compare continuous variables. For all statistical analyses, the level of significance was set at $p < 0.05$. Results are depicted as tables, bar graphs, and box plots, as needed. For the sample size calculation, if ten patients would enter this study, the probability would be 80% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments were 5.0 pH units (primary end point of > 50% reduction of AET).

Results

Patients

From January 2018 to May 2019, prolonged, 96-h Bravo esophageal pH monitoring studies were prospectively performed in 66 patients, 36 women [54%], median age 51 years [range 20-87]) as part of an investigation of esophageal symptoms suggestive of GERD. Upon entry into the study, all patients had typical reflux symptoms, such as heartburn and/or regurgitation (100%), 54% of patients had epigastric pain, 44% had dysphagia and 59% had belching. Tables 1 and 2 depict the general

Table 1 Baseline characteristics of the normal AET cohort ($n=34$)

Age	Sex	BMI	EGD	HH (cm)	HRM	PPI response	Diagnosis
87	M	25	BE	0	ND	Complete	BE
63	M	26	B	0	EGJOO	None	EE
20	M	21	N	0	IEM	Complete	FH
86	M	21	N	2	EGJOO	Incomplete	FH
52	F	39	N	0	N	Incomplete	FH
83	F	25	B	0	N	Incomplete	EE
25	F	26	EoE	0	N	Complete	EoE
26	F	27	N	0	N	None	FH
35	M	30	N	0	ND	None	FH
50	F	23	N	0	N	Incomplete	HE
32	M	23	N	0	IEM	Incomplete	FH
54	F	22	N	0	EGJOO	Incomplete	FH
58	F	21	N	0	N	Incomplete	HE
65	F	19	N	1	EGJOO	Incomplete	FH
55	F	15	N	0	EGJOO	Incomplete	FH
24	M	26	N	0	N	Incomplete	HE
21	F	21	N	0	JE	Incomplete	FH
71	F	35	N	5	JE	Incomplete	FH
48	F	20	N	0	N	None	FH
59	F	29	N	0	EGJOO	Incomplete	HE
38	M	24	N	0	EGJOO	Incomplete	FH
42	F	21	N	0	N	None	HE
44	F	21	N	0	IEM	None	FH
74	F	23	N	0	N	Complete	HE
66	F	19	N	0	JE	Incomplete	FH
50	F	24	B	0	N	Complete	FH
65	M	31	B	3	DES	Complete	EE
22	F	17	N	0	JE	None	HE
80	F	46	N	3	DES	None	FH
31	M	36	N	0	N	Not tried	FH
32	M	21	EoE	0	IEM	Incomplete	EoE
67	M	24	N	0	DES	Not tried	HE
66	F	29	N	1	DES	Incomplete	HE
36	M	27	N	0	JE	Complete	FH

N Normal, *NERD* Non-erosive reflux disease, *EE* Erosive esophagitis, *B* Grade B, *BE* Barrett's esophagus, *EoE* Eosinophilic esophagitis, *EGJOO* Esophago-gastric junction outlet obstruction, *IEM* Ineffective esophageal motility, *HE* Hypersensitive esophagus, *FH* Functional heartburn, *M* Male, *F* Female, *ND* Not done

demographics and endoscopic, histological, and manometric characteristics of the 2 cohorts (normal and abnormal baseline AET, respectively), the response to previous PPI therapy and their final clinical diagnoses. The mean BMI ($\pm$ SEM) in those with normal AET was 24.7 ± 1.9 while in those with abnormal AET was 26 ± 1.1 ($p=0.057$; 95% CI -6.2, 3.6); the mean hiatal hernia length ($\pm$ SEM) in those with normal AET was 0.8 ± 0.4 while in those with abnormal AET was 1.5 ± 1.6 ($p=0.3$; 95% CI -2.3, 0.7). Table 3 describes the symptom scores upon entry into the study, highlighting that the two groups, those with normal and abnormal AET, were similar in baseline symptom frequency and severity which, based on standard questionnaires, was considered mild to moderate.

Feasibility and Tolerability of 96-h pH Studies

Wireless pH studies were performed in all patients with the intention of collecting 96-h pH data (two consecutive 48-h periods on liberal and restricted diets, respectively). There were no transmission failures. Two patients had premature capsule detachment; hence, complete 4-day recordings were available only for 64 patients. Figure 1 shows a characteristic pH tracing exemplifying the improvement

Table 2 Baseline characteristics of the abnormal AET cohort ($n=32$)

Age	Sex	BMI	EGD	HH (cm)	HRM	PPI response	Diagnosis
44	M	24	N	0	EGJOO	None	NERD
58	F	31	N	4	N	Incomplete	NERD
79	F	22	B	0	ND	Incomplete	EE
83	F	24	B	5	DES	Complete	EE
69	M	27	N	0	IEM	Incomplete	NERD
72	M	25	N	2	IEM	None	NERD
75	M	27	N	0	N	Incomplete	NERD
67	F	31	N	4	IEM	Incomplete	NERD
50	M	23	N	0	ND	Incomplete	NERD
79	F	32	N	3	ND	Incomplete	NERD
78	M	24	B	5	IEM	None	EE
77	M	24	N	3	IEM	Incomplete	NERD
26	F	21	N	0	N	None	NERD
23	M	23	N	0	N	Incomplete	NERD
35	M	26	N	4	N	Incomplete	NERD
69	M	19	N	0.5	IEM	Incomplete	NERD
20	F	18	N	0	ND	Incomplete	NERD
37	M	29	N	0	IEM	Incomplete	NERD
59	F	26	N	0	JE	Complete	NERD
35	F	27	N	0	N	None	NERD
37	F	34	N	0	IEM	None	NERD
44	F	22	N	2	IEM	Complete	NERD
58	F	26	N	0	JE	Incomplete	NERD
34	F	23	N	0	EGJOO	Not tried	NERD
90	F	22	B	0	DES	Complete	EE
24	M	41	N	0	N	Not tried	NERD
68	M	30	N	0	N	None	NERD
36	M	26	N	4	N	Incomplete	NERD
59	M	26	N	0	N	None	NERD
32	M	33	B	0	DES	Complete	EE
69	F	22	N	0	N	Complete	NERD
71	M	21	N	2	DES	None	NERD

N Normal, *NERD* Non-erosive reflux disease, *EE* Erosive esophagitis, *B* Grade B, *BE* Barrett's esophagus, *EoE* Eosinophilic esophagitis, *EGJOO* Esophago-gastric junction outlet obstruction, *IEM* Ineffective esophageal motility, *FH* Functional heartburn, *M* Male, *F* Female, *ND* Not done

Table 3 Baseline (entry) symptom scores, based on study questionnaires, in patients with normal and pathologic AET by prolonged esophageal wireless pH monitoring

Symptom	Normal AET (< 6%)	Abnormal AET (> 6%)	*p* value
Epigastric pain (mean ± SEM)	0.9 ± 0.1	1.0 ± 0.2	0.82
Heartburn (mean ± SEM)	1.6 ± 0.2	1.8 ± 0.2	0.44
Acid regurgitation (mean ± SEM)	1.6 ± 0.2	1.5 ± 0.2	0.55
Dysphagia (mean ± SEM)	1.0 ± 0.6	0.4 ± 0.1	0.002
Belching (mean ± SEM)	1.0 ± 0.1	1.2 ± 0.2	0.5

(in this case, normalization) of the AET during the restrictive (anti-GER) diet. Two patients complained of minor retrosternal discomfort upon swallowing, but they did not limit their diet because of this. Endoscopic removal of the capsule was not needed in any of the patients. All patients were able to carry on with their normal activities of daily living including working and eating regularly. Nobody reported any limitations due to the presence of the capsule and the external data collector.

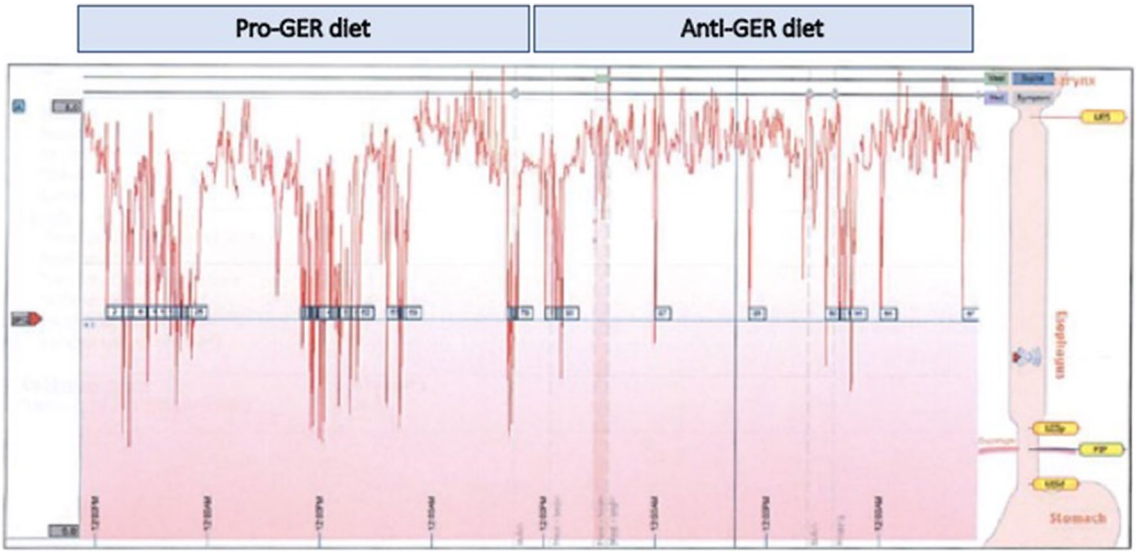

Fig. 1 Representative 96 h wireless, ambulatory esophageal pH monitoring study highlighting the degree of esophageal acid exposure during the first 48 h (on liberal, pro-GER diet) and during the latter 48 h (on restrictive, anti-GER diet)

Acid Exposure Times

Normal esophageal acid exposure (pH time < 4.0 of < 6%) was found in 34 (51.5%) during the initial 48 h (liberal diet) period [median % time < 4.0: 3.2 (95% CI, 1.9, 4.0)] and remained normal during the restricted diet period [median % time < 4.0: 2.6 (95% CI, 0.8, 3.4)] (Fig. 2a, b) Abnormal esophageal acid exposure (pH time < 4.0 of > 6%) was found in 32 patients (48.5%) during the initial 48 h liberal diet period [median % time < 4.0: 10.5, (95% CI 8.9, 12.6)], decreased significantly during the restricted diet period [median % time < 4.0: 4.5 (95% CI 3.1, 7.3)] ($p = 0.001$), and normalized (pH time < 4.0 of < 6%; primary end point) during the restricted diet in 21 of such patients (65.6%). Overall, based on pH data, only 11/66 patients were considered candidates for proton pump inhibitor use; 34 patients had either normal pH studies or normalized them while on restricted diet ($n = 21$). The upright reflux percentage decreased significantly with restricted diet only in the group with abnormal AET (11.3 ± 1.2 vs. 6.3 ± 0.9, 95% CI, 2.15. 7.7, $p = 0.001$). In contrast, the upright reflux was not different in those with normal AET (3.4 ± 0.4 vs. 2.9 ± 0.4 ($p = 0.4$) (Fig. 3a, b). The % supine pH < 4.0 was not affected by the restricted diet in patients with normal AET (2.07 ± 0.5 vs. 1.4 ± 0.4 ($p = 0.16$). However, the % supine reflux was significantly less in patients with abnormal AET while on restricted diet (7.8 ± 1.2 vs. 4.4 ± 1.1; $p = 0.02$; 95% CI 0.4, 6.4) (Fig. 4a, b). Even if analyzed as a whole group (64 patients), the anti-GER diet was significantly associated with reduced AET (% time < 4.0: 2.3 ± 0.2) as compared to 7.3 ± 0.7 ($p = 0.0001$, 95% CI 3.4, 6.5).

Symptoms

In either group, the number of reflux symptoms recorded during the 96 h period did not significantly improve with restricted diet (Fig. 4a, b). Indeed, both groups exhibited a similar frequency of heartburn and regurgitation events, irrespective of the underlying magnitude of AET or the diet, reflecting a discordance between symptoms and pH control. Four of the 34 patients with normal AET and 6 of the 32 patients with abnormal AET reached the secondary end point of the study (> 50% reduction in recorded symptoms) (Not significant). Similarly, in both groups, the SAP was not significantly different with restricted diet (data not shown).

Discussion

This proof-of-concept study demonstrates that extending wireless pH recording for up to 96-h is feasible and well tolerated by patients under investigation for acid reflux symptoms. Such prolonged study allows for 2×48 h wireless pH studies to be performed in tandem, first on liberal (pro-GER) diet, followed by restricted (anti-GER) diet. We found that, in patients with normal AET, there were no pH or symptom differences between pro-GER and anti-GER diets. In contrast, in those patients with pathologic AET, the restricted diet significantly reduced the magnitude of AET, in both upright and supine positions, but there was no reduction in symptoms despite restricted diet. After the study, if the results of the 96-h study were normal, we defined no need for PPI and stopped previous empiric PPI therapy. If pathologic AET occurred only with pro-GER diet, we

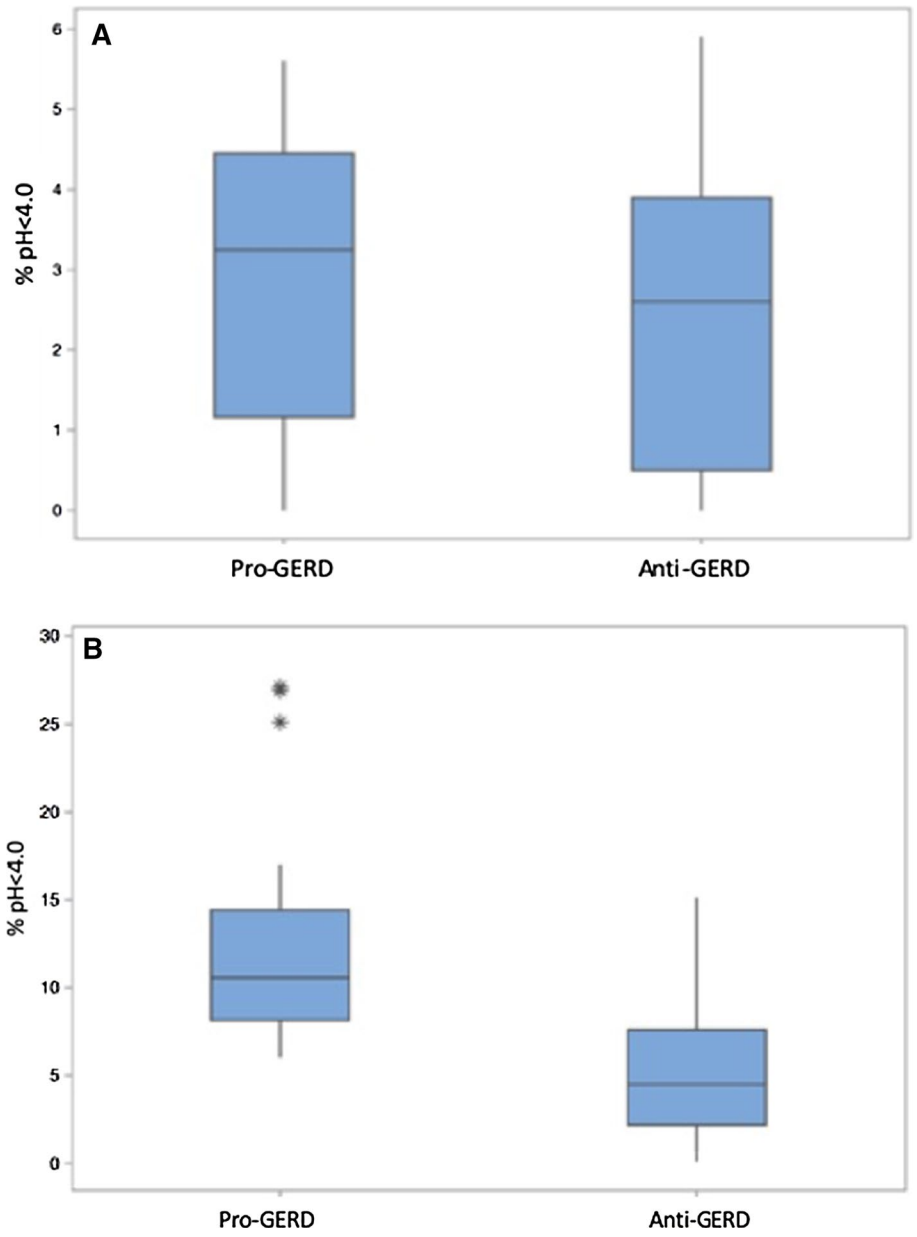

Fig. 2 Box plots of acid exposure times (AET) expressed as %pH < 4.0 in patients with normal (**a**, Top) and abnormal AET (**b**, Bottom) during the first 48 h (on liberal, pro-GER diet) and during the latter 48 h (on restrictive, anti-GER diet). Normal esophageal acid exposure (pH time < 4.0 of < 6%) was found in 34 (51.5%) during the initial 48 h (liberal diet) period [median % time < 4.0: 3.2 (95% CI, 1.9, 4.0)] and remained normal during the restricted diet period [median % time < 4.0: 2.6 (95% CI, 0.8, 3.4)]. Abnormal esophageal acid exposure (pH time < 4.0 of > 6%) was found in 32 (48.5%) during the initial 48 h liberal diet period [median % time < 4.0: 10.5, (95% CI 8.9, 12.6)] and decreased significantly during the restricted diet period [median % time < 4.0: 4.5 (95% CI 3.1, 7.3)] ($p = 0.0001$), and normalized (primary end point) during the restricted diet in 21 (65.6%) of such patients. The plots display the distribution of data as: minimum (bottom whisker), first quartile (lower part of box), median (line in box), third quartile (upper part of box), and maximum (top whisker). Asterisks are outliers

recommended restricted (anti-GER) diet as the preferred long-term approach, again avoiding PPI. If pathologic AET occurred even with the anti-GER diet, then PPI therapy (or endoscopic or surgical therapy) would be necessary. Further, if symptoms and AET were to match, the presence of GERD would be validated; if not, other therapies could be implemented for functional heartburn, using Rome IV criteria (Fig. 5).

Heartburn is frequent in the general population and it is highly suggestive for gastroesophageal reflux disease (GERD) [13, 14]. Patients reporting heartburn are a heterogeneous group including patients with typical symptoms and either increased esophageal acid exposure without esophagitis (non-erosive reflux disease, NERD) acid hypersensitivity, or those with functional heartburn (FH) [15]. Distinguishing between patients with true GERD or NERD and those with FH is important because the first two groups benefit from medical, endoscopic, or surgical therapy, whereas the latter group should not receive unnecessary PPI or anti-reflux surgery. Up to one-third of patients classified as FH by 24-h pH monitoring can be re-classified as NERD after a more prolonged pH recording [16]. Although this observation has an important clinical impact, it was not seen in our group of patients since their clinical diagnosis did not change from one study period to the other.

For a long time, diet and lifestyle modifications have been suggested as first-line therapy for patients with GERD. When an evidence-based approach was applied, there was

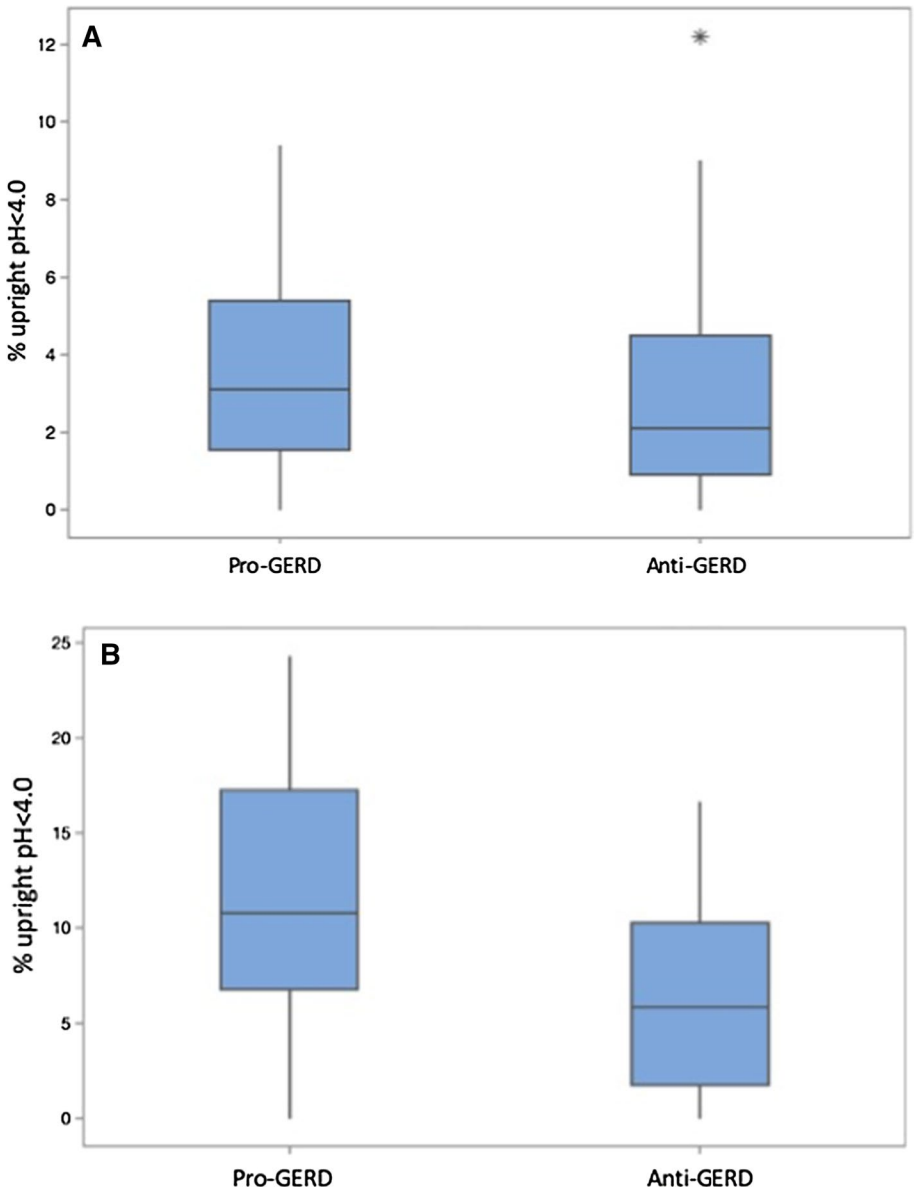

Fig. 3 Upright reflux was not different in those with normal AET (3.4 ± 0.4 vs. 2.9 ± 0.4 ($p = 0.4$) (**a**, Top). In contrast, upright reflux percentage decreased significantly with restricted diet in the group with abnormal AET (11.3 ± 1.2 vs. 6.3 ± 0.9, 95% CI, 2.15. 7.7, $p = 0.0001$) (**b**, Bottom). The plots display the distribution of data as: minimum (bottom whisker), first quartile (lower part of box), median (line in box), third quartile (upper part of box), and maximum (top whisker). Asterisks are outliers

no published evidence of the efficacy of dietary measures [17]. The restricted (anti-GER) diet we used in this study was recommended to us by Dr. Martin Riegler and his group at Reflux Medical GmbH, in Vienna, Austria, and published in his book (see "Appendix"). Given the diet's clinical efficacy in their practice as well as ours, we felt that it would be important to prove its merits in reducing and/or normalizing AET, thereby providing further incentive for patients to continue with its restrictions. As a result of this study, not only we were able to exclude patients as having pathologic reflux, but we were also able to convince patients with abnormal esophageal acid exposure to comply with the restricted diet as the primary tool in their GERD management. However, we do not have any long-term data on adherence and ultimate clinical success, going beyond one follow-up visit 1–2 months later. Therefore, the practical, long-term implications of this approach will require confirmation in larger, longitudinal trials that will examine its role in controlling GERD symptoms.

This study was performed in a "real-life" setting, during routine clinical practice in a community hospital and on patients with GER symptoms who had been previously treated with PPI and were either refractory to therapy or wished to discontinue it. Success with transoral deployment of the pH probe was 100%, and there were no important adverse effects related to the procedure. There were two patients who reported retrosternal discomfort, but all patients continued with normal activities of daily living and diet as instructed. These findings are consistent with previous reports that the wireless pH recordings are better tolerated

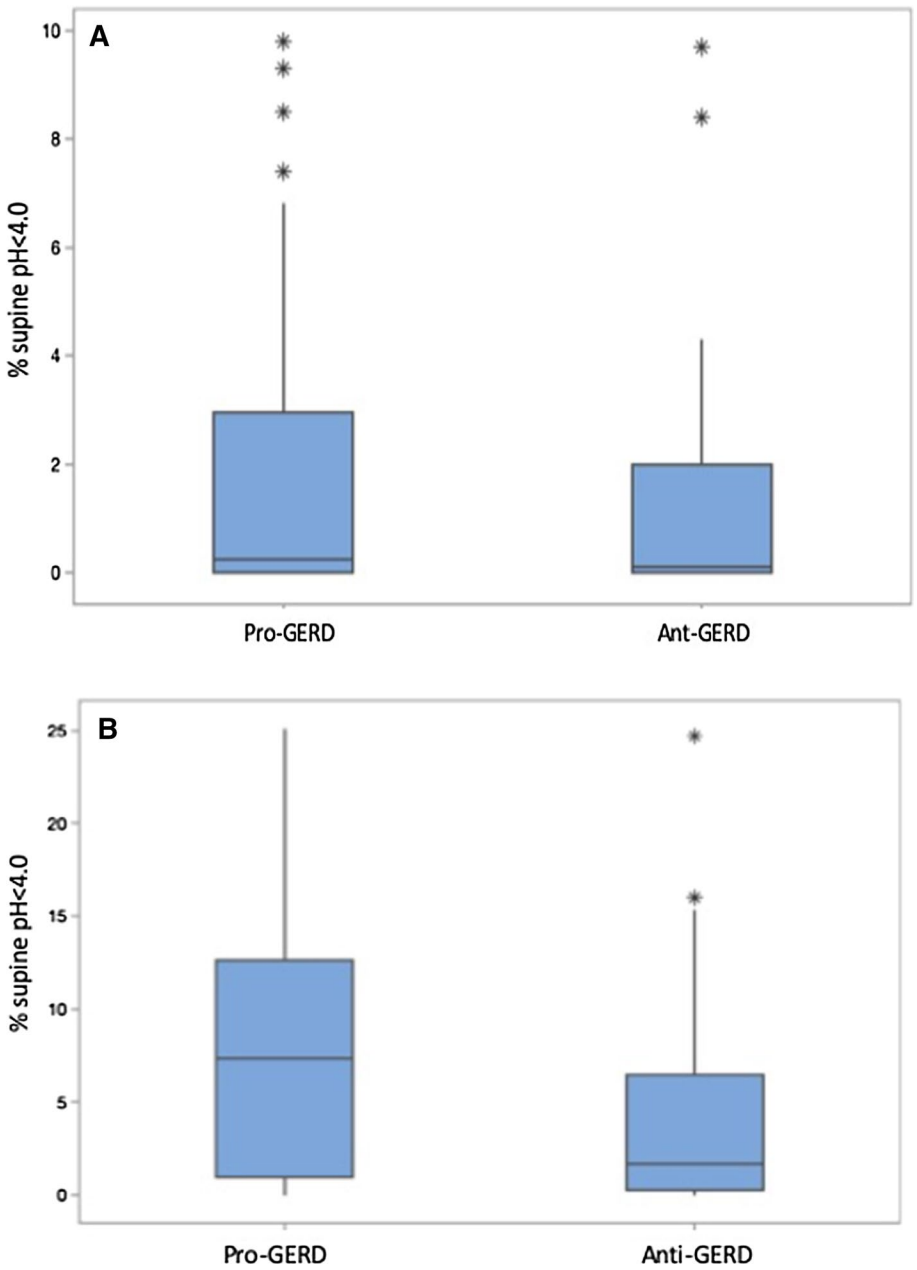

Fig. 4 Supine reflux was not different in those with normal AET (3.4 ± 0.4 vs. 2.9±0.4 ($p = 0.4$) (**a**, Top). In contrast, supine reflux percentage decreased significantly with restricted diet in the group with abnormal AET (11.3 ± 1.2 vs. 6.3 ± 0.9, 95% CI, 2.15. 7.7, $p = 0.002$) (**b**, Bottom). The plots display the distribution of data as: minimum (bottom whisker), first quartile (lower part of box), median (line in box), third quartile (upper part of box), and maximum (top whisker). Asterisks are outliers

than catheter-based pH measurement. All 66 patients were referred for investigation of suspected GERD-related symptoms and underwent wireless pH measurement with the intention of recording intra-esophageal pH for 96 h (two consecutive 48-h periods on different diets) and 64 patients had complete 96-h recordings. Although not always symptomatic, all patients completed the study diaries during every period of the study. The pH data for each study period were classified as normal or abnormal based on the AET ≥ 6%, and these data were then compared. We did not account for day-to-day variability in pH measurements during the 2 days on either diet. Previous studies have shown 48-h pH recording provides more reliable evidence on which to base clinical decisions than either 24-h period or the "worst" study day on which to diagnose GERD (higher positive likelihood ratio). Extending pH recording time increases the likelihood of a significant reflux–symptom relationship and it may improve the diagnostic accuracy or guide effective clinical management. However, this was not the intent of our study which aimed at exploring the role of diet in reducing or normalizing AET and symptoms.

Since we do not have specific information on the composition, consistency, or caloric value of either diets used, we cannot attribute our AET findings to any specific dietary elements. However, our data support the notion that the anti-GER diet reduces the % reflux, possibly because

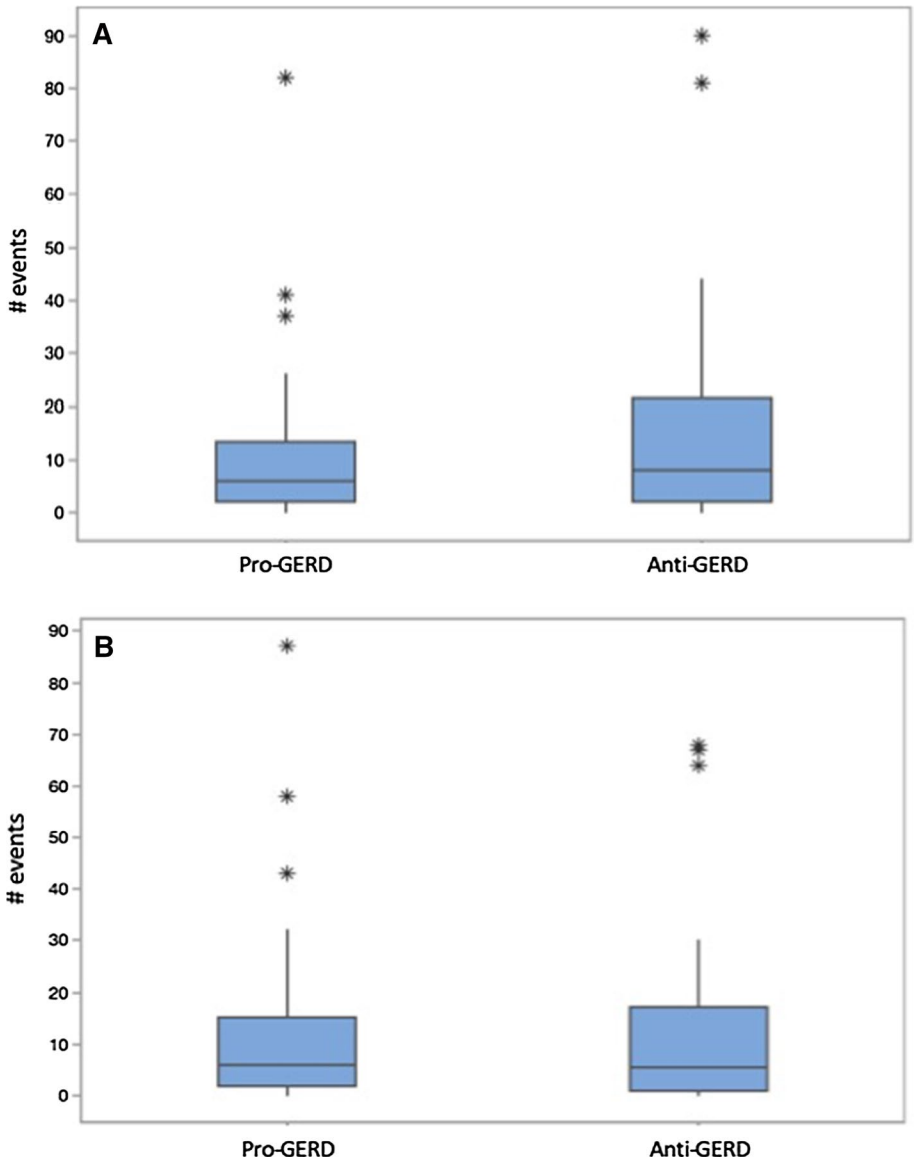

Fig. 5 Box plots of average number of recorded symptoms (marked events) in patients with normal (**a**, Top) and abnormal AET (**b**, Bottom) during the first 48 h (on liberal, pro-GER diet) and during the latter 48 h (on restrictive, anti-GER diet). Neither group improved significantly with restrictive diet (NS). The plots display the distribution of data as: minimum (bottom whisker), first quartile (lower part of box), median (line in box), third quartile (upper part of box), and maximum (top whisker). Asterisks are outliers

of a decrease in the volume of the refluxate (Fig. 3). Further study, utilizing standardized meals and proper dietary records, on the precise timing, and nature of the ingested meals and on larger number of patients will be important to clarify this issue. If confirmed and the specific variables characterized in these future studies, the potential for prepackaged meals, drinks and snacks may become a commercially lucrative option for patients with GERD who are responsive to dietary restriction, in a way similar to the management of obesity using the Weight Watchers or Jenny Craig approaches among others [18].

There are several strengths and weaknesses in our study. The study was prospective, following a real-life scenario and thereby generalizable to all patients with heartburn and regurgitation as their key presenting symptoms. Indeed, our cohort included 18 patients with hiatal hernia and 13 with ineffective esophageal motility, 8 with erosive esophagitis as well as 1 with long segment Barrett's esophagus, all suggestive of significant predisposition to GERD. The prior response to PPI therapy was also variable (13 with complete, 17 with no response, and 32 with incomplete response). The finding of many patients without pathologic AET is not surprising and highlights the merits of pH monitoring in classifying patients in proper clinical phenotypes (i.e., GERD, NERD, FH, etc.) prior to therapy. In this respect, our findings are commensurate with our recent retrospective cohort study showing that in patients with GER symptoms, esophageal pH monitoring may avert PPI use in 50% [19]. In the era of caution regarding PPIs, early testing, as shown in this as well as the current study, may provide assurance and justification for non-pharmacologic therapy. A possible criticism to

our study is the lack of significant effect of the restricted diet on symptoms, which we used as a secondary end point. This may reflect the known lack of perfect correlation between symptoms and acid exposure, the time lapse between acid control (documented by pH monitoring) and symptomatic relief, and the unstructured nature of symptoms recording which was based on patients' thresholds and disposition during the 4-day study period. It is also possible that those with abnormal acid exposure on pro-GER diet might have had sensitized esophageal mucosa and they were still symptomatic from reflux events despite them being less frequent/severe. Larger number of observations with more patients might also deliver the needed power to demonstrate a significant gain in symptoms with restricted diet. We are also uncertain about the long-term impact of the diet since it requires strict adherence which may not be practical or desirable by some. Nevertheless, our data provide a rationale for further use of our method in disease validation and management.

In conclusion, we believe that prolonged (96-h) wireless pH studies are feasible and well tolerated in routine clinical practice. Matched with dietary intervention, such studies can prove GERD and its control by dietary restrictions, limit PPI use and further assist in long-term medical and surgical management.

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Author's contribution Planning and/or conducting the study: GT; Collecting and/or interpreting data: All authors; Drafting the manuscript and revision: All authors.

Appendix: Silicon Valley Gastroenterology 96-h pH Monitoring Diet Instructions

Depending on your effort to comply with the following general directions, the next 4 days will:

1. Prove that you have significant esophageal acid reflux (or not)
2. Identify certain dietary elements that may induce your reflux symptoms
3. Allow you to learn about dietary changes that would help alleviate your reflux symptoms
4. Help us determine what would be the best method to treat your acid reflux (GERD)

Please read the following instructions very carefully and make the relevant diet changes to maximize the information obtained by the test.

The "idea" behind this test is to identify "good" or "bad" things in your diet that could be causing your acid reflux symptoms. As you go through the 4-day study, please:

1. Apply the principles below (requires careful reading and implementation)
2. Keep a diary of what you ate every 24 h of the study and return it to us for analysis
3. Start counting each 24-h period from the time you left the hospital forward. Break the study in 4 periods, each ideally including breakfast, lunch, and dinner (plus snacks).
4. You should use the first 2 days (0–48 h) to eat anything you like, particularly anything that you know might cause your acid reflux symptoms. A McDonald's meal, pizza, spaghetti with red sauce or alcohol, can be bad, particularly in large portions.
5. The last 2 days (48–96 h) should be very strict, based on the recommendations below (pages 2 to 5). During this time, you will have to avoid the "bad" things. General cooking suggestions are provided.
6. Please do not use a PPI (proton pump inhibitor) during the testing period (0–96 h). You can use antacids (such as Tums) for severe symptoms, as needed.

The following table helps you separate foodstuffs that cause reflux from those that either prevent reflux or alleviate it. Please read it carefully and apply its principles.

Good and bad foods

Foodstuffs with concentrated sugar that *cause* reflux and pain	Foodstuffs that *prevent* reflux or quickly *alleviate* symptoms
1. All grain products All kinds of bread and pastries, cakes, all kinds of Muesli or porridge; Noodles, dumplings, gnocchi, ravioli, rice, rice noodles, corn, and popcorn Artificial sweeteners, aromas, preservatives	1. Animal products Beef, pork, lamb, game, smoked meat, roast beef, ham and bacon without sugar (no packaged cold cuts, sausage, or ham!) Chicken and turkey, all kinds of fresh or smoked fish and fresh seafood (exception: seafood may be frozen) Hard-boiled eggs (no soft-boiled or fried eggs!)
2. Dairy products Any kind of milk, yoghurt, milk shakes, or yoghurt drinks; butter, cream, cheese, mayonnaise	

Foodstuffs with concentrated sugar that *cause* reflux and pain	Foodstuffs that *prevent* reflux or quickly *alleviate* symptoms
3. Vegetables Onions, beans, green beans, peas, cabbage, beets; yellow, orange, and red bell peppers, carrots*), pumpkin, soybeans, tofu, potatoes in any form (incl. chips, French fries, etc.)	3. Vegetables (always unpeeled) All kinds of lettuce, herbs, chicory, spinach, green peppers, tomatoes, cucumbers, radishes, fresh capers, chives, fennel, boiled asparagus, olives
4. Fruit Apples (except for the kinds listed at the right), oranges, mandarin oranges, bananas, pears, lemons, limes, apricots, greengages, plums, cherries, strawberries, dates, mangos, pineapples, kiwis, carambola	4. Fruit (always unpeeled) Green apples (e.g., Granny Smith), Pink Lady apples, russet apples
5. Beverages Cocoa, hot chocolate, fruit juices, all kinds of carbonated and lifestyle drinks (e.g., smoothies), energy drinks, even in low-calorie form! All kinds of alcohol: beer, wine, champagne, hard liquor	5. Beverages Mineral water, tea, coffee (espresso, without milk, sugar, or artificial sweeteners)
6. Preparation and spices No steaming (incl. woks) or breading, No pumpkin seed, canola, sunflower, flaxseed oil, and no margarine (not even diet margarine), No ready-to-use spice mixtures, mustard, ketchup, dips, etc. No vinegar No soups, as the concentrated sugar is dissolved	6. Preparation and spices Boil, grill, fry (pan or oven) Olive oil, salt, pepper, any kind of herb (parsley, chives, marjoram, thyme, basil, oregano, dill, chili pepper without sugar, etc.), cress, garlic

Strict Reflux Diet—Only "Good" Things

The following recommendations are for orientation—give your creativity free rein for combining different foods:

Breakfast:

- Green apple (Granny Smith) + olive oil, pepper, and salt
- Green salad, chicory, spinach leaves mixed with olive oil
- Green pepper (if it does not cause regurgitation), tomatoes, cucumber, radishes, fresh capers, chives, fennel, olives; mix salad with pepper, salt, (see spices below)
- Olive oil with no sugar or preservatives
- Prosciutto, ham with no sugar, bacon with no sugar
- Raw fish (sashimi), smoked fish (salmon, eel, tuna), seafood, cold pork roast, cold smoked meat, cold roast beef, cold chicken
- Hard-boiled egg (**no** soft-boiled or fried eggs, they contain concentrated sugar!).

Mornings:

A small snack every hour:

A piece of cucumber/green apple/radish/green pepper, olives with or without olive oil, ham, bacon, meat, hard-boiled egg.

Why every hour? Eating every hour provides the body with energy, neutralizes gastric acid, strengthens the lower esophageal sphincter, and thus prevents reflux in the morning.

Lunch:

You have a large selection for lunch:

Raw:

See breakfast, or:

Raw fish with salad with no rice (sashimi), smoked salmon (with no sugar or preservatives), seafood (shrimp, scampi, etc.) with sauce containing no sugar.

and/or:

Cooked:

e.g., **Beef:** Boiled pork or beef with spinach leaves and green salad, but with no soup (= contains sugar solution!)

e.g., **Boiled fish**: poached trout/char/whitefish

and/or:

Grilled:

Beef: T-bone steak, filet, tenderloin steak, roast beef, etc.

Pork: pork tenderloin, pork chop

Poultry: chicken, turkey, ostrich

Lamb, goat

All kinds of fish and seafood: Fresh or saltwater fish (trout, zander, char, salmon, cod, halibut, sole, tuna, sea bass, octopus, etc.), crustaceans (shrimp, scampi, crabs)

All grilled with olive oil

and/or:

Fried:

Pork: Smoked pork (warm or cold) with or without horseradish, warm or cold pork roast with garlic, cabbage salad with bacon, **but no** sugar!

Beef: Beef roast (do not add any artificial sauce!)

Poultry: Chicken, turkey

Lamb, goat

All kinds of fish and seafood: Fresh or saltwater fish (trout, zander, char, salmon, cod, halibut, sole, tuna, sea bass, octopus, etc.), crustaceans (shrimp, scampi, crabs)

All fried (oven or pan) in olive oil

Salads:

Green salad, chicory, cucumber, fennel, tomatoes, radishes, radicchio, olives, hard-boiled egg, spinach leaves, boiled asparagus;

Marinate with pepper, salt, olive oil, garden herbs, and cress. Do not use vinegar because it contains sugar!

Caution:

Do not use butter, canola oil, sunflower seed oil, or pumpkin seed oil for frying

Do not eat anything steamed with onions (e.g., goulash, roast beef with onions)

Do not prepare food in a wok, as this steams it and dissolves the sugar

Do not eat anything breaded (wiener schnitzel, cordon bleu, fried chicken, fish, etc.).

Afternoons:

Eat a small snack every hour; see the recommendations for mornings for ideas

Supper:

See the suggestions for breakfast and lunch for ideas

The same applies after the evening meal: a small snack every hour!

Beverages throughout the day:

Water, espresso, or small espresso diluted with hot water without sugar, artificial sweeteners, or milk; all kinds of tea without sugar, preservatives, or artificial sweeteners.

Some delicious suggestions for meals:

Warm dishes:

- Grilled chicken breast wrapped in bacon with tomato confit (chopped tomatoes with garlic and olive oil heated briefly in the oven) and basil pesto
- Beef steak with warm spinach salad and caper and olive sauce with garlic, herbs, and anchovies
- Roast pork shoulder marinated in garlic and marjoram with warm cabbage and bacon salad
- Medium rare roast beef with green peppers and hard-boiled egg
- Boiled beef with spinach and fresh Granny Smith apple horseradish
- Grilled seafood with tomato-pepper confit and green salad
- Fried char with tomato and cucumber salad

Cold dishes:

- Seafood with green salad, cucumber, tomato, radish, green apple, marinated with olive oil, pepper, and salt
- Smoked salmon with tomatoes, cucumber, olives, capers, hard-boiled egg, and green salad
- Prosciutto with cucumber, tomato, radishes, olives, capers, pepper, and salt
- Lamb kebabs with tomato, olives, cucumber, salt, and pepper

Translated and modified from: Riegler M, HÖnig-Robier, K. Nie wieder sodbrennen. Reflux verstehen und in den griff bekommen. maudrich-Verlag 2014.

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