

DOI: <https://doi.org/10.17816/mechnikov63311>

Correction of eating behavior in patients with erosive reflux esophagitis

© Sergey V. Tihonov, Vladimir I. Simanenkov, Natalya V. Bakulina, Nadezhda B. Lishchuk, Yuliya G. Topalova

North-West State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

AIM: To compare the efficacy of 1-month inhibitors of H⁺,K⁺-ATPase therapy and eating behavior correction over 6 months with initial 1-month and 5-month maintenance inhibitors of H⁺,K⁺-ATPase therapy in overweight and obese patients with erosive esophagitis.

MATERIALS AND METHODS: The randomized clinical study included 29 patients 54.8 ± 13.5 years with erosive esophagitis. 13 (45%) patients were overweight, 16 (55%) — obese, 26 (90%) had abdominal obesity. The patients were randomized into 2 groups: control group — 15 patients received 20 mg of omeprazole twice a day during 4 weeks and 20 mg of omeprazole once a day during 5 months; intervention group — 14 patients participated in the eating behavior correction program and received 20 mg of omeprazole once a day for 4 weeks initially. Clinical symptoms, the endoscopic and histological data, anxiety, depression and quality of life, motor disorders were under investigation.

RESULTS: At the end of the 4-week therapy, the control group had a lower frequency of heartburn (1.8 ± 0.08 vs 2.4 ± 0.6 points), intensity of heartburn (1.13 ± 0.51 vs 1.78 ± 0.89 points), healing of erosive esophagitis was more common (13 (86%) vs 5 (35%) patients), more % weakly acidic (2.5 ± 1.6 vs 0.8 ± 0.4) and % weakly alkaline time (0.44 ± 0.3 vs 0.15 ± 0.2) in the esophagus, more alkaline gastroesophageal refluxes (9.1 ± 9.8 vs 2.8 ± 3.9). By the end of the sixth month, the control group had higher frequency (3.46 ± 0.5 vs 2.28 ± 0.7 points) and the intensity of regurgitation (1.6 ± 0.5 vs 1.07 ± 0.26 points), more % weakly acidic (2.32 ± 1.86 vs 0.89 ± 0.57) and % weakly alkaline time (0.54 ± 0.72 vs 0.22 ± 0.28), lower quality of life according to GH scale and RE scale SF-36 questionnaire.

CONCLUSIONS: The superiority of an eating behavior correction strategy over inhibitors of H⁺,K⁺-ATPase therapy was demonstrated in this study. Weight loss leads to fewer symptoms of gastroesophageal reflux disease and improved gastroesophageal motility.

Keywords: gastroesophageal reflux disease; erosive esophagitis; overweight; obesity; esophageal pH-impedance; inhibitors of H⁺,K⁺-ATPase; proton pump inhibitors; eating behavior correction; weight loss.

To cite this article:

Tihonov SV, Simanenkov VI, Bakulina NV, Lishchuk NB, Topalova YuG. Correction of eating behavior in patients with erosive reflux esophagitis. *Herald of North-Western State Medical University named after I.I. Mechnikov*. 2021;13(1):71–84. DOI: <https://doi.org/10.17816/mechnikov63311>

DOI: <https://doi.org/10.17816/mechnikov63311>

Коррекция пищевого поведения у пациентов с эрозивным рефлюкс-эзофагитом

© С.В. Тихонов, В.И. Симаненков, Н.В. Бакулина, Н.Б. Лищук, Ю.Г. Топалова

Северо-Западный государственный медицинский университет имени И.И. Мечникова, Санкт-Петербург, Россия

Цель — сравнить эффективность одномесечной терапии ингибиторами H^+,K^+ -АТФазы и коррекции пищевого поведения на протяжении 6 мес. с инициальной одномесечной и пятимесечной поддерживающей терапией ингибиторами H^+,K^+ -АТФазы у пациентов с эрозивным эзофагитом и избыточным весом и ожирением.

Материалы и методы. В рандомизированном клиническом исследовании участвовали 29 пациентов (средний возраст — $54,8 \pm 13,5$ года) с эрозивным эзофагитом степени А. Избыточный вес выявлен у 13 (45 %) пациентов, ожирение — у 16 (55 %), абдоминальное ожирение — у 26 (90 %). Больных распределили в две группы: группу контроля — 15 пациентов, получавших 4 нед. омепразол в дозе 20 мг 2 раза в сутки, 20 нед. омепразол в дозе 20 мг 1 раз в сутки; группу вмешательства — 14 пациентов, получавших 4 нед. омепразол в дозе 20 мг 1 раз в сутки и 24 нед. участвовавших в программе по коррекции пищевого поведения. Эффективность терапии сравнивали при оценке симптомов; уровня тревожности, депрессии, качества жизни; заживления эрозивного эзофагита; показателей суточной рН-импедансометрии.

Результаты. На момент окончания четырехнедельной терапии в группе контроля была меньше частота изжоги ($1,8 \pm 0,08$ vs $2,4 \pm 0,6$ балла), интенсивность изжоги ($1,13 \pm 0,51$ vs $1,78 \pm 0,89$ балла), чаще отмечалось заживление эрозивного эзофагита [13 (86 %) vs 5 (35 %) пациентов], было больше слабокислое ($2,5 \pm 1,6$ vs $0,8 \pm 0,4$ %) и слабощелочное время ($0,44 \pm 0,3$ vs $0,15 \pm 0,2$ %) в пищеводе в течение суток (выраженное в процентах), больше количество щелочных гастроэзофагеальных рефлюксов ($9,1 \pm 9,8$ vs $2,8 \pm 3,9$). К 6-му месяцу терапии в группе контроля была больше частота ($3,46 \pm 0,5$ vs $2,28 \pm 0,7$ балла) и интенсивность регургитации ($1,6 \pm 0,5$ vs $1,07 \pm 0,26$ балла), больше слабокислое ($2,32 \pm 1,86$ vs $0,89 \pm 0,57$ %) и слабощелочное время ($0,54 \pm 0,72$ vs $0,22 \pm 0,28$ %) в пищеводе в течение суток, ниже качество жизни по шкале GH и RE опросника SF-36.

Заключение. В исследовании продемонстрировано преимущество коррекции пищевого поведения перед терапией ингибиторами H^+,K^+ -АТФазы у пациентов с эрозивным эзофагитом и избыточным весом и ожирением. Снижение веса характеризуется схожей с терапией ингибиторами H^+,K^+ -АТФазы эффективностью по влиянию на изжогу и эрозивный эзофагит, более выраженно воздействует на регургитацию, улучшает моторику верхних отделов желудочно-кишечного тракта.

Ключевые слова: гастроэзофагеальная рефлюксная болезнь; эрозивный эзофагит; избыточная масса тела; ожирение; рН-импедансометрия; ингибиторы H^+,K^+ -АТФазы; ингибиторы протонной помпы; снижение веса.

Как цитировать:

Тихонов С.В., Симаненков В.И., Бакулина Н.В., Лищук Н.Б., Топалова Ю.Г. Коррекция пищевого поведения у пациентов с эрозивным рефлюкс-эзофагитом // Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. 2021. Т. 13. № 1. С. 71–84. DOI: <https://doi.org/10.17816/mechnikov63311>

INTRODUCTION

Obesity and gastroesophageal reflux disease (GERD) are comorbid conditions [1–3]. According to the World Health Organization, the prevalence of obesity [body mass index (BMI) >30 kg/m²] has tripled over the past two decades, which can be regarded as a pandemic [4]. In most countries, 30% to 80% of the adult population is overweight (BMI >25 kg/m²) [4, 5]. GERD is the most common upper gastrointestinal disorder. Epidemiological studies have shown that GERD affects 18.1%–27.8% of the adult population in North America, 8.8%–25.9% in Europe, and at least 13.3% of the national population [6, 7].

Overweight and obesity are recognized as the main risk factors for the development of non-erosive reflux disease, erosive esophagitis (EE), Barrett's esophagus, and esophageal adenocarcinoma. The risk of developing these diseases is directly proportional to BMI and waist circumference (WC) [8–10]. This comorbidity is based on obesity-induced motor disturbances at the level of the esophagus body, lower esophageal sphincter, hiatal hernia, increased intra-abdominal and intragastric pressure, and gastroduodenal motility disorders [11–13]. In addition to mechanical action, metabolically active visceral adipose tissue has a systemic pro-inflammatory effect, which is also realized at the level of the esophagus, leading to the development of microscopic and macroscopic lesions of the mucous membrane [14–16].

The effectiveness of weight loss in patients with GERD and obesity has been evaluated in a number of clinical studies. A Norwegian population-based study HUNT 3, involving 44,997 people, found that weight loss is associated with a decrease in the clinical manifestations of GERD and an increase in the effectiveness of acid-suppressive therapy. Weight loss is accompanied by a decrease in the exposure time of an acid bolus (pH <4) in the esophagus during the day from 5.6%–8.0% to 3.7%–5.5% [17].

In a prospective cohort study of 332 patients with obesity, GERD was diagnosed in 37% of patients. Weight decrease by an average of 13 kg contributed to a decrease in the intensity of symptoms of reflux disease in 81% of patients, and the incidence of GERD decreased to 15% [18]. Fraser-Moodie et al. demonstrated that in 27 patients with a BMI >23 kg/m², a weight loss of 4 kg was associated with a 75% decrease in the severity of the clinical manifestations of GERD [19].

In 2015, Nicola de Bortoli et al. published the results of a prospective, non-randomized study involving 101 patients with EE. According to the authors, a low-calorie diet and regular exercise have several advantages over classical acid suppression therapy. Thus, a decrease in body weight by 10% or more and a decrease in the circumference of the waist and hips led to a weakening of heartburn and regurgitation,

healing of EE, and a decrease in dosage or withdrawal of H⁺,K⁺-ATPase inhibitors [20].

In a number of other studies, weight loss did not affect the GERD course. In a study by Kjellin et al., 20 patients with GERD and obesity, receiving therapy with inhibitors of H⁺,K⁺-ATPase, were randomized into two groups: a very low-calorie diet group and a control group. After 6 months, weight loss in the intervention group was 10.8 kg, while in the control group, the patients gained 0.6 kg. At the same time, the results of daily pH-impedance measurement and the severity of GERD symptoms did not differ between the groups. Subsequently, the patients in the control group were also prescribed a low-calorie diet, which led to a decrease in body weight by 9.7 kg, but not to a decrease in the manifestations of GERD and an improvement in the motility of the upper gastrointestinal tract [21]. Frederiksen et al. did not detect changes in esophageal acid bolus exposure in 15 patients with morbid obesity (average BMI 43 kg/m²) on very low-calorie diet on day 14 or 3 weeks after longitudinal resection of the stomach [22].

Thus, despite the urgency of the problem of co-existing GERD and obesity, the scientific medical literature presents an insufficient number of clinical studies devoted to the effectiveness of weight loss in patients with various forms of GERD, and their results are often contradictory. In addition, to the best of our knowledge, no randomized clinical trials have compared the effectiveness of weight loss and classical therapy with H⁺,K⁺-ATPase inhibitors at the initial and maintenance stages, including clinical assessment, psychometric testing, endoscopic examination, and pH measurement.

This study aimed to compare the effectiveness of 1-month therapy with H⁺,K⁺-ATPase inhibitors and correction of eating behavior for 6 months (initial 1 month and 5 months of maintenance therapy with H⁺,K⁺-ATPase inhibitors) in patients with EE and overweight and obesity.

MATERIALS AND METHODS

This randomized clinical trial included 29 patients [13 (45%) men and 16 (55%) women] with EE grade A (Los Angeles Endoscopic classification) and overweight (BMI >25 kg/m²) or obesity (BMI >30 kg/m²). The study did not include patients with ischemic heart disease, diabetes mellitus, cholelithiasis, gastric ulcer, duodenal ulcer, and other diseases that can affect the course of GERD.

This clinical study was approved at a meeting of the local ethics committee (No. 1, City Hospital No. 26, January 24, 2019). All patients signed an informed consent form approved by the local ethics committee.

The study participants were randomly divided (randomization using a table of random numbers) into two groups: control group with 15 patients and intervention group

Table 1. Study design**Таблица 1.** Дизайн исследования

Visit 1	RANDOMIZATION	
	CONTROL GROUP 15 patients	CONTROL GROUP 15 patients
Collection of complaints, anamnesis, physical examination, psychometric testing, EGDS, and daily pH-impedance measurement		
Visit 2		
Initial therapy	Omeprazole 20 mg 2 times/day	Omeprazole 20 mg 1 time/day Correction of eating behavior
Visit 3 (4 weeks)	Collection of complaints, physical examination, psychometric testing, EGDS, and daily pH-impedance measurement	
Supportive therapy	Omeprazole 20 mg 1 time/day	Correction of eating behavior
Visit 4 (12 weeks)	Collection of complaints, physical examination, and psychometric testing	
Supportive therapy	Omeprazole 20 mg 1 time/day	Correction of eating behavior
Visit 5 (24 weeks)	Collection of complaints, physical examination, psychometric testing, EGDS, and daily pH-impedance measurement	

Note. EGDS, esophagogastroduodenoscopy.

with 14 patients. The observation period was 6 months. The study design is presented in Table 1.

Patients participating in the eating behavior correction program additionally visited the research center every 2 weeks during the first 12 weeks, every 4 weeks from week 16 to week 24, to assess the dynamics of weight loss, correction of diet, and physical activity, if necessary. Patients from the control group visited the study site in accordance with the visit schedule at 4, 12, and 24 weeks from the start of the study.

During the physical examination, height (m), weight (kg), WC (cm), and BMI (kg/m²) of the patients were measured.

All participants underwent esophagogastroduodenoscopy (EGDS), and changes in the esophagus were assessed according to the Los Angeles endoscopic classification from 1994 [23]. The study included patients with EE grade A, i.e., the presence of one or more lesions no more than 5 mm long, limited to one fold of the esophageal mucosa.

The frequency and severity of the main symptoms of GERD (heartburn and regurgitation) were assessed as follows:

- Frequency of complaints: 0, no complaints; 1, less than 1 time per week; 2, once a week; 3, 2 times a week or more; 4, daily; 5, several times a day.
- Intensity of the complaint: 0, no complaint; 1, weak; 2, medium; 3, intensive; 4, extremely.

The functional activity of the upper gastrointestinal tract was investigated during daily pH-impedance measurement using an IAM-01 Gastroscan-IAM impedance-acidomonitor. To assess the correct placement of the pH-impedance probe (the distal esophageal sensor is located 5 cm above the diaphragm level), an X-ray examination was performed at the level of the gastroesophageal junction.

To assess dynamics, all patients underwent experimental psychological testing using the Spielberger-Khanin

questionnaire (level of reactive and personal anxiety), Beck Depression Inventory (level of depression), and 36-Item Short Form Survey (SF-36, quality of life) questionnaire at visits 1, 3, 4, and 5 [24].

Patients in the intervention group participated in an eating behavior correction program that included increased exercise and diet.

The participants' usual daily caloric intake, determined after undergoing the screening procedure when filling out a food diary for 10 days, was limited to 30%. On average, the limited daily caloric intake was 1650 ± 137 kcal per day in male patients and 1357 ± 117 kcal per day in female patients. Participants were recommended a diet balanced in terms of macronutrients, including proteins (15%–25%), fats (20%–40%), and carbohydrates (35%–65%). Additionally, the participants increased their physical activity to a level of at least 300 min of medium-intensity aerobic physical activity or at least 150 min of intense physical activity, evenly distributed throughout the week. This treatment option for patients with obesity complies with clinical guidelines [25].

Participants were monitored for their daily caloric intake and physical activity independently using electronic applications (software for calculating food calories and physical activity) based on fitness bracelets and smart-phones.

At follow-up visits every 2 weeks during the first 3 months and every 4 weeks from month 4 to month 6, the researcher analyzed the food diary for the past 2 weeks (daily calories and ratio of proteins, fats, and carbohydrates in the diet) and physical activity level. When violations of adherence to recommendations were identified, the participants discussed the potential causes of these violations and behavioral strategies that would be effective to prevent similar situations in the future.

Table 2. Baseline data of 24h pH-impedance monitoring of the upper gastrointestinal tract of 29 patients**Таблица 2.** Результаты суточной pH-импедансометрии верхних отделов желудочно-кишечного тракта 29 пациентов с эрозивным эзофагитом на момент включения в исследование

Parameters of pH-impedance measurement	Average value	Minimum value	Maximum value	Standard deviation
Sour GER, quantity	57.3	23	99	16.1
Weakly acidic GER, quantity	48.5	4	101	22.1
Weakly alkaline GER, quantity	11.1	0	40	12.7
Proximal acidic GER, number	16.7	0	53	12.4
Proximal weakly acidic GER, number	17.8	2	37	8.7
Proximal weakly alkaline GER, number	3.8	0	19	5.8
Longest GER, min	13.7	1.4	55.3	13.4
Acid time in the esophagus, %	4.8	2.3	8.1	0.8
Weakly acidic time in the esophagus, %	2.1	0.3	8.2	2.0
Weakly alkaline time in the esophagus, %	0.5	0	3.5	0.7
DeMeester index	18.3	9.7	29.7	5.8

Note. GER – gastroesophageal reflux.

The information obtained in the course of the study was entered into case report forms, and the participants were assigned an individual number, which at the same time served as a cipher in the electronic database. Data obtained were processed using the Statistica 10.0 software package by parametric and nonparametric statistics. The critical level of significance (p) of the null statistical hypothesis (about the absence of significant differences or factorial influences) was taken as equal to 0.05.

RESULTS

The study involved 29 patients [13 (45%) men and 16 (55%) women], with average age of 54.8 ± 13.5 years.

The average BMI of the participants was 30.9 ± 4.2 kg/m²; FROM – 104 ± 14.8 cm; the proportion of fat mass determined by impedance measurements was $31.8\% \pm 4.5\%$. Overweight (BMI 25–29.9 kg/m²) was detected in 13 (45%) patients, obesity degree I (BMI 30–34.99 kg/m²) in 12 (41%) patients, and obesity degree II (BMI 35–39.99 kg/m²) in 4 (14%) patients. Abdominal obesity (WC >80 cm in women, WC >94 cm in men) was found in 26 (90%) patients.

Endoscopic signs of hiatal hernia were recorded in 19 (66%) patients.

The duration of the existence of GERD was in average 8.1 ± 7.18 years. The severity and frequency of the main complaints at the time of inclusion were as follows: frequency and intensity of heartburn, 3.5 ± 1.3 points and 2.1 ± 1.9 points; frequency and intensity of regurgitation, 4.1 ± 1.9 points and 1.5 ± 0.98 points, respectively. Extra-esophageal manifestations of GERD (reflux-associated cough and sore throat) were observed in 14 (48%) patients.

At the screening stage, all 29 participants underwent daily pH-impedance measurements of the upper gastrointestinal

tract. The DeMeester index was higher than the reference value (14.7) in 25 (86%) patients, in accordance with the Lyon Consensus of 2018, and the pathological time of acid exposure in the esophagus (>6% of the time during the day) was determined in 21 (72%) patient [26]. The average values of the pH-impedance study are presented in Table 2.

Results of the psychometric test were as follows: Beck Depression Inventory questionnaire, 8.7 ± 7.5 points (normal); Spielberger–Khanin questionnaire, reactive anxiety with 47.0 ± 9.1 points (high anxiety) and personal anxiety with 36.6 ± 13.7 points (moderate anxiety); SF-36 questionnaire, scale of physical functioning with 79.5 ± 17.2 points, role functioning due to physical condition with 53.7 ± 45.2 points, pain intensity scale with 61.9 ± 26.4 points, general health (GH) with 51.2 ± 22.5 points, vital activity with 59.4 ± 20.0 points, social functioning (SF) with 70.3 ± 20.4 points, role functioning conditioned by the emotional state (RE) with 68.2 ± 36.4 points, and mental health with 63.7 ± 16.9 points.

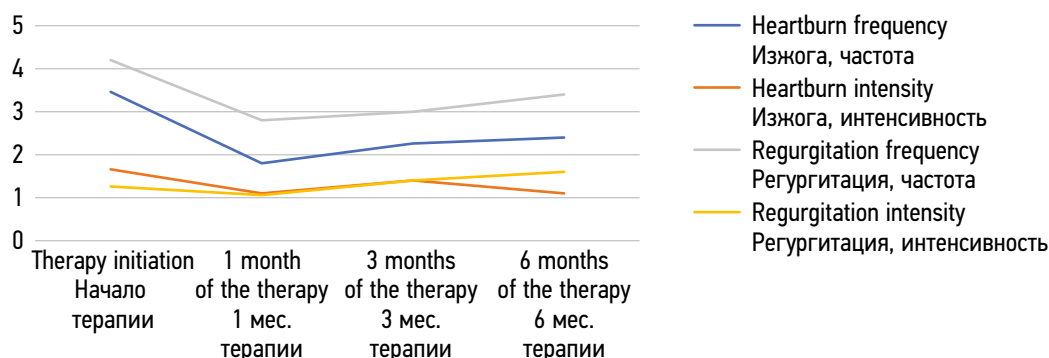
At the start of the study, the BMI of the patients correlated with their age (0.4, direct weak relationship), presence of extra esophageal manifestations of GERD (0.44, direct weak connection), and slightly alkaline time in the esophagus (%) (0.40, direct weak connection). WC did not correlate with clinical manifestations of GERD, as measured by daily pH-impedance and psychometric testing.

Dynamics of the state of patients from the control group within 6 months

The dynamics of the state of the patients in the control group within 6 months is presented in Table 3 and Fig. 1.

Table 3. Dynamics of anthropometric data and main symptoms of GERD in the control group within 6 months**Таблица 3.** Динамика антропометрических данных и основных симптомов гастроэзофагеальной рефлюксной болезни у пациентов в группе контроля в течение 6 мес.

Parameters	Visit 2 (n = 15)	Visit 3 (n = 15)	Visit 4 (n = 15)	Visit 5 (n = 15)
Body mass index, kg/m²	30.8 ± 3.2	30.2 ± 3.1	31.16 ± 3.0	31.2 ± 2.8
Comparison with the data at visit 2		<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> = 0.01
Waist circumference, cm	102.8 ± 12.7	101.3 ± 11.6	103.13 ± 13.8	104.0 ± 12.7
Comparison with the data at visit 2		<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> = 0.009
Heartburn, frequency	3.46 ± 1.3	1.8 ± 1.08	2.26 ± 1.4	2.4 ± 1.3
Comparison with the data at visit 2		<i>p</i> = 0.0008	<i>p</i> = 0.003	<i>p</i> > 0.05
Heartburn, intensity	1.66 ± 1.1	1.1 ± 0.5	1.4 ± 0.5	1.2 ± 0.6
Comparison with the data at visit 2		<i>p</i> = 0.04	<i>p</i> > 0.05	<i>p</i> > 0.05
Regurgitation, frequency	4.2 ± 1.0	2.8 ± 1.4	3.0 ± 1.6	3.4 ± 1.4
Comparison with the data at visit 2		<i>p</i> = 0.0044	<i>p</i> = 0.01	<i>p</i> > 0.05
Regurgitation, intensity	1.26 ± 0.88	1.06 ± 0.25	1.4 ± 0.5	1.6 ± 0.5
Comparison with the data at visit 2		<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05

**Fig. 1.** Dynamics of the main symptoms of GERD in the patients of the control group during 6 months of observation**Рис. 1.** Динамика основных клинических проявлений гастроэзофагеальной рефлюксной болезни у пациентов из группы контроля в течение 6 мес. наблюдения**Table 4.** Dynamics of anthropometric data and main symptoms of GERD in the intervention group within 6 months**Таблица 4.** Динамика антропометрических данных и основных симптомов гастроэзофагеальной рефлюксной болезни у пациентов из группы вмешательства в течение 6 мес.

Parameter	Visit 2 (n = 14)	Visit 3 (n = 14)	Visit 4 (n = 14)	Visit 5 (n = 14)
Body mass index, kg/m²	31.13 ± 5.3	30.47 ± 5.0	27.77 ± 4.1	27.98 ± 5.1
Comparison with data at visit 2		<i>p</i> = 0.02	<i>p</i> = 0.0005	<i>p</i> = 0.001
Waist circumference, cm	106.64 ± 17.1	103.0 ± 15.5	93.21 ± 10.8	94.28 ± 11.6
Comparison with data at visit 2		<i>p</i> = 0.015	<i>p</i> = 0.003	<i>p</i> = 0.002
Heartburn, frequency	3.71 ± 1.3	2.92 ± 0.8	2.85 ± 0.66	3.0 ± 0.96
Comparison with data at visit 2		<i>p</i> = 0.03	<i>p</i> = 0.04	<i>p</i> > 0.05
Heartburn, intensity	2.35 ± 1.2	2.0 ± 0.87	2.1 ± 0.55	1.35 ± 0.63
Comparison with data at visit 2		<i>p</i> = 0.04	<i>p</i> > 0.05	<i>p</i> = 0.01
Regurgitation, frequency	3.78 ± 1.4	3.0 ± 1.17	1.78 ± 0.57	2.28 ± 0.72
Comparison with data at visit 2		<i>p</i> > 0.05	<i>p</i> = 0.005	<i>p</i> = 0.009
Regurgitation, intensity	1.78 ± 1.05	1.57 ± 0.75	1.0 ± 0.11	1.07 ± 0.26
Comparison with data at visit 2		<i>p</i> > 0.05	<i>p</i> = 0.02	<i>p</i> = 0.04

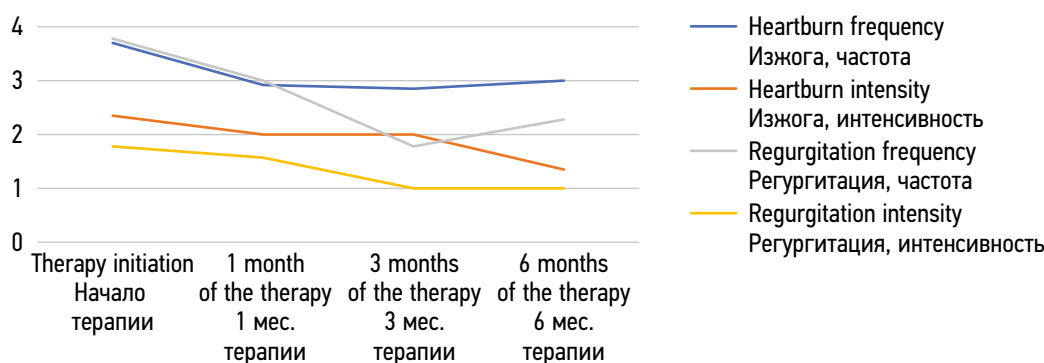


Fig. 2. Dynamics of the main symptoms of GERD in the patients of the intervention group within 6 months

Рис. 2. Динамика основных клинических проявлений гастроэзофагеальной рефлюксной болезни у пациентов из группы вмешательства в течение 6 мес.

Owing to the initial and maintenance acid-suppressive therapy, patients from the control group significantly has increased BMI and WC by month 6 of the study. The initial 1-month therapy had a significantly positive effect on the frequency and intensity of heartburn and frequency of regurgitation. However, by the end of the 5-month course of maintenance therapy, the intensity and frequency of these symptoms increased. At the final visit, the severity of the main clinical manifestations of GERD did not differ significantly from the data of visit 1.

Dynamics of the state of patients from the intervention group within 6 months

The dynamics of the state of patients from the intervention group within 6 months is presented in Table 4 and Fig. 2.

Table 5. Differences between the control and intervention groups after 4 weeks of therapy

Таблица 5. Отличия между группами контроля и вмешательства после четырехнедельной терапии

Parameter	Control group (n = 15)	Intervention group (n = 14)	p
Heartburn frequency, points	1.8 ± 0.08	2.4 ± 0.6	0.008
Heartburn intensity, points	1.13 ± 0.51	1.78 ± 0.89	0.01
Personal anxiety, points	39.4 ± 7.2	46.5 ± 7.0	0.01
Weakly alkaline gastroesophageal reflux, quantity	9.1 ± 9.8	2.8 ± 3.9	0.04
Weakly acidic time in the esophagus, %	2.5 ± 1.6	0.8 ± 0.4	0.007
Weakly alkaline time in the esophagus, %	0.44 ± 0.3	0.15 ± 0.2	0.005
Epithelialization of erosion	13 (85%)	5 (35%)	0.005

Таблица 6. Отличия между группами контроля и вмешательства после трехмесячной терапии

Table 6. Differences between the control and intervention groups after 3 months of therapy

Parameter	Control group (n = 15)	Intervention group (n = 14)	p
Body mass index, kg/m ²	31.2 ± 3.07	27.7 ± 4.9	0.017
Waist circumference, cm	103.13 ± 13.8	93.2 ± 10.8	0.017
Heartburn intensity, points	1.26 ± 0.6	2.0 ± 0.55	0.006
Regurgitation frequency, points	3.0 ± 1.25	1.8 ± 0.57	0.04
Intensity of regurgitation, points	1.4 ± 0.5	1.0 ± 0.0	0.009
Reactive anxiety, points	19.6 ± 9.2	30.0 ± 8.3	0.004
RE scale of the SF-36 questionnaire, points	86.5 ± 24.7	60.4 ± 28.9	0.017

Note. RE, role functioning conditioned by the emotional state.

Table 7. Differences between the control and intervention groups after 6 months of therapy**Таблица 7.** Отличия между группами контроля и вмешательства после шестимесячной терапии

Parameter	Control group (n = 15)	Intervention group (n = 14)	p
Body mass index, kg/m ²	31.2 ± 2.8	27.9 ± 5.02	0.02
Waist circumference, cm	104.06 ± 12.7	94.3 ± 1.6	0.04
Regurgitation frequency, points	3.4 ± 1.4	2.28 ± 0.7	0.02
Intensity of regurgitation, points	1.6 ± 0.5	1.07 ± 0.26	0.01
Personal anxiety, points	45.0 ± 8.05	33.1 ± 13.01	0.01
GF scale of the SF-36 questionnaire, points	43.46 ± 21.4	61.15 ± 15.05	0.02
RE scale of the SF-36 questionnaire, points	53.13 ± 32.9	82.0 ± 32.3	0.02
Weakly acidic time in the esophagus,%	2.32 ± 1.86	0.89 ± 0.57	0.01
Weakly alkaline time in the esophagus,%	0.54 ± 0.72	0.22 ± 0.28	0.03

Note. RE, role functioning conditioned by the emotional state.

Comparison of control and intervention groups after 6 months of therapy

By visit 5, the groups significantly differed in WC, BMI, frequency and intensity of regurgitation, personal anxiety, weakly acidic and weakly alkaline time (%) in the esophagus, score RE scale of the SF-36 questionnaire of general health (Table 7).

At visit 5, during EGDS, EE was detected in 2 (13%) patients in the control group and in 4 (28%) patients in the intervention group. Extraesophageal manifestations of GERD were found in 4 (26%) patients in the control group and in 3 (21%) patients in the intervention group. Differences between the groups in the presence of EE and extraesophageal clinical manifestations are insignificant.

By month 6 of the study, 33% of the patients from the control group did not take H⁺,K⁺-ATPase inhibitors regularly and 13% completely stopped taking the drug at month 5 of therapy.

After 6 months of therapy, patients with erosion (6 patients) and without erosion (23 patients) in the esophagus differed by WC (with EE, 110.5 ± 4.9 cm; without EE, 96.4 ± 12.9 cm; $p = 0.012$), BMI (with EE, 34.5 ± 3.0 kg/m²; without EE, 28.3 ± 3.7 kg/m², $p = 0.003$), reactive anxiety (with EE, 35.3 ± 9.7 points; without EE, 24.7 ± 8.2 points; $p = 0.017$), and score on the VT scale of the SF-36 questionnaire (with EE, 47.5 ± 21.0 points; without EE, 59.5 ± 12.6 points; $p = 0.017$).

At visit 5, the WC of the patients significantly correlated with personal anxiety (0.51, direct weak relationship), score on the GH scale of the SF-36 questionnaire (-0.43, weak feedback), and presence of extraesophageal manifestations of GERD (0.56, direct weak relationship). At visit, the BMI of patients correlated with personal anxiety (0.66, direct moderate relationship), score on the MH scale of the SF-36 questionnaire (-0.42, weak feedback), slightly alkaline time (%) in the esophagus (0.52, direct weak relationship),

erosion in the esophagus (0.67, direct moderate relationship), and extraesophageal manifestations of GERD (0.72, direct moderate relationship).

DISCUSSION

According to the results of the primary daily pH-impedance measurement, the pathological DeMeester index was determined in 25 (86%) patients. In terms of the Lyon Consensus of 2018, the pathological time of acid exposure in the esophagus was detected in 21 (72%) patients [26]. In our previous work, we found that a feature of the pathogenesis of GERD in patients with overweight status is the prevalence of mixed refluxes [3]. The listed criteria for the diagnosis of GERD are based on pH measurements and guided only by the presence of GER with pH <4. Further research is needed to determine the diagnostic value of mildly acidic and mildly alkaline GER, especially in patients with overweight or obese states.

At the start of the study, the BMI of the patients correlated with age, extraesophageal manifestations of GERD, and slightly alkaline time in the esophagus (%) and did not correlate with the WC values at the first visit. Previous studies have found that overweight and obesity adversely affect the course of GERD, causing symptoms and damage to the esophageal mucosa [8-10, 27]. Ivashkina et al. reported on the relationship between obesity and main indicators of daily pH measurement and manometry of the esophagus. Thus, the degree of obesity directly correlated with time (%) in the esophagus with pH <4 and inversely correlated with the tone of the lower esophageal sphincter [28, 29]. Moreover, in our previous work, RT, but not BMI, and body fat (%) were associated with various pH-impedance parameters, including the amount of alkaline GER, weakly acidic GER, and total bolus time in the esophagus [27]. This occurs because abdominal obesity is associated with an increase in intra-abdominal and intragastric pressure and

occurrence of duodenogastric and mixed GER. In the present study, the above pattern may not have been found because 90% of the patients had abdominal obesity.

The main aims of GERD treatment are the rapid relief of symptoms, complete healing of erosions, prevention or elimination of complications, prevention of relapse, and improvement of the quality of life of the patients [30, 31]. Currently, the basic drugs for the treatment of GERD are inhibitors of H^+,K^+ -ATPase. Despite the high efficacy and safety of these drugs, the frequency of insufficient reduction or complete preservation of GER symptoms reaches 10%, but this further increases to 40% in patients with overweight and obesity [32–34].

In the control group, the initial 1-month therapy had a significantly positive effect on the frequency and intensity of heartburn, and frequency, but not the intensity, of regurgitation. However, by the end of the 5-month course of maintenance therapy with H^+,K^+ -ATPase inhibitors, the intensity and frequency of these symptoms increased. At the final visit, the severity of the main clinical manifestations of GERD did not differ significantly from the manifestations at the first visit. In patients receiving H^+,K^+ -ATPase inhibitors, BMI and WC gradually increased. After 6 months, these parameters were significantly higher than those at the time of inclusion in the study. Apparently, the control of GERD and dyspepsia symptoms with long-term H^+,K^+ -ATPase inhibitor therapy leads to an extension of the diet and ultimately to a gradual weight gain and possible increased risk of relapse.

The effectiveness of H^+,K^+ -ATPase inhibitors in patients with obesity is lower than in those with normal body weight. According to Trukhmanov et al., heartburn can be stopped on day 3 in patients with $BMI < 25 \text{ kg/m}^2$ and on day 9 in patients with overweight status [35]. Another domestic cohort study showed that patients with overweight status and GERD more often have an incomplete response to standard treatment and have a lower increase in quality of life indicators than patients without obesity [36]. Potential reasons for the ineffectiveness of acid-suppressive therapy in patients with overweight, obesity, and GERD are duodenogastric refluxes, which cause the presence of mixed refluxate in the esophagus that also contains hydrochloric acid and bile acids; motor disorders including disorders of antroduodenal motility and delayed gastric transit; decreased tone of the lower esophageal sphincter; change in the anatomical configuration in the area of the gastroesophageal junction; hernia of the esophageal opening of the diaphragm; psychological problems; and disorders at the pre-epithelial, epithelial, and postepithelial levels of the esophageal mucosa [27, 37–39].

In this study, insufficient effectiveness of H^+,K^+ -ATPase inhibitors may be also associated with a decrease in adherence to treatment. Thus, by month 6 of the study,

33% of the patients from the control group did not take the drug regularly and 13% completely refused to take the drug at month 5 of therapy. The phenomenon of a dynamic decrease in adherence to maintenance therapy in patients with GERD was demonstrated in our previous work [31].

Patients in the eating behavior correction group showed a significant decrease in BMI and WC after 1, 3, and 6 months. The frequency of heartburn significantly decreased by month 1 and 3 but then increased and did not significantly differ from the initial one by month 6. The intensity of heartburn significantly decreased by months 1 and 6 and the frequency of regurgitation by months 3 and 6. Thus, correction of eating behavior and weight loss had a positive effect on the main symptoms of GERD and to a greater extent influenced the symptom of regurgitation. The positive effects depended on the severity of weight loss and were maximal at month 6 of the study.

The clinical and endoscopic efficacy of the initial 4-week therapy was higher in the group of patients treated with omeprazole at a dose of 20 mg 2 times/day than in the group of patients receiving therapy with omeprazole at a dose of 20 mg 1 time/day and participating in the eating behavior correction program. In the control group, the frequency and intensity of heartburn and personal anxiety were significantly lower, and healing of EE was more often observed, which may be associated with a more pronounced and prolonged decrease in pH in the stomach against the background of the use of a double dose of H^+,K^+ -ATPase inhibitors. At the same time, weight loss after 1 month, apparently, was insufficient to observe a significant positive effect on the motility of the upper gastrointestinal tract and changes in symptoms. Despite the participation in the weight loss program, the BMI and WC values of the patients in the intervention group did not differ from those in the control group. In the control group, after 1 month, the BMI of patients decreased by 0.6 kg/m^2 and WC decreased by 1.5 cm; in the intervention group, BMI decreased by 0.65 kg/m^2 and WC decreased by 3.6 cm (the differences between the groups were not significant). Weight loss was observed during the first month of therapy with H^+,K^+ -ATPase inhibitors in the control group, possibly because patients received standard dietary recommendations, which included information on the need to change the portion size, limit the intake of fatty foods, and reduce the daily calorie intake. As a rule, adherence to recommendations of this kind is maintained at a sufficient level only in the initial period.

The only advantages of eating behavior correction program compared with the control intervention after 1 month of therapy were functional changes in the gastroesophageal and duodenogastric zones, determined by daily pH-impedance measurement. The weight loss

group had significantly less acidic and slightly alkaline time (%) in the esophagus during the day. These significant differences can be explained by the association of the initial decrease in weight and WC with improved motility at the esophageal-gastric junction and duodenogastric zone and a decrease in the number of duodenogastric refluxes as well as mixed GER. However, these changes are not yet so pronounced to manifest clinically.

By the end of month 3, patients in the intervention group had significantly lower than BMI and WC and less frequent and intense regurgitation. At the same time, patients in the control group had less intense heartburn and reactive anxiety and better quality of life according to the RE scale of the SF-36 questionnaire (reflects the extent to which the emotional state interferes with the performance of work or other daily activities). Despite a decrease in acid production in the stomach, H⁺,K⁺-ATPase inhibitors have a less pronounced effect on the symptom of regurgitation and to a greater extent reduce the intensity of heartburn. Moreover, a decrease in intra-abdominal and intragastric pressure associated with weight correction is most likely associated with a decrease in the esophageal-gastric pressure gradient and a decrease in the number of volumetric GERs.

After 6 months in the eating behavior correction group, patients had significantly less BMI and WC, lower intensity and frequency of regurgitation symptom, lower level of personal anxiety, and better quality of life according to the GH and RE scales. Participants of the eating behavior correction program also differed in terms of daily pH-impedance measurement, with less weakly acidic and slightly alkaline time (%) during the day. In a control endoscopic examination performed after 6 months, erosions in the esophagus were detected less frequently in the control group, but the differences between the groups were not significant.

Thus, correction of eating behavior has a number of advantages over classical therapy with H⁺,K⁺-ATPase inhibitors in patients with EE and overweight and obesity, which can be explained by the normalization of the eating stereotype (decrease in the amount of food intake and refusal of harmful foods) and the effect of weight loss on the main pathogenetic mechanisms of GERD.

The results of this study presents that a greater efficacy of weight loss in comparison with classical maintenance therapy using H⁺,K⁺-ATPase inhibitors may be associated with additional factors. Thus, patients in the intervention group visited the research center every 2 weeks during the first 3 months and monthly thereafter to assess the effectiveness and safety of weight loss; in addition, patients often carried out telephone consultations with a doctor about physical activity and diet. Conversely, patients from the control group visited the research center in accordance

with the visit schedule. This approach is consistent with standard clinical practice, but is associated with a decrease in adherence to the therapy. Thus, by month 6 of the study, 33% of the patients from the group receiving maintenance therapy with H⁺,K⁺-ATPase inhibitors admitted that they did not take the drug regularly and 13% completely refused to take the drug at month 5 of therapy.

CONCLUSION

Obesity and GERD are comorbid diseases. Features of the pathogenesis of GERD in patients with obesity are increased intra-abdominal and intragastric pressure, decreased tone of the lower esophageal sphincter, impaired rheology and kinetics of bile, and presence of duodenogastric and mixed GER.

Weight loss is an effective strategy in patients with both obesity and GERD. Initial and maintenance therapy with H⁺,K⁺-ATPase inhibitors relieves clinical manifestations and leads to the healing of EE, but does not affect the motility of the upper gastrointestinal tract. In particular, it has a negative effect on mixed GER, which plays an important role in patients with obesity. Considering this finding, as well as the problem of treatment adherence, H⁺,K⁺-ATPase inhibitor therapy often turns out to be insufficiently effective in patients with overweight and obese. In addition, cessation of maintenance therapy with H⁺,K⁺-ATPase inhibitors is associated with a high risk of relapse due to persistent motor impairments.

Correction of disordered eating behavior and normalization of weight are an effective approach in patients with GERD. Weight loss is characterized by an efficacy similar to H⁺,K⁺-ATPase inhibitor therapy in affecting heartburn and EE, while more pronouncedly affects regurgitation and to a greater extent reduces the non-acidic and slightly acidic bolus time in the esophagus. The positive effects of eating behavior correction with a decrease in BMI on the course of GERD appear delayed in time.

Eating correction is an effective strategy in patients with EE. A weight loss program is a labor-intensive activity for both patients and medical personnel; therefore, further assessment of the economic component of this approach is required. A possible solution to this issue is to assess the additional positive effect of weight loss on the course of other comorbid obesity diseases (arterial hypertension, diabetes mellitus, hypercholesterolemia, etc.). Potentially, the organization of schools for patients with GERD and obesity and active use of modern communication technologies can increase the economic feasibility of this approach.

Conflict of interest. The authors declare no conflict of interest.

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AUTHORS INFO

***Sergey V. Tikhonov**, MD, Cand. Sci. (Med.);
address: 41 Kirochnaya str., Saint Petersburg, 191015, Russia;
ORCID: <https://orcid.org/0000-0001-5720-3528>;
eLibrary SPIN: 6921-5511;
e-mail: sergeyvt2702@gmail.com

Vladimir I. Simanenkov, MD, Dr. Sci. (Med.), Professor;
ORCID: <https://orcid.org/0000-0002-1956-0070>;
eLibrary SPIN: 8073-2401;
e-mail: visimanenkov@mail.ru

Natalya V. Bakulina, MD, Dr. Sci. (Med.), Assistant Professor;
ORCID: <https://orcid.org/0000-0003-4075-4096>;
eLibrary SPIN: 9503-8950; Scopus Author ID: 7201739080;
ResearcherId: N-7299-2014; e-mail: natalya.bakulina@szgmu.ru

ОБ АВТОРАХ

***Сергей Викторович Тихонов**, канд. мед. наук;
адрес: Россия, 191015, Санкт-Петербург, ул. Кирочная, д. 41;
ORCID: <https://orcid.org/0000-0001-5720-3528>;
eLibrary SPIN: 6921-5511;
e-mail: sergeyvt2702@gmail.com

Владимир Ильич Симаненков, д-р мед. наук, профессор;
ORCID: <https://orcid.org/0000-0002-1956-0070>;
eLibrary SPIN: 8073-2401;
e-mail: visimanenkov@mail.ru

Наталья Валерьевна Бакулина, д-р мед. наук, доцент;
ORCID: <https://orcid.org/0000-0003-4075-4096>;
eLibrary SPIN: 9503-8950; Scopus Author ID: 7201739080;
ResearcherId: N-7299-2014; e-mail: natalya.bakulina@szgmu.ru

AUTHORS INFO

Nadezhda B. Lishchuk, MD, Cand. Sci. (Med.);
ORCID: <https://orcid.org/0000-0002-0703-9763>;
eLibrary SPIN: 4346-8011;
e-mail: lishchuk.nadezhda@mail.ru

Yuliya G. Topalova, MD;
ORCID: <https://orcid.org/0000-0003-3999-6848>

ОБ АВТОРАХ

Надежда Биржановна Лищук, канд. мед. наук;
ORCID: <https://orcid.org/0000-0002-0703-9763>;
eLibrary SPIN: 4346-8011;
e-mail: lishchuk.nadezhda@mail.ru

Юлия Геннадьевна Топалова;
ORCID: <https://orcid.org/0000-0003-3999-6848>