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The Role of Duodenogastroesophageal Reflux in the Progression of Gastroesophageal Reflux Disease: From Esophagitis to Adenocarcinoma

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Aim: to present data on the role of bile acids in the progression of Barrett's esophagus (BE) and the development of esophageal dysplasia and adenocarcinoma and to provide a rationale for the use of ursodeoxycholic acid in addition to basic therapy in patients with gastroesophageal reflux disease (GERD).
Key points. The prevalence of GERD in the world is 13.98 %. In the absence of the necessary treatment or non-compliance with the recommended regimens and duration of drug use, complications of GERD develop such as stricture, bleeding, BE, which, in turn, is a risk factor for the development of esophageal adenocarcinoma (EAC). The basic therapy for GERD is proton pump inhibitors (PPIs), but up to 40 % of patients do not fully respond to PPI monotherapy, which indicates the need to consider, among the factors in the pathogenesis of GERD, the persistence of weakly acidic and weakly alkaline refluxes, the presence of which can be diagnosed by performing 24-hour impedance-pH monitoring. It has been proven that refluxate is predominantly acidic in nature in 50 % of patients with GERD, acidic with a bile component in 39.7 %, and 10.3 % of patients have bile reflux. The weaklly alkaline nature of reflux, due to the presence of duodenal contents, significantly increases the incidence of intestinal metaplasia with dysplasia and EAC compared to acidic pH values. Therefore, stopping duodenal reflux may be an important step in preventing the development of EAC. Among the components of duodenal contents that have a damaging effect on the mucous membrane of the esophagus, the role of bile acids has been most studied. The presence of hydrophobic bile acids, namely deoxycholic acid (DCA), is associated with oxidative DNA damage in lesions of intestinal-type columnar cell metaplasia. Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, is a natural competitive inhibitor of DCA and prevents DNA damage and nuclear factor-κB (NF-κB) activation caused by toxic bile acids in BE epithelial cells. The cytoprotective effect of UDCA, aimed at preventing DNA damage and increasing the reparative capacity of cells in the metaplastic epithelium of the BE, allows us to consider this drug as a means of chemoprophylaxis in patients diagnosed with GERD.
Conclusion. The addition of UDCA drugs to the basic therapy is pathogenetically justified in patients with GERD in the presence of duodenogastroesophageal reflux. Prescribing complex therapy will reduce the incidence of esophagitis, progression of BE with the development of dysplasia and adenocarcinoma caused by exposure to bile acids.
Keywords: duodenogastroesophageal reflux, bile acid, gastroesophageal reflux disease, Barrett's esophagus, esophageal adenocarcinoma, impedance-pH monitoring, ursodeoxycholic acid
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Роль дуоденогастроэзофагеального рефлюкса в прогрессировании гастроэзофагеальной рефлюксной болезни: от эзофагита до аденокарциномы

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Цель: представить данные о роли желчных кислот в прогрессировании пищевода Баррета (ПБ) и развитии дисплазии и аденокарциномы пищевода (АКП) и дать обоснование применению урсодезоксихолевой кислоты дополнительно к базовой терапии у пациентов с гастроэзофагеальной рефлюксной болезнью (ГЭРБ).
Основные положения. Распространенность ГЭРБ в мире составляет 13,98 %. При отсутствии необходимого лечения или несоблюдении рекомендованных схем и длительности приема препаратов развиваются такие осложнения ГЭРБ, как стриктура, кровотечение, ПБ, который, в свою очередь, является фактором риска развития АКП. Базовой терапией ГЭРБ являются ингибиторы протонной помпы (ИПП), однако до 40 %

пациентов не отвечают полностью на монотерапию ИПП, что свидетельствует о необходимости учитывать среди факторов патогенеза ГЭРБ персистенцию слабокислых и слабощелочных рефлюксов, наличие которых возможно диагностировать при проведении суточной pH-импедансометрии. Доказано, что рефлюктат имеет преимущественно кислый характер у 50 % больных ГЭРБ, кислый с желчным компонентом — у 39,7 %, и 10,3 % пациентов имеют желчный рефлюкс. Слабощелочной характер рефлюктата, обусловленный наличием дуоденального содержимого, достоверно увеличивает частоту развития кишечной метаплазии с дисплазией и АКП по сравнению с кислыми значениями pH. Следовательно, купирование дуоденального рефлюкса может быть важным этапом профилактики развития АКП. Среди компонентов дуоденального содержимого, оказывающего повреждающее действие на слизистую оболочку пищевода, наиболее изучена роль желчных кислот. Присутствие гидрофобных желчных кислот, а именно дезоксихолевой кислоты (ДХК), связано с окислительным повреждением ДНК в очагах цилиндроклеточной метаплазии кишечного типа. Урсодезоксихолевая кислота (УДХК), гидрофильная желчная кислота, является природным конкурентным ингибитором ДХК и предотвращает повреждение ДНК и активацию ядерного фактора-κB (NF-κB), вызванные токсичными желчными кислотами в эпителиальных клетках пищевода при ПБ. Цитопротективный эффект УДХК, направленный на предотвращение повреждения ДНК и повышение репаративной возможности клеток в метаплазированном эпителии ПБ, позволяет рассматривать этот препарат в качестве средства химиопрофилактики у пациентов с диагнозом ГЭРБ.

Заключение. Добавление к базовой терапии препаратов УДХК патогенетически обосновано у пациентов с ГЭРБ в случае наличия дуоденогастроэзофагеального рефлюкса. Назначение комплексной терапии снизит частоту развития эрозивного эзофагита, прогрессирования ПБ с развитием дисплазии и аденокарциномы, обусловленных воздействием желчных кислот.

Ключевые слова: дуоденогастроэзофагеальный рефлюкс, желчная кислота, гастроэзофагеальная рефлюксная болезнь, пищевод Баррета, аденокарцинома пищевода, pH-импедансометрия, урсодезоксихолевая кислота

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The prevalence of gastroesophageal reflux disease (GERD) is steadily increasing in the world, and therefore issues related to its diagnosis and treatment remain relevant and occupy a significant place in gastroenterology. Symptoms of the disease reduce the patients' quality of life, entail changes in their lifestyle, and sometimes require constant medication and surgical intervention. A recent meta-analysis of 102 studies estimated the global prevalence of GERD to be 13.98 % (95 % confidence interval (CI): 12.47–15.56 %) [1].

In Russia, in recent years, a number of large studies have been conducted to analyze the prevalence of heartburn and GERD itself. In 2006–2007, a population survey was conducted in six cities — St. Petersburg, Krasnoyarsk, Kazan, Kemerovo, Ryazan and Saransk, and among 7828 respondents, 47.5 % of respondents indicated that they had ever experienced heartburn [2]. In another multicenter study, the results of which were published in 2022, 7216 outpatient clinic patients aged 18 to 90 years were surveyed, and 6132 questionnaires were analyzed during the course of the work. According to the results of this study, the prevalence of GERD among outpatient clinic patients was 34.2 % [3].

In the absence of the necessary treatment or non-compliance with the recommended regimens and duration of drug use, complications of GERD develop, such as stricture, bleeding, Barrett's esophagus (BE), which in turn is a risk factor for the development of esophageal adenocarcinoma (EAC) [4].

L.H. Eusebi et al., summarizing the results of 44 studies, conducted a meta-analysis, according to which the frequency of histologically verified BE in patients with GERD was 7.2 % (95 % CI: 5.4–9.3 %), while endoscopic signs of BE were detected in 12.0 % of patients (95 % CI: 5.5–20.3 %) [5]. Moreover, the risk of developing EAC in patients with BE without epithelial dysplasia is about 0.2–0.5 % per year, in the presence of low-grade dysplasia, the annual risk increases to 0.7 %, and in patients with high-grade dysplasia, the risk of developing neoplasia is already about 7 % per year [6]. In Russia, according to epidemiological studies, the incidence of esophageal cancer in 2010 was 5.2 cases per 100,000 population, and in 2020 — 5.4 cases per 100,000 population [7]. The average annual growth rate of incidence was 0.96 %, the increase in incidence over 10 years was 10.18 % [8].

The pathogenesis of GERD is based on dysfunction of the esophagogastric junction in combination with impaired esophageal clearance [4, 9]. Pathological gastroesophageal reflux (GER) causes the release of inflammatory cytokines and chemokines that contribute to the development of esophagitis and its clinical manifestations [10].

According to the Montreal classification, clinical manifestations in patients with GERD are divided into esophageal and extraesophageal. Among esophageal complaints, heartburn and regurgitation should be highlighted first as the most specific for patients with GERD [11, 12].

In the minds of many doctors, the development of heartburn and damage to the mucous membrane is traditionally associated with the presence of acid reflux, which is stopped by taking antisecretory drugs, which, in fact, promotes the healing of erosive lesions of the esophagus in patients with GERD. Previously, such healing was considered a therapeutic success, but it is now becoming clear that the intensity of symptoms, particularly heartburn, does not correlate well with the presence and severity of esophagitis, and symptoms may persist despite healing of erosions. This relationship is most clearly demonstrated by the lower response rates to antisecretory therapy in patients with non-erosive reflux disease (NERD) compared with the erosive form of the disease. Therefore, not only the presence of acid reflux is the cause of the development of heartburn. It is therefore not surprising that over the past decade there has been a paradigm shift in the treatment of patients with heartburn, especially in patients with NERD [13].

Duodenogastroesophageal reflux (DGER), commonly called "bile reflux", is the reflux of duodenal contents, including bile, through the stomach into the esophagus. Duodenogastric reflux (DGR), a condition that necessarily precedes DGER, can occur sporadically during the interdigestive period and postprandially in healthy volunteers [14], and in patients with GERD — also when antroduodenal coordination is impaired during the night and morning hours [15]. Gastric pH-metry is recognized as an objective method for diagnosing DGR, the graphs of which are presented in Figure 1. Reflux is defined as an increase in pH in the stomach above 5.0 (up to 8.0) units, which is not associated with food intake. DGR is considered severe if the duration of all its episodes exceeds 10 % of the time of gastric pH monitoring. To verify reflux containing bile acids, trypsin and lysolecithin in the lumen of the esophagus, various methods have been proposed. In early studies at the end of the last century, researchers determined the presence of bile, trypsin and alkaline substances in aspiration material during endoscopic biopsy and scintigraphy [16–18]. Later, a more modern method for quantitative assessment of the bilirubin level in refluxate was recognized as the fiber optic spectrophotometry method, based on determining the absorption spectrum of bilirubin (for example, using the Bilitec™ 2000 device, Medtronic, USA) [19]. Subsequently, the method of multichannel intraesophageal impedance-pH monitoring, capable of identifying the presence of reflux into the esophagus, regardless of the pH of the refluxate being thrown in, became widely used, that is, it became possible to determine not only acidic (pH < 4), but also weakly acidic (4 < pH < 7) and weakly alkaline (pH > 7) GER, as well as their physical characteristics (liquid, gas, mixed composition). Simultaneously with the introduction of esophageal impedance-pH monitoring into widespread clinical practice, the use of Bilitec™ 2000 almost completely ceased. However, it should be taken into account that the identification of "non-acidic" or "alkaline" reflux is not completely equivalent to "bile reflux", since outpatient studies of pH and Bilitec™ 2000 in the absence of acid suppressive therapy have shown that DGER can also occur at acidic pH levels [20–22].

Among the components of duodenal contents that have a damaging effect on the mucous membrane of the esophagus, the role of bile acids has been most studied. It has been established that bile salts conjugated with taurine (taurodeoxycholate and taurocholate) have a more pronounced damaging effect on the esophageal mucosa at an acidic pH value (the dissociation constant of both acids (pKa) is 1.9), which determines their synergy with hydrochloric acid in the pathogenesis of esophagitis. It should be noted that conjugated bile acids in an acidic environment weaken the toxic effect of pepsin on the esophageal mucosa. Unconjugated bile acids are more toxic at pH levels between 5 and 8. Thus, when the acid-producing function of the stomach is suppressed, the damaging effect of refluxate containing unconjugated bile acids increases. These data may explain the insufficient clinical response to monotherapy with antisecretory drugs in 15–20 % of patients [23, 24].

A recent systematic review by C. Basnayake et al., including 66 scientific articles, examined the prevalence of DGER among patients with GERD. When analyzing aspiration contents from the esophagus, carried out in 5 studies, and performing fiber optic spectrophotometry, the chosen diagnostic method in 23 studies, the prevalence of GER among patients with GERD varied between 20–94 and 10–97 %, respectively, and the difference did not reach statistically significant differences. Moreover, the percentage of time during which DGER was recorded using fiber optic spectrophotometry, according to different authors, ranged from 2.4 to 19 % of the study time [25].

According to the data obtained, DGER is more often detected in patients with erosive reflux disease (ERD) than NERD (22–80 % vs. 10–63 %, respectively). An analysis of 23 studies proved that in the group of patients with ERD complicated by Barrett's esophagus, the prevalence and severity of DGER were significantly higher compared to the group of patients with ERD with an uncomplicated course, NERD and a group of healthy volunteers ($p < 0.05$). The prevalence of reflux among patients with BE varied from 50 to 100 %, and the percentage of time of recorded DGER ranged from 7.8 to 48 % [25].

In addition, when analyzing 8 studies in patients with histologically proven BE, the relationship between the prevalence of DGER and the length of the BE segment, the presence or absence of signs of dysplasia and EAC was studied. The authors showed that a greater prevalence and duration of DGER occurred among patients with the development of dysplasia, EAC, and a long segment of BE than in patients without dysplasia, esophageal adenocarcinoma, or with a short segment of BE. Thus, it becomes

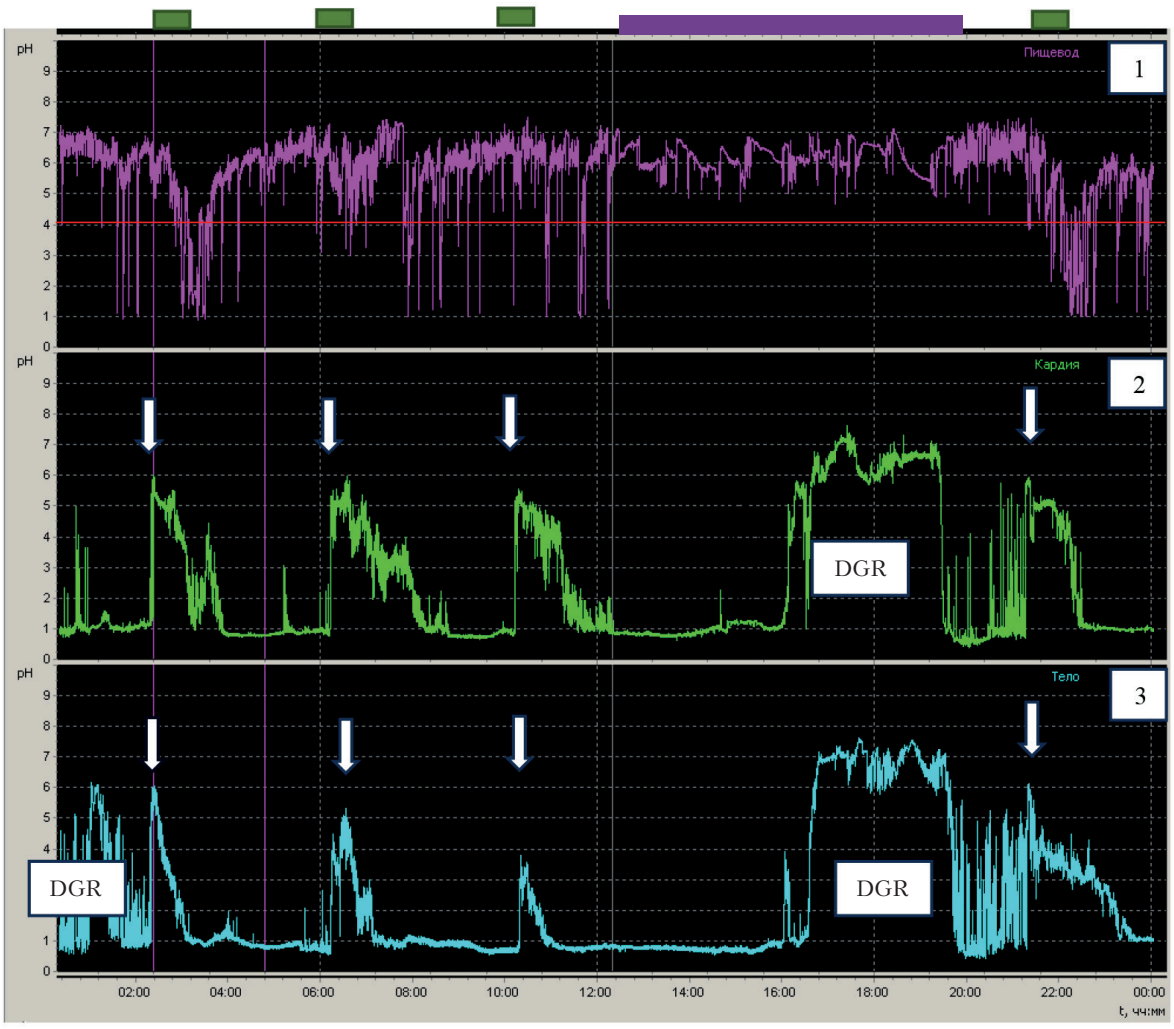

Figure 1. pH-metry of the esophagus, cardia and body of the stomach: *1* — pH graph in the esophagus (acid GER — decrease in pH below 4 units); *2* — pH graph in the cardia; *3* — pH graph in the body of the stomach; green horizontal line — food intake; white arrow — buffering effect of food; purple horizontal line — lying position; DGR — duodenogastric reflux (hereinafter — own data from the V.Kh. Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology)

Рисунок 1. pH-метрия пищевода, кардиального отдела и тела желудка: *1* — график pH в пищеводе (кислые ГЭР — снижение pH ниже 4 единиц); *2* — график pH в кардиальном отделе желудка; *3* — график pH в теле желудка; зеленая горизонтальная линия — прием пищи; белая стрелка — буферное действие пищи; фиолетовая горизонтальная линия — положение лежа; DGR — дуоденогастральный рефлюкс (здесь и далее — собственные данные клиники пропедевтики внутренних болезней, гастроэнтерологии и гепатологии им. В.Х. Василенко)

obvious that the presence of duodenal contents in the refluxate significantly aggravates the course of GERD [25].

It has been shown that the presence of hydrophobic bile acids, namely deoxycholic acid (DCA), in the refluxate is associated with oxidative DNA damage in foci of intestinal-type columnar cell metaplasia. Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, is a natural competitive inhibitor of DCA and prevents DNA damage and nuclear factor-κB (NF-κB) activation caused by toxic bile acids in epithelial cells in BE [26–28].

Of interest is the work of X. Huo et al., which studied the damaging effects of the weakly acidic environment of the stomach (pH = 5.5) in combination with bile acids on the mucous membrane of the esophagus. *In vitro* studies of esophageal biopsies from patients with BE demonstrated that weakly acidic solutions of bile salts, similar in composition to the gastric juice of patients receiving antisecretory therapy with proton pump inhibitors (PPIs), generate reactive oxygen species and cause oxidative DNA damage in metaplastic columnar cell epithelium of Barrett's esophagus and further development

of adenocarcinoma. Thus, DNA damage caused by gastric acid reflux in patients receiving PPIs may contribute to carcinogenesis of Barrett's esophagus and underlie the increasing incidence of EAC despite the widespread use of PPIs. In addition, the authors studied in detail the role of the *p38* gene in the response of BE to oxidative damage to epithelial DNA and in subsequent repair under the influence of toxic bile acids. It has been demonstrated that activation of *p38* causes a decrease in the proportion of cells entering S-phase division, which may give these cells time to repair their damaged DNA before replication. And the addition of UDCA in the experiment contributed to an increase in *p38* activity, which proves its high efficiency in preventing DNA damage and increasing the reparative capacity of cells in metaplastic epithelium. These results identified new potential targets for chemoprophylaxis in patients with Barrett's esophagus [29].

In another experimental study conducted on rats, Chinese researchers modeled the development of duodenogastroesophageal reflux by performing esophagoduodenostomy on the animals. Next, the authors determined the effect of refluxate pH level on the development of esophageal adenocarcinoma 40 weeks after surgery. It was shown that the weakly alkaline nature of reflux, due to the presence of duodenal contents, significantly increases the incidence of intestinal metaplasia with dysplasia and EAC compared to the group with acidic pH values ($p < 0.01$). Therefore, stopping duodenal reflux may be an important step in preventing the development of EAC [30].

The cytoprotective effect of UDCA was proven in experimental work by E. Ojima et al., conducted on laboratory rats. The study animals, after creating a model for the development of DGER in them, were divided into a main group, which received food supplemented with UDCA for 40 weeks, and a control group, which was given food without additives. In the group taking UDCA, esophagitis was less severe, the incidence of BE was significantly lower ($p < 0.05$), and no cases of esophageal cancer were observed, while in the control group several cases of EAC were detected ($p < 0.05$). The amount of UDCA in bile was 32.7 ± 11.4 mmol/L in the group of rats receiving this drug and 0.82 ± 0.33 mmol/L in the control group ($p < 0.05$). In addition, the intensity of NF-κB expression was higher in the control group than in the UDCA group ($p < 0.05$). Thus, the cytoprotective effect of UDCA can be used to prevent the development of esophageal adenocarcinoma [31].

As noted above, UDCA protects esophageal cells from oxidative stress caused by cytotoxic bile acids. In a recent study, American researchers studied the cytoprotective effect of drugs containing UDCA on the esophageal mucosa in 29 patients with GERD with histologically confirmed BE and the presence of GERD. Patients were treated with UDCA at a daily dose of 13–15 mg/kg of body weight for 6 months. The clinical effectiveness of UDCA was determined by assessing changes in the composition of bile acids in the gastric contents and markers of oxidative DNA damage in biopsies from the BE segment. Bile acid concentrations were measured by liquid chromatography/mass spectrometry. Initially, the amount of UDCA was 18.2 % of the total conjugated and unconjugated bile acids. After a course of treatment with UDCA drugs, the content of this acid increased significantly and amounted to 93.4 % of the total amount of bile acids ($p < 0.0001$). Thus, when analyzing the gastric contents of these patients, positive changes were observed in the composition of bile acids towards an increase in non-toxic forms. The expression of markers of oxidative DNA damage was assessed in biopsies of Barrett's esophagus by immunohistochemistry. The expression of tissue biomarkers (8-hydroxydeoxyguanosine, 8OhdG; markers of cell proliferation (Ki67) and apoptosis (cleaved caspase-3)) did not change after 6 months of UDCA treatment. The data obtained indicate the need for further study of the therapeutic spectrum of UDCA use in reflux esophagitis and BE [32].

At the same time, during a 5-year prospective randomized study to research the effectiveness of treatment for BE in elderly patients, two groups of patients were observed: Group A continuously received PPI monotherapy (omeprazole 20 mg twice a day), Group B was prescribed a combination treatment with PPI (omeprazole 20 mg twice a day) and UDCA (at a dose of 10 mg/kg of body weight per day). At the end of the observation period, in the group receiving PPI monotherapy, there was a decrease in the incidence of BE by 6.7 % of cases, while in patients receiving combined treatment with PPI and UDCA, the incidence of BE decreased by 32.3 % ($p = 0.03$). After 5 years of treatment, esophagitis was diagnosed in 53.3 % of patients in Group A and only in 12.9 % of patients in Group B ($p = 0.002$). Separately, it should be noted that in both groups, dysplasia was not detected before treatment. In Group A, after 5 years of PPI monotherapy, dysplasia occurred in 16.7 % of patients (OR = 0.08; 95 % CI: 0.00–1.44; $p = 0.06$). In Group B, after 5 years of observation, dysplasia was not diagnosed in any of the patients. The difference between groups in the incidence of dysplasia approached a significant level (OR = 13.59; 95 % CI: 0.72–257.49; $p = 0.06$). Thus, the authors concluded that combination therapy of PPIs and UDCA is more effective than PPI monotherapy for Barrett's esophagus and esophagitis in elderly patients [33].

Today, impedance-pH monitoring, recognized as the "gold standard" for diagnosing GERD, is in clinical practice the only research method that allows one to evaluate the physical and chemical characteristics of reflux [34–38]. The term "alkaline reflux" is used in the literature, but it is obvious that "pure" alkaline reflux is possible only in patients with complete cessation of hydrochloric acid secretion, that

is, in a state of anacidity, which can only be discussed with confidence under the condition of total gastrectomy. In clinical practice, in most patients, reflux is a mixture of alkaline duodenal secretion and acidic gastric juice, which determines the value of intraesophageal pH, namely the concentration of H^+ ions, depending on the predominance of one or another component, which can be determined by impedance-pH monitoring.

In scientific work carried out at the V.Kh. Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, the degree of damage to the mucous membrane of the esophagus was studied depending on the nature of the refluxate affecting it. Patients with GERD (n = 151) underwent daily impedance-pH monitoring using a domestically produced device "Gastroscan-IAM" (Research and Production Enterprise "Istok-System", Fryazino), esophagogastroduodenoscopy, morphological examination of biopsy material was carried out in 111 cases. When studying biopsy samples, the severity and activity of inflammation, the presence and type of metaplasia, the presence and severity of dysplasia were assessed. Subsequently, the results of objective, endoscopic and morphological studies were compared with 24-hour impedance-pH monitoring to determine the morphofunctional features of GERD depending on the nature of the reflux disease. As a result of the analysis of the data obtained, the authors concluded that in the group of patients with GERD with a predominantly alkaline refluxate (Fig. 2), the degree and activity of inflammation did not differ from the group of patients with GERD with a predominantly acidic nature of the refluxate, however, in this group there was a more frequent development of intestinal epithelial metaplasia esophagus and dysplasia, which were detected in 42.9 and 9.5 % of patients, respectively [39].

The main groups of drugs used in the treatment of GERD are PPIs and potassium-competitive proton pump blockers. As additional therapy in various combinations, including with the listed antisecretory drugs, H_2-histamine receptor blockers, ursodeoxycholic acid, esophagoprotectors, alginates, antacids, prokinetics, rebamipide can be used [4, 40].

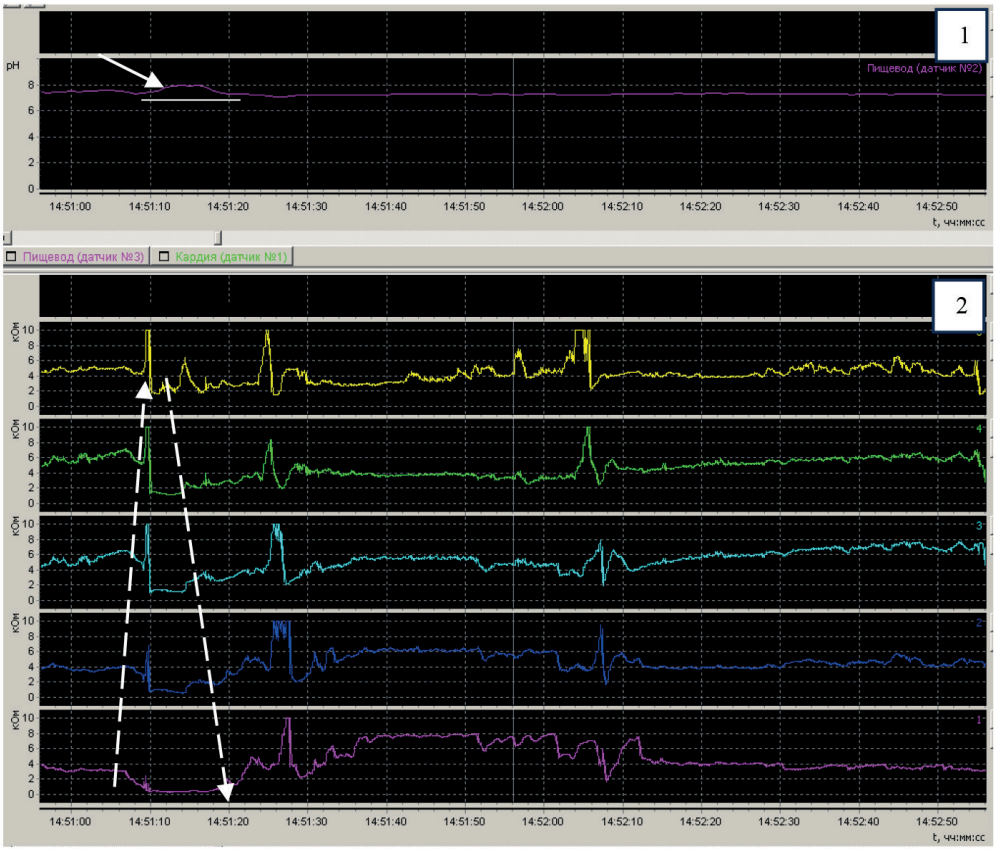

Figure 2. pH impedance monitoring of the esophagus: *1* — graph of pH in the esophagus; *2* — impedance graphs in the esophagus; during reflux (dashed arrow), weakly alkaline pH values are recorded in the esophagus — 8 units (solid arrow)

Рисунок 2. pH-импедансометрия пищевода: *1* — график pH в пищеводе; *2* — графики импеданса в пищеводе; во время рефлюкса (пунктирная стрелка) в пищеводе регистрируются слабощелочные значения pH — 8 единиц (сплошная стрелка)

Today, in clinical practice, doctors most often prescribe PPIs. However, up to 40 % of patients do not fully respond to PPI monotherapy [41], which indicates the need to consider, in addition to the effects of hydrochloric acid, other factors in the pathogenesis of GERD, namely impaired esophageal clearance, persistence of weakly acidic and weakly alkaline refluxes, etc. In his dissertation thesis, A. Trukhmanov showed that gastroesophageal reflux is predominantly acidic in 50 % of patients with GERD, acidic with a bile component in 39.7 %, and 10.3 % of patients have bile reflux [42]. Consequently, in this case, antacids, UDCA drugs, prokinetics, gastroprotectors and other drugs can be additionally prescribed in various combinations. The basis for the use of UDCA in esophagitis and BE caused by DGER is its cytoprotective effect, including high efficiency in preventing DNA damage and increasing the reparative capacity of cells in the metaplastic epithelium of Barrett's esophagus, which were mentioned above.

Thus, the presence of duodenal contents in the esophageal reflux can lead to the progression of Barrett's esophagus and the development of dysplasia and adenocarcinoma. The effectiveness of therapy with UDCA drugs is due to a decrease in the proportion of hydrophobic toxic bile acids in bile with a simultaneous increase in the proportion of hydrophilic UDCA. Considering the high prevalence of alkaline and mixed reflux among patients diagnosed with GERD and its more severe course, the addition of UDCA drugs to basic therapy seems appropriate in the vast majority of cases. This strategy may reduce the incidence of esophagitis and Barrett's esophagus caused by components of duodenogastroesophageal reflux. The cytoprotective effect of UDCA, aimed at preventing DNA damage and increasing the reparative capacity of cells in metaplastic epithelium, allows us to consider this drug as a method of chemoprevention in patients diagnosed with gastroesophageal reflux disease.

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