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Functional Dyspepsia and Gastroesophageal Reflux Disease: From Pathogenesis to Current Treatment Strategies

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Aim: to present a modern view on the combination of functional dyspepsia (FD) and gastroesophageal reflux disease (GERD) and to evaluate the effectiveness of acotiamide in patients with FD and GERD.
Key points. The high frequency of the combination of FD and GERD is caused by common pathogenetic mechanisms and presents an urgent problem in clinical practice. The concurrent occurrence of these diseases alters the clinical picture, complicates differential diagnostics, and leads to inadequate prescription of drugs. Medical treatment for patients with FD and GERD includes the use of proton pump inhibitors (PPIs) and prokinetics. Currently, acotiamide is recognized as an effective drug that affects the motility of the upper gastrointestinal tract. Acotiamide is an antagonist of muscarinic M1 and M2 receptors and a reversible inhibitor of acetylcholinesterase. The clinical efficacy of this drug has been demonstrated not only in patients with FD but also in those with a combination of FD and GERD.
Conclusion. Administration of acotiamide is pathogenetically justified in patients with the combination of GERD and FD.
Keywords: functional dyspepsia, gastroesophageal reflux disease, prokinetics, acotiamide
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Функциональная диспепсия и гастроэзофагеальная рефлюксная болезнь: от патогенеза к современным возможностям терапии

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Цель обзора: представить современный взгляд на проблему сочетания функциональной диспепсии (ФД) и гастроэзофагеальной рефлюксной болезни (ГЭРБ) и оценить эффективность применения акотиамида у пациентов с ФД и ГЭРБ.
Основные положения. Высокая частота сочетания ФД и ГЭРБ обусловлена общностью патогенетических механизмов и является актуальной проблемой в клинической практике. Сочетанное течение этих двух заболеваний изменяет клиническую картину, усложняет дифференциальную диагностику и ведет к неадекватному назначению лекарственных препаратов. Медикаментозное лечение пациентов с ФД и ГЭРБ включает применение ингибиторов протонной помпы и прокинетиков. В настоящее время эффективным препаратом, влияющим на моторику верхних отделов желудочно-кишечного тракта, является акотиамид. Акотиамид — антагонист мускариновых М1- и М2-рецепторов и обратимый ингибитор ацетилхолинэстеразы. Клиническая эффективность данного препарата продемонстрирована не только у пациентов с ФД, но и при сочетании ФД и ГЭРБ.
Заключение. Назначение акотиамида патогенетически обосновано у пациентов с сочетанием ГЭРБ и ФД.
Ключевые слова: функциональная диспепсия, гастроэзофагеальная рефлюксная болезнь, прокинетики, акотиамид
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Introduction

Functional dyspepsia (FD) and gastroesophageal reflux disease (GERD) are common gastrointestinal (GI) diseases. Epidemiologic studies indicate that dyspepsia symptoms occur in 20 % of the global population [1], with the prevalence of FD being 8.4 % [2]. The global prevalence of GERD ranges from 8.8 to 33.1 % (average — 13.3 %), while in the Russian Federation it ranges from 11.3 to 23.6 % [3, 4]. GERD is a chronic recurrent disease caused by regular reflux of gastric and sometimes duodenal contents into the esophagus due to motor-evacuation disorders of the gastroesophageal organs [3]. Currently, non-erosive reflux disease (NERD), which occurs in 70 % of cases, and erosive reflux esophagitis are distinguished.

According to the Rome IV criteria, FD is defined as a complex of symptoms (feeling of fullness and bloating in the pancreatic region, early satiety, pain, and burning in the epigastric region) observed in a patient during the last three months, with a total duration of at least six months, in the absence of organic causes [5]. Depending on the predominant symptoms, there are two clinical variants of FD that can be combined: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). In patients with EPS, the main complaints are pain and a burning sensation in the epigastric region. In PDS, patients more often complain of a feeling of fullness and bloating in the epigastric region and early satiety.

Certain common pathogenetic mechanisms form the basis for the combination of these two diseases. Clinically, the combination of FD and GERD complicates differential diagnosis and leads to low therapy effectiveness due to inappropriate prescription of medications.

The frequency of the combination of GERD and FD varies widely and may reach 70 % [6–11]. The wide range in rates and difficulties in establishing the true prevalence of the combination of these diseases can be explained by the fact that some authors assessed the frequency of the combination of GERD and dyspepsia symptoms, but not FD. Additionally, in some studies, the analysis was based only on the completion of respective questionnaires [8]. The situation is further complicated by the heterogeneity inherent in both diseases. Gastroesophageal reflux symptoms are detected not only in patients with GERD but also in patients with esophageal hypersensitivity to reflux (occurrence of heartburn/pain behind the sternum in response to physiological gastroesophageal reflux in the absence of pathological acid exposure in the esophagus and normal endoscopic findings). Thus, FD may be combined with functional esophageal disorders with symptoms similar to those of GERD, presenting further challenges in differential diagnosis and effective therapy.

The data on the combination of FD with different forms of GERD is also contradictory. According to some authors, FD occurs in 74.3 % of patients with non-erosive GERD and in 10.5 % with erosive esophagitis [12]. Other researchers report that FD occurs with equal frequency in both non-erosive and erosive GERD. However, it should be noted that PDS is detected in such patients in 47.9 % of cases, EPS in 25.0 %, and a mixed variant in 27.1 % [10].

Clinical manifestations in patients with a combination of these diseases are more noticeable compared to patients with isolated GERD or FD [13]. Additionally, the combined pathology is more often accompanied by a lower quality of life, sleep disorders, and a high level of depression.

According to modern concepts, the pathophysiologic basis for the development of the combination of FD and GERD includes impaired motility of the upper GI tract, hypersecretion of hydrochloric acid, visceral hypersensitivity, duodenal eosinophilia, and inflammation in the duodenum.

Upper GI tract motility disorders

Motility of the upper GI tract is regulated by the interaction of nervous and humoral factors, with central processing of impulses occurring in the cerebral cortex [14]. Normal peristalsis is created by the coordinated action of excitatory and inhibitory factors, and an imbalance between these factors leads to motor impairment and changes in anthro-duodenal coordination.

Currently, the leading mechanism of FD symptoms is gastric and duodenal motility disorders [15]. These include gastric accommodation disorder (the ability of the fundal part of the stomach to relax after a meal), impaired antroduodenal coordination, and impaired motility of the gastric antrum, resulting in delayed gastric emptying [14, 16]. According to electrogastrography, 36–66 % of patients with FD show disorders of gastric myoelectric activity (GMA, brady- or tachygastria), and 40–60 % show accommodation disorders [17–19].

Depending on the clinical variant of FD, the leading pathogenetic links contributing to symptoms may differ. For example, hypersecretion of hydrochloric acid is usually more frequently detected in patients with EPS and is the main cause of epigastric pain [16]. Gastric and duodenal motility disorders and visceral hypersensitivity determine the development of PDS. Thus, the choice of

drug treatment in patients depends on the clinical manifestations of FD.

Patients with impaired accommodation usually complain of bloating in the epigastrium and early satiety. Deterioration of antroduodenal coordination leads to a feeling of heaviness in the epigastric region, abdominal bloating, regurgitation, air burping, and heartburn. The weakened motor function of the gastric antrum, including that accompanied by increased intragastric pressure, is accompanied by a feeling of fullness, heaviness in the epigastrium, heartburn, regurgitation, and air burping [14].

GERD is considered a disease resulting from disorders of the upper GI tract motor function, leading to pathological gastroesophageal refluxes [3]. An important role in the occurrence of refluxes belongs to transient lower esophageal sphincter relaxations (TLESRs), during which the anti-reflux barrier between the stomach and esophagus disappears for 10–15 seconds [20]. TLESRs are considered a physiological mechanism of belching and can be the cause of gastroesophageal reflux episodes in 85 % of cases in healthy individuals [21]. In patients with GERD, the number of TLESRs is increased. Elevated pressure gradient between the stomach and esophagus after a meal, especially during delayed gastric emptying, promotes increased frequency of TLESRs.

In patients with PDS, impaired gastric accommodation may contribute to TLESRs, leading to gastroesophageal reflux [22, 23]. This explains the high frequency of the combination of FD and GERD.

Changes in gastric emptying in patients with FD, GERD, and their combination were studied by S. Gonlachanvit et al. [24]. A total of 83 patients underwent gastric emptying scintigraphy (GES) to characterize the motor function of the proximal and distal parts of the stomach. The results were compared with those in healthy subjects. Delayed gastric emptying was observed in 56 % of patients with FD, 45 % with GERD, and 55 % with the combination of these diseases. After a meal, a delay in the proximal part of the stomach was predominantly diagnosed in GERD patients compared to those with FD only and those with the combination of FD and GERD. The authors also noted that symptoms such as nausea, early satiety, vomiting, abdominal bloating, and regurgitation were associated with proximal motility disorders. Thus, this study emphasizes the importance of gastric motor abnormalities in the occurrence of symptoms in FD and GERD.

Visceral hypersensitivity

Visceral hypersensitivity plays an important role in the pathogenesis of FD. Increased sensitivity of the stomach to distension and impaired processing of signals from the upper GI tract in the central nervous system are recognized by experts at the ESNM consensus meeting on FD as proven pathophysiological mechanisms of the disease [15]. Visceral hypersensitivity occurs in 34–66 % of patients with FD and is associated with epigastric pain after meals, belching, and weight loss [25]. Compared to healthy controls, pain in these patients occurs with a much smaller increase in intragastric pressure.

Patients with NERD are hypersensitive to esophageal balloon distension and hydrochloric acid [26, 27]. The influence of esophageal distension on the occurrence of NERD symptoms is due to indirect activation of pain receptors and occurs in 20 % of cases [27]. M. Cicala et al. showed that patients with NERD have significantly more proximal acid refluxes and higher sensitivity to short-term refluxes compared to erosive esophagitis [26]. The increased sensitivity to acid is due to the expansion of intercellular spaces that occurs when acid is applied to esophageal mucosa, leading to the breakdown of tight junction proteins [28]. This results in increased epithelial permeability and penetration of hydrogen ions and various components of refluxate into the submucosal layer of the esophagus, where it stimulates the nerve endings responsible for the development of clinical symptoms.

Role of duodenal inflammation and eosinophilia in the pathogenesis of FD and GERD

The duodenum plays an important role in the pathogenesis of FD, as it regulates gastroduodenal motility, visceral hypersensitivity, and affects gastric emptying and accommodation through nervous and endocrine pathways [29]. In about 40 % of patients, duodenal hypersensitivity resulting from inflammation leads to impaired relaxation of the fundic gastric area, contributing to delayed gastric emptying, which may lead to TLESR causing pathological gastroesophageal reflux [22].

Inflammation correlates with increased permeability of the duodenal mucosa in patients with FD, and structural and functional neuronal changes [30]. T. Liebregts et al. demonstrated that the severity of symptoms in patients with FD is associated with increased cytokine release and higher levels of T cells in the small intestinal mucosa [31]. Significantly higher levels of TNF-α, IL-1β, and IL-10 were observed in patients with FD compared to controls. Thus, in *H. pylori*-negative patients with FD, the key factor in the development of clinical manifestations may be the activation of cellular immunity with an increase

in the number of T cells in the small intestinal mucosa, attracting eosinophils and mast cells to the sites of inflammation. The release of proinflammatory mediators during degranulation of these cells leads to dysfunction of the epithelial barrier and changes in the function of nerve endings (sensory receptors) in the upper GI tract [32].

The cytokine-mediated mechanism of disease development and progression is also considered in GERD. Cytokines in GERD patients may predetermine its course depending on their activity (anti- or pro-inflammatory). In a study by K.B. Dunbar et al., an increase in the number of intraepithelial T cells in the esophagus was found after discontinuation of proton pump inhibitors (PPIs) in patients with reflux esophagitis [33]. To date, there is evidence that the appropriate phenotype of macrophages (M1 or M2) determines an impaired immune response in the form of an imbalance between humoral (Th2) and cellular (Th1) links of immunity. Thus, it is believed that in the development of erosive esophagitis, the Th1 immune response is activated and in Barrett's esophagus, the Th2 immune response is activated [34, 35]. Macrophages also produce reactive oxygen species, transcription factors (NF-κB, TGF-β), and phospholipids that determine the body's immune response [36]. A study of blood macrophage phenotype in GERD patients revealed the predominance of surface M1 macrophages, characteristic of the proinflammatory Th1 immune response [37].

The link between FD and GERD through cytokine-mediated reactions requires further investigation, as it may become a new target for treating patients with the combination of these diseases. Suppressing inflammation in the duodenum will improve impaired accommodation of the fundic gastric tract and reduce pathological gastroesophageal reflux [38].

Duodenal eosinophilia in FD, which is not associated with *H. pylori* infection or esophageal eosinophilia, has been demonstrated in several studies [39–42]. Elevated eosinophil counts in the duodenum are more common in patients with PDS, characterized by early satiety, and occur in 47 % of cases [43]. Additionally, eosinophilia in the duodenum has been found in postinfectious FD and in children with FD [44–46]. According to M.M. Walker et al., an increase in the number of eosinophils to an average of 49 in the field of view at high magnification was associated with the diagnosis of FD [40]. The factors contributing to the development of duodenal eosinophilia have not been fully established. A possible role of increased permeability of the duodenal mucosa, mast cell dysregulation, and smoking cannot be excluded [47].

The role of acid-peptic factor in the development of gastroesophageal reflux disease and functional dyspepsia

GERD is an acid-dependent disease in which hydrochloric acid is the main damaging factor causing clinical symptoms [3]. In addition to hydrochloric acid, the refluxate may contain pancreatic enzymes and bile components (bile acids, lysolecithin, and trypsin). Only 10.3 % of patients show bile reflux, 39.7 % have acid reflux with bile components, and the predominant majority (50 %) have acid reflux [48]. It is proven that a significant increase in hydrochloric acid secretion leads to an increased risk of GERD development.

The number of refluxes and the duration of acid exposure in the esophagus correlate with the degree of damage to the esophageal mucosa. According to 24-hour pH-impedance testing, the time with pH < 4 in the esophagus during the day should be less than 4 %.

The role of acid in the pathogenesis of FD is primarily determined by acidification of the duodenum, which leads to inhibition of gastric relaxation during meals, delayed gastric emptying, and increased gastric sensitivity to distension. Several studies have demonstrated increased hydrochloric acid exposure in the duodenum in patients with FD, despite normal levels of hydrochloric acid secretion in the stomach [49, 50].

Patients with FD and increased hydrochloric acid exposure in the duodenum exhibit more dyspepsia symptoms compared to those with normal exposure [51–53]. Moreover, acidification of the duodenum leads to complaints primarily in FD patients, not in healthy people.

In patients with epigastric pain syndrome and excessive hydrochloric acid secretion, along with hypersensitivity of the gastric and duodenal mucosa, contribute to pain and burning sensation in the epigastric region [16]. However, the pathogenetic role of gastric acid sensitivity has not been fully established. While some FD patients report reduced severity of complaints with antisecretory therapy, most FD patients have normal levels of hydrochloric acid secretion in the stomach.

Y.L. Xiao et al. investigated pathological acidic gastroesophageal reflux in FD patients with predominant symptoms of pain, burning in the epigastric region, early satiety, and feeling of fullness after eating [54]. The prevalence of reflux among respondents with FD was 31.7 %. Pathological acidic gastroesophageal reflux occurred in 36.6 % of PDS patients and in 28.7 % of epigastric pain syndrome patients. J. Tack et al. also demonstrated an increase the acid exposure pH < 4 more than 5% of time in the esophagus in

patients with PDS, noting that individuals with epigastric pain syndrome are more prone to these changes [55].

Diagnosis of functional dyspepsia and gastroesophageal reflux disease

Functional dyspepsia is a diagnosis of exclusion since dyspeptic symptoms can occur in various diseases. According to the European Society of Neurogastroenterology and Motility, it is possible to treat FD patients without performing esophagogastroduodenoscopy (EGD) in the absence of "alarm symptoms" [15]. However, this approach is fraught with diagnostic errors, as even in young adults, gastric cancer can occur without "alarm symptoms" that appear at later stages of the disease [56]. In the Clinical Guidelines of the Russian Gastroenterological Association for the Diagnosis and Treatment of FD, performing EGD in patients with dyspepsia symptoms is mandatory [16].

Examination of patients with GERD symptoms should include EGD (with biopsy if necessary) to assess the severity of changes in the esophageal mucosa, 24-hour pH-impedance testing, and in some cases, high-resolution esophageal manometry [3].

Daily pH-impedance testing allows for differential diagnosis between functional heartburn, esophageal hypersensitivity to reflux, and NERD, and exclusion of their combination in patients with confirmed GERD. In NERD, patients with a normal esophageal endoscopic picture have an increased percentage of time with a pH < 4 greater than 4.0. Individuals with functional heartburn are characterized by normal esophageal acid exposure (pH < 4 — less than 4.0) and no association between the onset of symptoms and episodes of gastroesophageal reflux. In esophageal hypersensitivity to reflux, pH-impedance testing is characterized by normal esophageal acid exposure (percent of time with pH < 4 — less than 4) and the presence of an association between the onset of symptoms and episodes of physiological gastroesophageal reflux.

Approaches to medical therapy in patients with a combination of functional dyspepsia and gastroesophageal reflux disease

Effective FD and GERD combination treatment strategies can be tricky. Therapy in this case should begin with general measures, including lifestyle and nutrition changes.

Currently, the main treatment strategy for these conditions involves proton pump inhibitors and prokinetics [3, 16].

PPIs have demonstrated their effectiveness in the treatment of FD, mainly in epigastric pain syndrome. A Cochrane meta-analysis, which included 18 randomized controlled trials (6172 patients), showed that PPIs significantly reduce the overall symptoms of FD compared to placebo [57]. In a recent meta-analysis of 38 studies, it was also shown that the effectiveness of prokinetics significantly exceeded that of placebo in alleviating FD symptoms (odds ratio — 0.81; 95 % confidence interval (95 % CI): 0.74–0.89) [58]. The highest effectiveness of PPIs was observed in overweight patients with a combination of FD and GERD [59].

In patients with GERD, PPIs are currently the drugs of choice for both non-erosive and erosive forms of the disease [3]. PPIs maintain a gastric pH > 4 for more than 18 hours, promoting the healing of esophageal erosions [60]. Additionally, by reducing hydrochloric acid production, they alleviate GERD symptoms. According to large systematic reviews and meta-analyses, PPIs are recognized as the most effective drugs in GERD therapy.

The important role of motility disorders in the pathogenesis of FD forms the basis for prescribing motility-affecting drugs — prokinetics. A Cochrane meta-analysis, which included 24 studies (13,178 patients with FD), showed that the effectiveness of prokinetics significantly exceeds that of placebo (57 and 47 %, respectively) [61]. A recent meta-analysis of 38 studies demonstrated the alleviation of FD symptoms with the prescription of drugs in this group (odds ratio — 0.81; 95 % CI: 0.74–0.89) [58].

In GERD, the use of prokinetics is also pathogenetically justified [3]. According to available data, the effectiveness of prokinetics is due to the stimulation of gastric motility, resulting in a decrease in the number of TLESRs, improved esophageal clearance, and restoration of the normal physiological state of the esophagus. A meta-analysis of 14 studies demonstrated a more pronounced reduction in GERD symptoms with the addition of a prokinetic to a PPI compared to PPI monotherapy (odds ratio — 1.185; 95 % CI: 1.042–1.348; $p = 0.010$) [62]. Moreover, this combined therapy is effective in patients with refractory disease. It has been noted that in cases of combined GERD and FD, prokinetics have the greatest effect [13].

In patients with FD, *H. pylori* infection must be excluded [63]. The implementation of eradication therapy, with subsequent persistent disappearance of symptoms in patients with chronic gastritis and dyspepsia symptoms, allows excluding these patients from the FD group. If symptoms persist after anti-Helicobacter treatment,

H. pylori-infected individuals are considered FD patients [64, 65].

Effectiveness of acotiamide in the treatment of functional dyspepsia and gastroesophageal reflux disease

In 2023, acotiamide, an antagonist of muscarinic acetylcholine receptors (M-receptors) types 1 and 2, as well as an acetylcholinesterase (AChE) inhibitor, was registered in the Russian Federation. By inhibiting AChE activity and M1 and M2 cholinergic receptors, acotiamide enhances acetylcholine-induced contraction and motility of the antral and body parts of the stomach [66]. As a result, postprandial antral motility increases, fundic accommodation normalizes, and delayed gastric emptying accelerates.

It is also important to note acotiamide's ability to increase plasma ghrelin levels [67]. According to modern concepts, one of the mechanisms of FD development is a disruption in the synthesis of acylated ghrelin (the active form of the molecule) [68, 69]. In patients with PDS and NERD, a significant reduction in the level of this peptide hormone is noted compared to healthy individuals and patients with epigastric pain syndrome [69].

In patients with FD, acotiamide at a dose of 300 mg per day reduces the severity of symptoms: the overall relative risk (OR) was 1.29 (95 % CI: 1.19–1.40; $p < 0.00001$; $I^2 = 15$ %) compared to placebo [70]. In patients with PDS, the overall relative risk for overall symptom reduction was 1.29 (95 % CI: 1.09–1.53; $p = 0.003$; $I^2 = 0$ %), and for epigastric pain syndrome – 0.92 (95 % CI: 0.76–1.11; $p = 0.39$; $I^2 = 0$ %).

The evidence base for the effectiveness of acotiamide in FD continues to grow and includes more than 10 studies [66, 71–80]. Available data demonstrates not only a significant reduction in FD symptoms with this prokinetic, but also an improvement in the quality of life and work capacity in patients with epigastric pain syndrome and PDS. Acotiamide has a good safety profile [77]. Its use over one year is associated with a reduction in FD recurrence [75]. During eradication therapy, acotiamide reduces FD symptoms but does not affect *H. pylori* detection [79].

Combined therapy with acotiamide and PPIs also demonstrates high clinical effectiveness. Adding this prokinetic to esomeprazole at a dose of 300 mg per day in patients for whom PPI monotherapy was ineffective led to a reduction of symptoms and severity of PDS and epigastric pain syndrome [81].

Currently, acotiamide as a prokinetic for treating FD patients is included in the clinical guidelines of the British and Japanese Gastroenterological Societies [52, 82].

The effectiveness of acotiamide in GERD patients has been demonstrated by H. Yamashita et al. [83]. This randomized double-blind placebo-controlled study showed a reduction in GERD symptoms in patients taking this prokinetic in combination with PPIs. After two weeks, 28.6 % of patients receiving PPIs and acotiamide at a dose of 300 mg per day noted a reduction in symptom severity, compared to 14.3 % in the PPI monotherapy group. Among patients with NERD, these figures were 29.6 and 7.1 %, respectively.

In a study by K. Muta et al., a reduction in symptoms associated with reflux and FD was shown in patients with esophageal motility disorders [78]. Additionally, researchers found that acotiamide can normalize lower esophageal sphincter relaxation in patients with esophagogastric junction outflow obstruction without affecting normal esophageal motility.

In another double-blind placebo-controlled study of FD patients complaining of PPI-refractory heartburn due to non-erosive GERD, including acotiamide in the treatment regimen led to a reduction in heartburn severity and a feeling of fullness in the epigastric region [84].

The effectiveness of combined PPI and acotiamide administration in patients with combined GERD and FD refractory to rabeprazole monotherapy was demonstrated by T. Takeuchi et al. [85]. The authors noted that adding this prokinetic is an alternative to a double dose of PPIs.

Conclusion

The high frequency of the combination of functional dyspepsia and gastroesophageal reflux disease is a relevant problem in clinical practice. The concurrent occurrence of these diseases in a patient complicates the differential diagnosis, leads to inappropriate prescription of medications, and results in low therapy effectiveness. Currently, the drugs of choice are proton pump inhibitors and prokinetics, whose use is pathogenetically

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