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Review

MODERN APPROACH TO DYSPEPSIA

Barbara Medić[1], Žarko Babić[2,3,4], Marko Banić[2,3,5,6] and Lana Ljubičić[1]

[1]Zagreb Health Center-Center, Zagreb, Croatia;
[2]Department of Gastroenterology, Hepatology and Clinical Nutrition, Dubrava University Hospital, Zagreb, Croatia;
[3]School of Medicine, University of Zagreb, Zagreb, Croatia;
[4]Division of Interventional Gastroenterology, Dubrava University Hospital, Zagreb, Croatia;
[5]School of Medicine, University of Rijeka, Rijeka, Croatia;
[6]Division of Inflammatory Bowel Disease and Clinical Nutrition, Dubrava University Hospital, Zagreb, Croatia

SUMMARY – Dyspepsia is a disorder characterized by dyspeptic symptoms which are located in the epigastrium and related to digestion of food in the initial part of the digestive system. In functional dyspepsia, unlike organic dyspepsia, there is no underlying organic disease that would cause dyspeptic symptoms. Immune and mucosal function changes, gastric dysmotility, different composition of the gastrointestinal microbiota, and altered central nervous system processing are considered responsible for the onset of the disorder. The diagnosis is based on history, clinical presentation, and exclusion of other organic diseases of the gastrointestinal tract manifested by dyspeptic symptoms. Therapy includes eradication of *Helicobacter pylori* infection, proton pump inhibitors, prokinetics, neuromodulators, and herbal preparations. Unfortunately, in some patients, this therapy leads to little or no improvement. The prevalence of functional dyspepsia is increasing. It has become one of the more common gastroenterological diagnoses. In order to reduce the costs associated with the diagnosis and treatment of the disorder itself, its mechanisms need to be fully elucidated and thus enable finding appropriate therapy for all patient subgroups.

Key words: *Dyspepsia; Helicobacter pylori; Hypersensitivity; Visceral pain; Microbiota*

Introduction

Dyspepsia is characterized by a set of symptoms related to the digestive system and localized in the epigastrium. Symptoms include pain, nausea, vomiting, early satiety, heartburn, postprandial fullness, belching, etc. Dyspepsia may be subdivided into organic and functional. Organic dyspepsia is caused by other diseases. The most common are peptic ulcer, gastroesophageal reflux disease, esophageal and gastric cancer, biliary and pancreatic disorders, intolerance to food and drugs, and some systemic and infectious diseases[1]. The Rome Criteria IV were enacted in 2016 as the result of research on the intestinal microenvironment, brain-gut interactions, pharmacogenomics, biopsychosocial, sexual and cultural influences in the development of functional disorders. According to them, functional disorders of the digestive system are now called disorders of the gut-brain interaction (DGBI), and the whole area has been renamed as neurogastroenterology[2,3]. According to the Rome Criteria IV, patients with functional dyspepsia (FD) can be divided into two subgroups. The first subgroup is postprandial distress syndrome (PDS), which is dominated by postprandial fullness and early satiety, and dyspeptic symptoms are induced by meal. The second subgroup is epigastric pain syndrome (EPS), in which the predominant symptom is epigastric pain or burning, and symptoms

Correspondence to: *Prof. Žarko Babić, MD, PhD*, Department of Gastroenterology, Hepatology and Clinical Nutrition, Dubrava University Hospital, Zagreb, Avenija Gojka Šuška 6, HR-10000 Zagreb, Croatia
E-mail: zarko.babic@zg.t-com.hr
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do not occur only postprandially. The symptoms of these two subgroups may overlap[4,5]. The pathophysiologic mechanisms essential for the onset of dyspeptic symptoms include motility disturbance, altered immune and mucosal function, altered gut microbiota, visceral hypersensitivity, and altered central nervous system processing[3].

Pathophysiology

Gastric motility

The primary function of the stomach is to convert the ingested food into the chyme and deliver it to the small intestine. This is called gastric emptying. The rate of gastric emptying is mediated by two parallel neural circuits, namely, the gastric inhibitory vagal motor circuit and gastric excitatory vagal motor circuit. They consist of preganglionic cholinergic neurons in the dorsal motor nucleus of the vagus and postganglionic inhibitory and excitatory neurons in the myenteric plexus and affect the smooth muscles, most of all the stomach muscle. Different anatomic parts of the stomach form a pressure and peristaltic pump. They play an important role in gastric emptying. The cholecystokinin and glucagon-like peptide 1 hormones inhibit gastric emptying in the digestive period. Motilin and ghrelin accelerate gastric emptying in the interdigestive period[6].

Immune changes of the mucosa

More recent studies have shown the important role of chronic duodenal low-grade inflammation in the etiopathogenesis of FD. It is thought that inflammation can lead to motor and sensory abnormalities in gastrointestinal (GI) and neural system interactions. Still, the exact cause of inflammation is unknown. Some patients have a history of gastroenteritis[7]. Studies have confirmed higher levels of small bowel homing T cells and higher levels of circulating tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β and IL-10 cytokines in patients with FD compared to healthy controls. They have been correlated with the symptoms of dyspepsia and delayed gastric emptying[8]. Duodenal biopsy in patients with FD showed duodenal eosinophilia[9]. The major basic eosinophil protein causes vagal muscarinic M2 receptor dysfunction and directly enhances smooth muscle reactivity[10]. Vanheel *et al*. demonstrated duodenal infiltration by mucosal mast cells and eosinophils, abnormal cell-to-cell adhesion protein expression at the level of tight junctions, adherence junctions and desmosomes in patients with FD compared to healthy controls. They also demonstrated increased paracellular passage, which indicates that mucosal integrity is also impaired[11].

Microbiota

The gut microbiome mediates the physiological processes of the GI system such as immune development, GI motility and secretion, epithelial barrier integrity, and brain-gut communication. It plays an important role in the pathogenesis of DGBI[12]. In patients with FD, significant difference was demonstrated in total microbiota, number and composition in gastric fluid, and a much lower prevalence of bacteria of the genus *Prevotella* compared to healthy population. The treatment of patients with probiotic yogurt containing bacteria of the strain *Lactobacillus gasseri* led to attenuation of postprandial symptoms, which was explained by increase in the bacteria of the genus *Prevotella* in gastric fluid[13].

Visceral hypersensitivity

Disorders of the gut-brain interaction are characterized by visceral pain. Peripheral and central mechanisms are involved in the process of visceral nociception, and changes at any of their levels can lead to visceral hypersensitivity. Inflammatory mediators in the digestive system activate and sensitize the afferent nerves reducing their transducing threshold. They lead to the expression and recruitment of previously silent nociceptors. As a result, pain sensitivity at the site of injury is increased, which is called primary hyperalgesia. An individual's physiologic systems, stress responses, genetic and psychological factors, and the GI microbiota itself modulate visceral perception. Therefore, the threshold and sensation of visceral pain is each patient's individual experience[14].

Stress and chronic visceral pain

Stressful events in early life are the main stimulus for neural circuits involved in the processing of painful and stressful stimuli and they also cause increased sensitivity in response to stimuli at a later age. Adverse childhood conditions such as abuse, neglect and pov-

erty are risk factors for the development of visceral pain. Epigenetic modulations of gene expression involving alterations in DNA methylation and histone acetylation patterns within the brain lead to enhanced production of pro-nociceptive neurotransmitters. Stressors activate the hypothalamic-pituitary-adrenal axis. In response to that activation, corticosterone is secreted and it binds to glucocorticoid and mineralocorticoid receptors throughout the body. It enhances the sensitivity of neurons to harmful and innocuous stimuli. Sex hormones can modulate neuronal sensitivity and synaptic connections; thus women have a greater biologic tendency to develop chronic visceral pain. It follows that chronic visceral pain is a result of genetic and environment interaction[15].

The gut-brain axis

The gut microbiota regulates brain biochemical compounds and affects the neuro-endocrine system, which is responsible for responses to stress, anxiety, and memory functions. Some strains of bacteria exert specific biochemical effects on brain tissue. The central nervous system acts on microbiota composition by disrupting the mucosal or luminal environment[16]. Changes in brain parts and brain pathways involved in the processing of sensory information contribute to the development of visceral pain. Viscerosensory input signals from the GI system involving tonic contractions due to motor disorders, signaling molecules of various bacterial strains, and activated immune cells can lead to alteration in brain regions[17]. In FD, endogenous pain modulation is abnormally regulated[18]. Excessive vagal nerve afferent signaling that sends information to the brain about the arrival, amount and chemical composition of food leads to dyspeptic symptoms in PDS, early satiety and postprandial fullness. Excessive afferent vagal response to mechanical and chemical stimuli leads to central modulation of the pain pathway, which is essential for the onset of pain in EPS[19]. These data indicate that the gut-brain axis involves bidirectional communication[16].

Epidemiology

Functional dyspepsia is a disorder with a high prevalence of 15% to 20% in the general population[20]. Dyspeptic symptoms in FD can be severe and disabling, and reduce the quality of life, but diagnosis of FD has no long-term impact on mortality[21]. A study conducted on employees diagnosed with FD found that these patients generated higher direct and indirect costs and were less productive than employees without that diagnosis. Therefore, there is a need to develop a strategy to reduce the burden of disease and economic losses[22].

Etiology

The exact etiologic cause of the FD onset is unknown. One study found that dyspeptic symptoms occurred post infection in some patients. These patients were younger, had a lower body mass index, higher incidence of early satiety, weight loss, nausea, vomiting, and impaired gastric accommodation compared to patients who had unspecified-onset dyspepsia[23]. One cohort study found that the relative risk of developing FD was five times higher in patients after acute *Salmonella* gastroenteritis compared with patients who did not suffer from *Salmonella* gastroenteritis. Long-term abdominal pain and vomiting were positive predictors for developing FD[24]. Patients who have *Helicobacter pylori* (*H. pylori*) infection may have dyspeptic symptoms even if they do not have macroscopic changes on gastroduodenal mucosa[25]. Fatty foods, foods containing carbohydrates, milk and dairy products, citrus fruits, spicy foods, and alcohol are recognized as triggers of dyspeptic symptoms in a proportion of patients with FD[26]. A higher incidence of C825T polymorphism in G-protein β polypeptide-3 gene was demonstrated in patients with FD compared to healthy controls. This polymorphism has been shown to alter intracellular signal transduction[27].

Diagnosis

The Rome Criteria IV defining FD are as follows:

- persistent or recurrent dyspepsia lasting for more than three months in the last six months;
- a possible organic cause of the symptoms cannot be demonstrated on upper gastrointestinal endoscopy; and
- dyspeptic symptoms are not relieved by defecation and are not associated with stool irregularities.

The last criterion was set to rule out irritable bowel syndrome as a possible cause of dyspeptic symptoms[5]. Other organic diseases of the digestive system with

dyspeptic symptoms must be excluded[21]. Patients most commonly report long duration and variability of stress-dependent symptoms without progression and pain of variable locations without unintentional weight loss. If laboratory tests which involve blood counts, electrolytes, liver and kidney function, erythrocyte sedimentation rate, C-reactive protein, and sometimes thyroid parameters are within the reference range, some other tests may be run. These include testing for *H. pylori* infection, esophagogastroduodenoscopy, abdominal ultrasonography, and sometimes endoscopic examination of the colon if there are symptoms associated with the lower part of the digestive system, and always if they are alarming[5,28]. The guidelines recommend upper GI endoscopy for patients older than sixty presented with dyspeptic problems to exclude organic disease. For patients under sixty, endoscopy is recommended if there is a higher risk of developing a malignant tumor, e.g., a positive family history or childhood spent in a country where there is a high risk of gastric cancer. Noninvasive testing for *H. pylori* infection and its eradication are first recommended for patients younger than sixty. If there is no *H. pylori* infection or there is no improvement after eradication of *H. pylori* infection, proton pump inhibitor therapy is recommended. Patients whose upper GI endoscopy does not show organic pathology are defined as patients with FD[29]. For patients with severe reflux symptoms, a useful method is esophageal 24-h pH/impedance monitoring[30]. Patients with gallbladder dyskinesia may have dyspeptic symptoms, most commonly refractory. They need to be evaluated for gallbladder function in order not to get a wrong diagnosis and therapy[31].

Therapy

Treatment of Helicobacter pylori infection

Helicobacter pylori eradication therapy has positive effects on the reduction of dyspeptic symptoms in patients with FD. This has been consistently shown in Asian, European and American populations[32]. One study showed the long-term benefit of eradication of *H. pylori* infection. Eradication reduces the possibility of developing FD and gastric cancer associated with *H. pylori* infection for many subsequent years, thus providing economic savings. It is necessary to develop a program of screening for and eradication of *H. pylori* infection in the population, especially in populations with a high incidence of infection[33]. The Maastricht V Conference was held in 2015 in Florence and reported recommendations for treating *H. pylori* infection based on the best evidence available. In the areas with *H. pylori* resistance to clarithromycin lower than 15%, the first-line empiric treatment is triple therapy. It involves a double dose of proton pump inhibitor, clarithromycin and amoxicillin or metronidazole for fourteen days. In the areas where *H. pylori* resistance to clarithromycin is higher than 15% and metronidazole resistance is still low, triple therapy consisting of a proton pump inhibitor, amoxicillin and metronidazole for fourteen days is recommended as the first-line treatment. In the areas where *H. pylori* resistance to clarithromycin and metronidazole is greater than 15%, the first-line treatment is quadruple bismuth therapy. It consists of a proton pump inhibitor, clarithromycin, amoxicillin and nitroimidazole with bismuth for fourteen days. If there is a failure of these treatments or allergy to any of these drugs, further recommendations of the Maastricht V consensus should be followed[34].

Proton pump inhibitors

Proton pump inhibitors are used to treat dyspeptic symptoms in patients with FD[35]. The efficacy of lansoprazole 15 mg daily for four weeks in reducing dyspeptic symptoms, especially epigastric pain and burning in a subset of patients with EPS was proven in a study by Suzuki *et al.*[36]. A study by van Rensburg *et al.* showed the efficacy of pantoprazole 20 mg daily over a four-week period to relieve epigastric pain in patients with FD compared to placebo[37]. Four-week treatment with rabeprazole 10 mg a day was effective in reducing dyspeptic symptoms in a subset of patients with PDS and EPS[38]. Four-week treatment with 20 mg omeprazole a day was efficient in reducing dyspeptic symptoms[39].

Prokinetics

Prokinetics are drugs that stimulate motor function of the GI tract. They act as beta-blockers of dopamine receptors, inhibitors of acetylcholine esterase, and 5-HT4-receptor agonists. They are widely used in patients with FD[40].

Itopride

Itopride has antagonistic effects on dopamine D2-receptors and inhibits the acetylcholinesterase enzyme.

It improves symptoms in patients with FD, especially early satiety and postprandial fullness while rarely causing adverse effects[41].

Acotiamide

Acotiamide works by increasing the effect of acetylcholine in the enteric nervous system and by enhancing gastric contractions. It also accelerates delayed gastric emptying[42]. A dose of 100 mg acotiamide three times a day for four weeks led to improvement of dyspeptic symptoms in patients with PDS compared to placebo. It led to successful elimination of meal-related dyspeptic symptoms, too. A positive effect of drug manifested during the second week of treatment, without rapid relapse of symptoms upon therapy completion. It should be included in the treatment of FD because of its good tolerability and safety, especially in the subset of patients with PDS[43].

Neuromodulators

Antidepressants, anxiolytics, antipsychotics, and visceral analgesics are now called neuromodulators. More recent studies have shown their value in the treatment of DGBI, based on the growing knowledge in the field of neurogastroenterology. They exert effect by acting on the central nervous system and by modulating peripheral neurotransmitters. Empiric evidence confirms their value in reducing symptom severity and improving quality of life in patients with these disorders. Peripheral neuromodulators are sufficient in patients with mildly intense or intermittent symptoms, or symptoms associated with bowel movements. Central neuromodulators are added to existing therapy in patients with chronic and serious symptoms, especially if they include abdominal pain, nausea or vomiting, along with extra-intestinal symptoms[44,45].

Tricyclic antidepressants

Tricyclic antidepressants should be prescribed in low doses due to the potential adverse side effects. Amitriptyline 50 mg a day for ten weeks proved beneficial in relieving symptoms in a subset of patients with FD. Escitalopram 10 mg a day did not show such good efficacy[46].

Tetracyclic antidepressants

Daily dose of 15 mg mirtazapine for eight weeks showed efficacy in ameliorating early satiety, nutrient tolerance, weight loss, and improving quality of life in patients with FD[47].

Atypical antipsychotics

Quetiapine showed efficacy in patients with severe DGBI. In addition to its independent analgesic effect, it is believed to increase the effect of other antidepressants. It can be prescribed to patients with associated anxiety and sleep disturbance[48].

Azapirones

A dose of 10 mg buspirone three times a day for four weeks was effective in reducing dyspeptic symptoms and increasing gastric accommodation in patients with FD compared to placebo. It significantly ameliorated postprandial fullness, early satiety, and upper abdominal bloating[49].

Motilitone

Motilitone is a botanic drug that acts by exerting prokinetic effects, fundus relaxation and visceral analgesia. In clinical studies, it led to improvement of dyspeptic symptoms and GI functions in patients with FD. The drug is currently available in Korea[50].

Iberogast

Iberogast is a natural product composed of nine plant extracts and acts by multiple mechanisms. It normalizes GI motility and the microbiota, reduces hypersensitivity and gastric acid hypersecretion, and suppresses inflammation in the stomach. It showed efficacy in patients with FD and in those with irritable bowel syndrome. It relieves symptoms of upper and lower GI tract. It proved to be safe and well tolerated for use in patients independently of other comorbidities. Therefore, it has a great advantage of being used because dyspepsia is the most common chronic disorder[20].

Conclusion

Dyspepsia is a disorder characterized by dyspeptic symptoms, and is divided into organic and functional types. Some upper GI organic diseases may have dyspeptic symptoms. By treating organic disease, dyspeptic symptoms also disappear. Alteration of GI microbiota and the interaction between the enteric and central nervous systems are now proposed as essential

etiologic and pathologic factors for the onset of FD. There are attempts to restore the damaged balance of digestive system functions by drugs that act on the brain and brain neurotransmitters. The prevalence of FD is increasing. Dyspeptic symptoms in some patients are chronically present, and in some patients, there are periods of remission and relapse of symptoms. Existing therapy eliminates or reduces the intensity of dyspeptic symptoms in some patients. However, some patients are refractory and there is no improvement of their condition. They are a major clinical problem due to frequent consultations and examinations, and the use of healthcare, producing high costs. In these patients, the quality of life is severely impaired due to refractoriness and severity of symptoms. Further researches need to elucidate the etiologic cause and the pathophysiologic mechanism leading to FD in order to find effective therapy for all patients.

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Sažetak

SUVREMENI PRISTUP DISPEPSIJI

B. Medić, Ž. Babić, M. Banić i *L. Ljubičić*

Dispepsija je poremećaj koji obilježavaju dispeptički simptomi lokalizirani u žličici i vezani uz razgradnju hrane u početnom dijelu probavnoga sustava. Kod funkcijske dispepsije, za razliku od organske dispepsije, ne postoji podležeća organska bolest koja bi prouzrokovala dispeptičke simptome. Imune i promjene funkcije sluznice te motiliteta želuca, drukčiji sastav mikrobiote i obrada signala u središnjem živčanom sustavu smatraju se odgovornim za nastanak poremećaja. Dijagnoza se postavlja na temelju anamneze, kliničke slike i isključenjem drugih organskih bolesti probavnoga sustava koje se očituju dispeptičkim simptomima. Terapija uključuje eradikaciju infekcije bakterijom *Helicobacter pylori*, inhibitore protonske pumpe, prokinetike, neuromodulatore, biljne pripravke. Nažalost, kod dijela bolesnika navedena terapija dovodi do slabog ili nikakavog poboljšanja. Učestalost funkcijske dispepsije sve više raste. Postala je jedna od češćih gastroenteroloških dijagnoza. Kako bi se smanjili troškovi vezani uz dijagnostiku i liječenje poremećaja potrebno je do kraja rasvijetliti mehanizme te tako omogućiti pronalazak odgovarajuće terapije za sve podskupine bolesnika.

Ključne riječi: *Dispepsija; Helicobacter pylori; Preosjetljivost; Visceralna bol; Mikrobiota*