Chronic Abdominal Pain: Gastroenterologist Approach

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Keywords

Abdominal pain · Dyspepsia · Irritable bowel syndrome · Gastritis · Peptic ulcer · Chronic pancreatitis

Abstract

Background: Abdominal pain is a common symptom of gastroenterology examination. Chronic abdominal pain is present for >3 months. **Summary:** Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal diseases encountered by both gastroenterologists and general practitioners. GERD is usually a chronic disease presented with a set of symptoms including heartburn and/or regurgitation, and less commonly epigastric pain. Epigastric pain syndrome is characterized by the following symptoms: epigastric pain and/or burning. It does not necessarily occur after meal ingestion, may occur during fasting, and can be even improved by meal ingestion. Duodenal ulcers tend to cause abdominal pain that is localized in the epigastric region and commence several hours after eating, often at night. Hunger provokes pain in most of the cases and decreases after meal. Gastric ulcer pain occurs immediately after eating, and consuming food increases pain. Pain is localized in the epigastrium and can radiate to the back. Abdominal pain in irritable bowel syndrome is related to defecation. A typical symptom of chronic pancreatitis is pain that radi-

ates to the back. In Crohn's disease, inflammation causes pain. **Key Messages:** Pain can occur at different locations with diverse intensity and propagation and is often associated with other symptoms. For any gastroenterologist, abdominal pain is a big challenge.

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Introduction

Chronic abdominal pain is pain that prolongs for >3 months. Abdominal pain is a common symptom encountered by gastroenterologists. It can be associated with various diseases of the abdomen or extra-abdominal diseases. The pain can occur at various locations, with diverse intensities and propagation, and it is often associated with other symptoms.

The problem of abdominal pain represents one of the major challenges in today's gastroenterology practice [1]. The goal is to make an accurate diagnosis in the shortest possible time. Many diseases can cause chronic abdominal pain: gastroesophageal reflux disease (GERD), chronic gastritis, gastric and duodenal ulcers, Crohn's disease, dyspepsia, irritable bowel syndrome (IBS), and chronic pancreatitis (CP).

Gastroesophageal Reflux Disease

GERD is one of the most common gastrointestinal diseases faced by both gastroenterologists and general practitioners. GERD is usually a chronic disease presented with a set of symptoms including heartburn (>90% of patients) and/or regurgitation (>60% of patients), and less commonly with epigastric pain that occurs mostly after a fat meal, lasting 2 or more days per week [2]. However, the presence of heartburn is indicative of GERD. Typical reflux symptoms can be presented without esophageal injury in nonerosive reflux disease (NERD), while GERD with esophageal injury is presented with erosive esophagitis and complications like strictures, Barrett esophagus, or even esophageal adenocarcinoma. The prevalence of GERD is increasing in the last decades in Europe, North America, and East Asia and is estimated between 15 and 25% worldwide, probably due to “Western lifestyle” with risk factors like fast food diet, alcohol, smoking, reduced physical activity, and overweight. Medications like non-steroidal anti-inflammatory drugs have also been reported as risk factors for GERD. According to recent data, the GERD prevalence in Europe is approximately 25%, but is even higher in some populations like in Greece, reaching >50% [3, 4]. Moreover, many studies showed that health-related quality of life is significantly impaired in patients with GERD, regardless of the endoscopic findings [5].

Therapeutic interventions for GERD include lifestyle changes which are frequently overlooked by doctors and not followed by patients. Lifestyle modifications include cessation of alcohol and cigarettes, consuming spicy and fatty food, losing weight in addition to elevating the head of the bed, and not eating at least 3 h prior to bedtime. Medical therapy includes proton pump inhibitors (PPIs), antacids, prokinetics, histamine 2 receptor antagonists, Gaviscon, Carafate, and baclofen in some countries. However, over the past 3 decades, PPIs have been the most effective medical therapy for GERD as compared to all other medical therapies. Nowadays, it is well-known that the “top-down” strategy of PPI therapy is recommended, which means that treatment should begin with the most effective therapy (twice a day) and subsequently be stepped down to a regimen of PPI that controls individuals’ symptoms [6]. However, approximately about 30% of individuals are resistant to PPI therapy. The reason for PPI treatment failure may be compliance and timing of PPI, and discussion with the patient on this issue should be the first step. If this is not the case, the potential mechanisms of treatment failure are that many of these patients do not have GERD but suffer from functional

dyspepsia (FD). It is estimated that up to 60% of individuals with refractory GERD would qualify as having functional heartburn. Other differential diagnosis includes visceral hypersensitivity, duodenogastroesophageal reflux, impaired esophageal mucosal integrity, acid pocket, weakly acidic reflux, or nocturnal acid breakthrough (NAB) [7]. However, the reason for refractory GERD may be gene polymorphisms on cytochrome P450C19 [8].

Functional Dyspepsia

FD affects up to 10% of the population [9]. Approximately 80% of individuals with dyspepsia have no structural explanation for their symptoms and have FD [10]. The pathophysiology of FD is multifactorial and not fully understood; it is possibly related to dysregulation of the gut-brain axis, gastroduodenal dysmotility, visceral hypersensitivity, alterations in gastrointestinal microbiota, duodenal inflammation, and duodenal eosinophilia [9].

According to the Rome IV criteria, FD is defined by the presence of any combination of 4 symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning that is severe enough to interfere with the usual activities and occurs at least 3 days per week over the last 3 months with an onset of at least 6 months in advance, with no significant pathological findings at upper endoscopy. FD patients were divided into 2 groups: those with epigastric pain syndrome (EPS) and those with postprandial distress syndrome (PDS).

EPS is characterized by the following symptoms: epigastric pain and/or burning. Burning in the epigastrium should be distinguished from retrosternal burning (heartburn), although FD and GERD do overlap quite often. PDS is characterized by postprandial fullness and an early satiety, inability to finish a normal-sized meal. Also, there is often an overlap between PDS and EPS. Epigastric pain (or epigastric burning) that characterizes EPS does not necessarily occur after meal ingestion, may occur during fasting, and can be even improved by meal ingestion. Both types of pain in EPS are similar to pain in peptic ulcer or gastro-esophageal reflux disease. PDS and EPS both are characterized by meal-induced dyspeptic symptoms and epigastric pain or burning [11]. FD involves different symptoms in the upper abdomen, such as discomfort, bloating, belching, nausea, and vomiting [12].

Diagnosis of FD is made based on typical symptoms and patients’ history, and exclusion of other diseases of the upper gastrointestinal tract and upper abdominal or-

gans that may present with dyspeptic symptoms. Diagnosis of FD is also based on abdominal ultrasonography, testing for *Helicobacter pylori*, and esophagogastroduodenoscopy because normal endoscopy is required to diagnose FD [13]. However, the current guidelines suggest that endoscopy is not recommended for patients younger than 55 years, as well as for patients without alarming symptoms [10].

Treatment for FD includes PPIs, prokinetics, and phytotherapy. The second therapeutic options for patients with refractory symptoms were tricyclic antidepressants and psychotherapy. Symptoms of patients diagnosed with *H. pylori*-associated dyspepsia are treated by eradication therapy [10]. Organic causes of dyspepsia are peptic ulcer, GERD, gastric or esophageal cancer, pancreatic or biliary disorders, intolerance to food or drugs, and other infectious or systemic diseases [12].

Chronic Gastritis and Ulcer Disease

Epigastric pain is a common symptom of chronic gastritis. Chronic gastritis is still a relatively frequent disease. The prevalence of chronic gastritis decreases with the decrease in the prevalence of *H. pylori* infection [14].

H. pylori gastritis as an infectious disease with the recommendation for treatment of all *H. pylori*-infected subjects [15]. There is a strong correlation between the prevalence of *H. pylori* and the incidence of its related diseases, including peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma.

People with nonatrophic antral predominant gastritis have high stimulated acid production; therefore, duodenal ulcer and non-ulcer dyspepsia are common in this group. In contrast, people with atrophic gastritis (involving both antrum and corpus mucosa) have impaired acid production, and gastric proximal ulcers and gastric cancer are common in this group.

The use of aspirin and nonsteroidal anti-inflammatory drugs increases the risk of ulcer disease in *H. pylori*-infected subjects because they must be treated with eradication therapy [16]. Infection with *H. pylori* and use of nonsteroidal anti-inflammatory drugs and acetylsalicylic acid are the most common etiological factors in the development of peptic ulcer.

Systematic review of the symptom patients with peptic ulcer disease showed that 81% had abdominal pain, 81% epigastric pain, and 46% heartburn or acid regurgitation [17]. Duodenal ulcers tend to cause abdominal pain which is localized in the epigastric region and commences

several hours after eating, often at night. Hunger provokes pain very often and decreases after meal. Gastric ulcer pain occurs immediately after eating, and consuming food increases pain. It is localized in the epigastrium and can radiate to the back.

However, ulcer pain correlates poorly with the presence or severity of ulceration. Some patients have persistent pain even after ulcer healing by medications. In many patients, peptic ulcer is completely asymptomatic.

Irritable Bowel Syndrome

IBS is very common functional gastrointestinal disorder. According to the official Rome IV publications by the Rome Foundation, the name FGID has been changed to disorder of gut-brain interaction [18].

The global prevalence of IBS is about 11.3%, with a range of 9–23%. These differences depend on demographic and cultural factors and the application of different diagnostic criteria [19]. A recent meta-analysis reported that the prevalence of IBS in studies based on the Rome IV criteria was 3.8% and that based on the Rome III criteria was 9.2%. This suggests that the Rome IV criteria are more restrictive than Rome III [19, 20].

The pathogenesis of IBS is heterogeneous which includes psychosocial factors, increased intestinal membrane permeability, the brain-gut interaction, food intolerance, visceral hypersensitivity, small intestine bacterial overgrowth, and motility dysregulation, and the serotonin plasma level may be important in the development of IBS.

The diagnostic Rome IV criteria for IBS imply recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, with symptom onset at least 6 months before diagnosis associated with 2 or more of the following criteria: related to defecation, associated with a change in frequency of stool, or associated with a change in the form (appearance) of stool [11].

The abdominal pain is a very important symptom in IBS. Unlike the Rome III criteria, pain is crucial to make diagnosis of IBS. Also, it is necessary that the frequency of abdominal pain be present at least 1 day per week during the past 3 months. Pain must be chronic and last for at least 6 months.

Stool consistency can be determined based on the Bristol Stool Form Scale (BSFS): type 1 is hard stool, type 2 is lumpy stool, type 6 mushy stool, type 7 watery stool, and types 3, 4, and 5 are normal stool consistency [21]. In the Rome IV criteria, stools should be hard in >25% of bowel

Table 1. Therapy of IBS

Constipation	Diarrhea	Pain	Bloating
Laxatives	Loperamide	Antispasmodics	Rifaximin
Linaclotide	Cholestyramine	Eluxadoline	Eluxadoline
Lubiprostone	Alosetron	Linaclotide	Lubiprostone
Prucalopride	Eluxadoline	Cholestyramine	Linaclotide
	Rifaximin	Probiotics	Probiotics
		TCA's	FODMAPs
		SSRIs	
		Psychological therapy	

FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; SSRIs, selective serotonin re-uptake inhibitors; TCAs, tricyclic antidepressants; IBS, irritable bowel syndrome.

movements in IBS-C (constipation) or loose in >25% of bowel movements in IBS-D (diarrhea). For IBS-M (mixed), there should be >25% loose stools and >25% hard stools, and for IBS-U (unsubtyped), <25% loose stools and <25% hard stools [11].

Diagnosis of IBS includes clinical history, information about lifestyle and diet, psychological interview, the Rome IV diagnostic questionnaire, normal physical examination, and laboratory tests – complete blood count to exclude anemia or leukocytosis, C-reactive protein and fecal calprotectin to rule out IBS in patients with diarrhea, fecal occult blood test, thyroid check, and serology for celiac disease if clinically suspected. It is necessary to exclude alarm symptoms, if they presence [22]. Routine colonoscopy is not recommended in patients younger than 45 years with IBS symptoms without warning signs [23].

Nonpharmacological therapies for IBS include lifestyle modification – stress reduction and increased physical activity, dietary modification – gluten-free, lactose-free diet, FODMAP diet, and increased fiber intake. According to experts, pharmacological therapy of IBS should be focused on the predominant symptoms – constipation, diarrhea, abdominal pain, or bloating [24]. Therapy of IBS is shown in Table 1.

Chronic Pancreatitis

CP is a chronic fibroinflammatory syndrome of the pancreas in patients with persistent pathologic responses to parenchymal injury or stress. The end-stage disease characteristics are as follows: pancreatic atrophy, fibrosis, duct distortion, strictures, and calcifications, with pancreatic exocrine and endocrine dysfunction and eventually dysplasia. It is typically present in patients with risk

factors including genetic predisposition, or environmental factors [25, 26]. The typical symptom is abdominal pain, but patients may have symptoms derived from exocrine pancreatic insufficiency and diabetes mellitus. However, the duration of disease is the most important etiologic risk factor for endocrine insufficiency. The most common environmental factors are alcohol use, smoking, genetic polymorphisms, and previous recurrent attacks of acute pancreatitis. Tobacco use may play an important role in the development of diabetes mellitus. Advances in the last decades changed our view of understanding of CP and consequently changed approaches in diagnosis and management of the disease [27].

Diagnosis is usually made with cross-sectional imaging, endoscopic ultrasonography (EUS), pathohistology, and pancreatic function tests. The gold standard is computed tomography or magnetic resonance imaging. EUS should be used if there is doubt after computed tomography (or magnetic resonance imaging), due to its invasiveness and lack of specificity. Magnetic resonance cholangiopancreatography is reserved for individuals with a clinical and/or laboratory suspicion for extrahepatic bile duct obstruction or pancreatic duct stones.

Pancreatic function tests, including CCK stimulation test, secretin stimulation test, serum trypsinogen and alpha 1 antitrypsin, have low to moderate sensitivity for pancreatic insufficiency. Moreover, they have very limited specificity and are not widely available. Histologic evaluation can be considered in individuals with inconclusive results with cross-sectional imaging or EUS [28].

Therapeutic interventions for CP include lifestyle changes including alcohol and tobacco cessation. Individuals with pancreatic duct obstructions due to stones or strictures may undergo therapeutic endoscopic retrograde cholangiopancreatography with pancreatic sphinc-

terotomy as a decompressive procedure, with stone clearance or dilatation of stricture or pancreatic duct stenting. Interventional EUS with placement of a transluminal pancreatic duct stent may be offered as a decompression procedure.

Treatment with antioxidants may result in a long-term pain relief [29]. Opiates can be used only for pain relief in individuals in whom other therapeutic approaches have been exhausted. Pancreatic enzyme supplementation may improve symptoms like diarrhea and abdominal cramping, but it seems that they do not primarily relieve pain in CP. Celiac plexus blockade with a combination of local anesthetic and steroids can be performed through endoscopic ultrasound, interventional radiology, or surgical approaches. This procedure is reserved only for patients with chronic pain refractory to other therapeutic options [30].

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD), which are chronic lifelong inflammatory disorders of unknown etiology characterized by a relapsing and remission course that can result in progressive bowel damage and disability. CD and UC may affect individuals of any age from children to the elderly. Up to 30% of individuals with CD have complicated disease at the first presentation including strictures, fistula, or abscesses. As the etiology of CD and UC remains unknown, a curative therapy is not yet available [31, 32].

Abdominal pain can be a common symptom of IBD and is typically present in about 50–70% of IBD patients in exacerbation. Pain may arise through several mechanisms, including severe intestinal inflammation, gut distention, intestinal obstruction, and/or abscesses. During the relapse of disease, most of the patients will experience abdominal pain due to active inflammation and will gradually improve as disease activity decreases. Pain is one of the most typical manifestations of inflammation, due to inflammatory cytokines and mediators that sensitize primary afferent neurons. Patients with stenotic form of CD may have strictures requiring surgical interventions.

However, the past 2 decades have witnessed great advances in ability to treat IBD with a new era of biologics that has significantly improved and changed the natural course of UC and CD. Thus, novel therapies are very efficient in treating the underlying inflammatory processes

and IBD complications. Thus, medical treatment for CD and UC has greatly improved over the past 2 decades and can be effective in the majority of IBD patients. However, a small percentage of IBD patients continue to experience abdominal pain, despite resolving inflammation and achieving clinical, laboratory, even endoscopic, and histology remission. According to several studies, about 20% of IBD patients in clinical and endoscopic remission continue to experience significant symptoms including abdominal pain [33]. Current evidence suggests that pain processing and activation of sensory pathways are modulated by several factors including inflammation, as well as cognitive factors and emotions. Thus, stress may be an important link between inflammation, emotion, and pain. Current evidence indicates that emotional problems constitute a significant burden to IBD patients and may have a huge impact on their quality of life [34]. Moreover, according to several studies, psychological treatments can be very effective in treating functional gastrointestinal disorders in patients with IBD [35]. Thus, improving the underlying inflammation with novel therapeutic modalities, together with altering emotional and/or cognitive functions, may be key to release of symptoms in IBD patients. Having that in mind, the functional gastrointestinal abnormalities in IBD patients need to be recognized and addressed more effectively, and in addition, emotional factors significantly contribute to the clinical presentation of disease including abdominal pain and other symptoms.

Conclusion

The prevalence of GERD, FD, IBS, CP, and IBD is increasing, except the prevalence chronic gastritis and peptic ulcer, which are decreasing. FD is divided into EPS) and PDS. Pain in EPS is localized in the upper stomach and is not meal-related. IBS implies pain that is related with defecation. Ulcer pain correlates poorly with the presence or severity of ulceration. The typical symptom of CP is abdominal pain, but patients may have symptoms derived from exocrine pancreatic insufficiency. Abdominal pain can be a common symptom of IBD and is typically present in about 50–70% of IBD patients with exacerbation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors contributed equally to the manuscript. Snezana Lukic, Dragana Mijac, and Branka Filipovic wrote the manuscript. Ratko Tomasevic, Aleksandra Sokic-Milutinovic, Miodrag Krstic, and Tomica Milosavljevic prepared the concept for the paper and analyzed and corrected the paper. All the authors reviewed the final version of the manuscript.

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