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GASTROINTESTINAL COMPLICATIONS OF PATIENTS WITH DIABETES MELLITUS: ISSUES OF DIAGNOSIS AND TREATMENT

Abdusattarov A.A.
Department of Internal Medicine
Andijan State Medical Institute
Andijan, Uzbekistan

Resume. Diabetes mellitus (DM) is a disease characterized by multiple organ lesions, the formation of complications such as diabetic neuropathy, retinopathy, nephropathy, etc. About 75% of patients with DM report the presence of clinically significant gastrointestinal symptoms during examination and treatment. The food canal in DM is affected throughout, starting from the oral cavity and esophagus and ending with the large intestine and anorectal area. At the same time, clinical manifestations are often mosaic in nature and can vary significantly. The classic gastrointestinal symptoms in DM are abdominal pain, bloating, nausea, a feeling of rapid satiety, postprandial discomfort, diarrhea and/or constipation, and the frequency of symptoms characteristic of gastroesophageal reflux disease (heartburn, dysphagia) reaches 41% of cases.
Key words: confidence interval, gastrointestinal tract, coronary heart disease, body mass index, odds ratio, diabetes mellitus, glomerular filtration rate, mucous membrane.

Esophageal complications in patients with diabetes mellitus. The thoracic esophagus and the lower esophageal sphincter (NPS) consist of smooth muscle fibers innervated by the mesenteric plexus, the lesion of which is diabetic neuropathy, as well as structural remodeling of the muscular layer of the esophagus can contribute to the formation of abnormal peristalsis, the appearance of spontaneous contractions, a decrease [7] or impaired relaxation of the NPS [5]. It has been shown that with diabetes, the morphological and biomechanical properties of the esophagus change significantly [8]. It was noted that the prevalence of esophageal dysfunction in diabetes reaches 63% [16], regardless of the type of diabetes, gender of patients, associated with the duration of diabetes. Erosive esophagitis is more common in patients with diabetic neuropathy (66.7% of cases), as a rule, with low-symptomatic manifestations, which requires mandatory endoscopic examination of the esophagus to assess the severity of its damage [2].

In many cases, esophageal complications associated with diabetes can be successfully treated. For example, in GERD, proton pump inhibitors (pantoprazole 40 mg per day, rabeprazole 20 mg per day, esomeprazole 40 mg per day, dexlansoprazole 30 mg per day), which are commonly used to treat acid reflux, can be effectively managed. All proton pump

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inhibitors, with the exception of dexlansoprazole, are taken in the morning, 30-40 minutes before meals. However, it should be borne in mind that even the most effective PPIs to date do not affect the root cause of the disease – impaired function of the locking mechanism of the cardia, motility of the stomach and duodenum, therefore, after discontinuation of their administration, a relapse of the disease occurs relatively quickly in most patients. In some cases, PPIs do not eliminate some symptoms, most often associated with impaired motility of the esophagus and stomach, hypersensitivity of the stomach to stretching. In such cases, the use of prokinetics is additionally indicated in the treatment of GERD patients [2]. Prokinetics contribute to the restoration of the physiological state of the esophagus by acting on the pathogenetic mechanisms of GERD, reducing the amount of incoming relaxation of the lower esophageal sphincter and improve esophageal clearance by stimulating the motor function of the underlying digestive tract. A meta–12 randomized controlled trials on the use of prokinetics (dopamine receptor blockers, selective gamma-aminoximabutyric acid GABA(B) receptor agonists], 5-HT4 receptor agonists) in GERD and including 2403 patients showed that the addition of prokinetics to PPIs contributed to a more significant decrease in the severity of clinical.

Therefore, according to L. H. Ren, et al. (2014) [4], the combination of prokinetics and PPIs may be a new direction in the treatment of patients with GERD in whom PPIs monotherapy is insufficiently effective. Currently, the most well–known dopamine receptor blockers - metoclopramide and domperidone enhance the contractility of the stomach and prevent its relaxation, accelerate evacuation from the stomach, improve antroduodenal coordination. However, in clinical practice, metoclopramide finds very limited use due to the high frequency (up to 25%) of side effects, which include extrapyramidal disorders (muscle hypertension, facial muscle spasm, hyperkinesis), undesirable effects from the central nervous system (headache, dizziness, drowsiness, anxiety, depression, etc.) as well as hormonal effects (hyperprolactinemia, galactorrhea, menstrual disorders, gynecomastia). The appointment of domperidone requires control of the duration of the Q–T interval, especially in patients over 60 years of age. New prokinetics with a combined mechanism of action include itopride hydrochloride, which is both a dopamine receptor antagonist and an acetylcholinesterase blocker. The drug activates the release of acetylcholine and prevents its degradation, enhances the propulsive motility of the stomach and accelerates its emptying. An important advantage of itopride hydrochloride compared to other prokinetics is its high safety profile, which was specifically emphasized in the Rome Criteria for Functional Disorders IV revision (2016) [19]. In the Recommendations of the RGA on the diagnosis and treatment of GERD, itopride hydrochloride (at a dose of 50 mg 3 times a day) is positioned as a drug for the pathogenetic treatment of GERD, since it normalizes the motor function of the upper digestive tract (level of reliability of evidence 1, level of persuasiveness of recommendations A) [1].

Adsorbents can be used both as monotherapy in the clinical manifestations of non-erosive reflux disease and as part of the complex therapy of GERD, especially in mixed (acid + bile) reflux. Dioctahedral smectite is prescribed 1 sachet (3 g) 3 times a day [1]. For patients

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with oral and esophageal candidiasis, glycemic control and the use of fluconazole (150 mg once a day for 14 days) are very important. Gastroparesis is one of the most common complications of diabetes. Gastric emptying disorders are noted in 27-65 % of papatients with type 1 diabetes and about 30% of patients with type 2 diabetes [4], more common in women [9]. Common risk factors for the development of diabetic gastroparesis (BPH) are elevated levels of glycated hemoglobin, diabetes duration of more than 10 years and the presence of macro- and microvascular complications. Obesity is an independent predictor of the occurrence of symptoms indicating gastroparesis in patients with type 2 diabetes and neuropathy [3]. BPH is considered as a slowdown in the flow of contents from the stomach to the duodenum of varying severity in the absence of a mechanical obstacle [7].

At the same time, the second meaning of the term "gastroparesis" is a severe form of violation of the motor evacuation function of the stomach, lack of peristalsis and evacuation. The main symptoms of this complication are prolonged nausea (observed in 92% of patients with diabetes and diagnosed gastroparesis), vomiting (in 84% of patients), bloating (in 75% of patients), a feeling of early satiety (up to 60% of patients). Abdominal pain with predominant localization in the underlying area worries up to 90% of patients [4]. A clinically adverse consequence of delayed gastric emptying in patients is difficulty in achieving glycemic control, which is manifested by an episode of my hypo- and hyperglycemia. Hypoglycemia in the postprandial period is caused by a slowdown in the intake of carbohydrates into the small intestine. In the postabsorption period, there is a mismatch between the absorption and effect of insulin it leads to hyperglycemia. Spikes in the level of glycemia potentiate the development of late complications of diabetes, and they are poorly tolerated by patients. Slow evacuation also negatively affects the effectiveness of oral medications and complicates the postoperative period. Gastric emptying depends on the tone of the fundal part of the stomach and the phase contractions of its antrum in parallel with the inhibition of pyloric and duodenal contractility, which requires a clear interaction between smooth muscle muscles, enteric and autonomic nervous systems, specialized gastric rhythm driver cells and interstitial Cajal cells. The pathogenesis of the development of clinical symptoms of GP is based on violations of vagal regulation, which leads to impaired motor activity of the antrum of the stomach, discoordination of the functioning of the pyloric sphincter of the duodenum 12. Hyperglycemia itself can reversibly worsen gastric motility and reduce the effectiveness of prokinetics. It reduces the contractility of the antrum of the stomach and inhibits the 3rd antrum phase of the migrating motor complex, promotes relaxation of the fundal part of the stomach, increases the contractility of its pyloric department, causes gastric dysrhythmia (mainly tachygastria), as a result of which the rate of gastric emptying slows down significantly 9, 10,].

Neurohumoral factors, including glucagon-like peptide-1 (GLP-1), may play a role in the pathogenesis of gastric motor disorders, therefore, the use of exenatide and liraglutide may lead to the development of symptoms of gastroparesis. The diagnosis of GP is usually a diagnosis of exclusion, when other potential causes of symptoms are excluded and postprandial stagnation in the stomach is confirmed [6]. To diagnose gastroparesis, a special questionnaire

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Gastroparesis Cardinal Symptom Index (GCSI) can be used, based on three scales: feeling full after eating or early satiation (4 signs), nausea/vomiting (3 signs) and abdominal distension in the epigastric region (2 signs) [22], and its modification GCSI-DD (GCSI-Daily Diary, 2009) for daily assessment of gastroparesis symptoms [13, 17].

Depending on the severity of symptoms, gastroparesis is divided into 3 degrees of severity [10, 37]. With mild gastroparesis (grade 1), the symptoms are relatively easy to control, there is no loss of body weight with a regular or slightly modified diet. Gastroparesis of moderate severity is compensated, characterized by moderately pronounced symptoms, partially controlled by pharmacotherapy, dietary modification and lifestyle, finally, severe gastroparesis is characterized by refractory symptoms and decompensation of gastric function, despite pharmacotherapy, frequent visits to a doctor and hospitalizations, the inability to maintain an adequate level of nutrition with oral food intake. Such patients, in addition to drug combination therapy, often require enteral or parenteral nutrition, endoscopic or surgical treatment. Treatment of this gastrointestinal complication includes recommendations to improve blood glucose control, increase fluid volume, eat smaller portions of food, and stop using tobacco and alcohol. The choice of liquid food is due to the fact that liquids move in the intestine under the influence of gravity and the gradient of gastroduodenal pressure and do not depend on the work of the pyloric sphincter, the function of which in patients with severe gastric emptying delay may be impaired. Qualitative dietary changes should also be made, namely, reducing the consumption of insoluble dietary fiber, high-fat foods and alcohol. A recent prospective study in patients with diabetic GP demonstrated that eating small portions of food consisting of soft, digestible foods with no products in the peel, membranes, and seeds improves the symptoms of GP compared to a standard diet [3].

Proteins and fats slow down the emptying of the stomach, so foods with these food components should also be excluded. If possible, patients should stop taking hypoglycemic agents that exacerbate disorders of gastric motility, in particular, GLP-1 receptor agonists [10]. In addition, it should be remembered that the deterioration of gastric motility can be mediated by anticholinergic drugs [3]. Ondansetron can be used to relieve nausea and vomiting [23]. It is available in tablet form orally, as well as in the form of soluble tablets taken sublingually, in liquid form for intravenous administration. In patients with vomiting, the use of 8 mg of the drug sublingually has advantages over oral use and, if necessary, is used up to three times a day. It is more often used in hospitalized patients with continuous vomiting, or those who are immune to the oral form of the drug. To improve the motor function of the stomach, prokinetic drugs are used that increase the contractile activity of the antrum of the stomach, correct gastric dysarrhythmias, increase the coordinated functioning of the antrum and duodenum, contributing to the promotion of stomach contents. The effectiveness of these drugs is assessed by changing the clinical picture. Currently, metoclopramide, a derivative of benzamide structurally similar to procainamide, is used for the treatment of gastroparesis. Its main action is to antagonize dopamine D2 receptors, but it also stimulates 5-HT4 receptors. This effect manifests itself in the release of acetylcholine in the intestinal wall, which, in turn, leads to a

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decrease in the tone of the lower esophageal sphincter, contractility of the antrum, and the tone of the fundus. At the same time, the drug is able to penetrate the blood-brain barrier, which makes its use currently limited due to the development of pronounced side effects of a "central" nature: extrapyramidal disorders, headache, dizziness, drowsiness, depression and hormonal disorders (hyperprolactinemia with galactorrhea, gynecomastia, menstrual disorders). Current guidelines recommend using metoclopramide for no more than 12 weeks at the lowest possible dose and with careful monitoring of early signs of extrapyramidal side effects [9]. An alternative may be to use the dopamine receptor antagonist domperidone. Its main action is similar to that of metoclopramide. It accelerates gastric emptying by inhibiting the relaxation of its fundus and enhancing antroduodenal coordination. However, when using it, it is necessary to control the duration of the QT interval and possibly with an initial QT of □ 470 ms in men and QTc of □ 450 ms in women [9]. The drug is prescribed 15-20 minutes before meals per day.

The recommended dose is 30 mg (10 mg 3 times a day). In a number of studies in patients with diabetic gastroparesis, it has been noted that itopride hydrochloride effectively stimulates the contractility of the stomach, eliminates discoordination of the antrum of the stomach and the duodenum. Activates the release of acetylcholine, suppresses its destruction. It has a specific effect on the upper gastrointestinal tract, accelerates transit through the stomach, improves its emptying [4, 9,].

The drug has a dual mechanism of prokinetic action: it enhances the motility of the gastrointestinal tract due to antagonism with D2-dopamine receptors and inhibition of acetylcholinesterase. Itopride hydrochloride is used in a daily dose of 150 mg (three times before meals). Electrostimulation of the stomach is increasingly used for persistent nausea and vomiting, which are unsuitable for other methods of treatment. However, the mechanism of action of gastric electrical stimulation is still unclear. The data indicate a possible modulation of the biomechanical activity of the stomach. Electrical stimulation of the stomach is an invasive method of treatment, which is always accompanied by risks of postoperative complications. Therefore, this type of treatment should be considered only as an alternative [31]. Refractory gastroparesis is defined as the absence of regression of symptoms on drug therapy, accompanied by an inability to provide the nutritional needs of the patient. In patients suffering from severe gastroparesis, surgical and endoscopic treatment can be used. Herostomy should be performed with frequent hospitalization due to developing pneumonia. In a retrospective study of the surgical treatment of diabetic dehydration and the need for parenteral nutrition. Laparoscopic eunostomy is a fairly safe operation. The main complications: intestinal obstruction and aspiration gastroparesis, a decrease in nausea and vomiting was noted in 39%, the frequency of hospitalizations decreased in 52% of patients, 56% noted better absorption of food, 83% felt healthy. If laparoscopic intervention is not possible, laparotomy is resorted to [9]. The issue of the need for eradication of Helicobacter (H.) pylori in the detection of its colonization remains very difficult. The presence of an ulcer, confirmed morphologically or by examination of pepsinogen I, II and gastrin-17 in the blood, chronic atrophic gastritis, the need

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for long-term administration of proton pump inhibitors in the coexistence of GERD and DM, taking nonsteroidal anti-inflammatory drugs and anticoagulants undoubtedly require eradication of H. pylori. In addition, according to Ju Huang (2017) [6], H. eradication pylori can effectively improve symptoms associated with dyspepsia and delayed gastric emptying in patients with DHR. The lesion of the small intestine is characterized by impaired peristaltic activity, the development of intestinal pseudoobstruction, excessive bacterial growth, diarrhea and steatorrhea. In conditions of delayed peristalsis in the small intestine, favorable conditions are created for excessive reproduction of intestinal microflora and the development of excessive bacterial growth syndrome (SIBR). Due to damage to the brush border of enterocytes, the development of secondary disaccharidase and dipeptidase insufficiency, through impaired deconjugation of bile acids, excessive bacterial growth can cause osmotic diarrhea and steatorrhea in patients with DM [8].

Chronic diarrhea is more common in patients with type 1 diabetes. Fecal masses have a watery character, diarrheal syndrome occurs both at night and during the day and in one third of patients is accompanied by fecal incontinence [18]. It should be noted that there is no abdominal pain syndrome, and the presence of pain obliges to exclude other causes of diarrheal syndrome. In the presence of diarrheal syndrome, treatment is mainly empirical and includes adequate fluid intake, addition of electrolytes and maintaining the best control of glycemia. Antidiarrheal medications should be taken only on a one-time basis [21, 41]. Loperamide at a dose of 2 mg 1-6 times a day is used as a symptomatic remedy for relieving diarrhea. When detecting SIBR, an important aspect of treatment is to achieve glycemic control [43], antibiotic treatment is indicated, and, above all, rifaximin 600-800 mg per day, and a daily dose of 1200-1600 mg is effective in 80% of cases [5, 14,].

Changes from the colon most often include constipation. Very typical for patients with type 2 diabetes is the addition of anorectal disorders, manifested by imperative urges, fecal incontinence. Bowel movement disorders occur in 60% of DM patients, being the most common manifestation of diabetic enteropathy [7, 8]. Prevalence studies conducted in the USA, Europe and Hong Kong show that the incidence of chronic constipation in patients with diabetes, it is 10%, 13-22% and 27.5%, respectively. In another cross-sectional study, 13.9% of 224 Indian patients with functional constipation had diabetes [35]. Changes on the part of the colon in the most typical cases are expressed not only in the development of constipation, up to the picture of an "inert colon". In addition, diabetic neuropathy leads to a decrease in rectal sensitivity and/or impaired function of the external sphincter, which lead to symptoms of rectal dysfunction, such as urge to defecate and a feeling of incomplete emptying [4, 6].

According to an observational study conducted in Japan in 2015, the main factors associated with constipation in patients with diabetes are, the level of glycated hemoglobin ≥ 8.0%, body mass index (BMI) <25 kg/m2, the use of insulin [12]. The pathogenesis of the formation of chronic constipation in DM is complex, primarily associated with the development of diabetic neuropathy and disorders of the autonomic innervation of the intestine [7]. It is assumed that the main reason for the formation of symptoms in patients with DM is

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desynchronization of intestinal peristalsis and the work of the sphincter apparatus [21]. A significant contribution to the development of motor disorders of the large intestine in DM is made by a decrease in the number of enteral neurons [11], enteroglucagon- and serotonin-immunoreactive cells along the intestine [15]. Additional factors playing a role in the pathogenesis of diabetic entropathy are changes in the secretion of intestinal hormones and proinflammatory cytokines, along with genetic predisposition [21]. The role of acute and chronic hyperglycemia in the formation of Cajal cell dysfunction in DM is discussed, and a decrease in their density is noted. In both type 1 and type 2 diabetes, the level of insulin growth factor-I (IGF-1) decreases, which can lead to smooth muscle atrophy, which also contributes to impaired intestinal function [21].

Other candidate mechanisms involved in the pathogenesis of enteropathy in diabetes include impaired synthesis of neuronal nitric oxide, which is an important neurotransmitter in the intestine [30]. An important role in the violation of regular bowel movement in patients with diabetes is played by the loss of the "gastrocolytic reflex" [7]. The role of the intestinal microbiota in the formation of chronic constipation in patients with diabetes is discussed. A relative decrease in the proportion of Firmicutes (Bacteroides vulgatus, Faecalibacterium prauznitzii) and Bifidobacterium and Roseburia is shown, along with an increase in Bacteroidetes and Proteobacteria [4]. The basis for the treatment of constipation in patients with diabetes is proper hydration, diet and physical activity of treatment [21]. Dietary treatment should consist of a diet with asd produced fibers (20-30 g per day). The most common treatment for chronic constipation is osmotic laxatives – lactulose (usually prescribed from 15 to 45 ml in the first 3 days, then switch to a maintenance dose of 10-25 ml. It is better to take the drug 1 time a day in the morning with meals), polyethylene glycol (1-2 sachets, dissolving 1 sachet in 50 ml of water) and lactitol [2 sachets per day, during meals, mixed with various drinks (water, tea, coffee, juices, etc.) or liquid food, 1 time a day day)]. Thus, gastroenterological symptoms in patients with diabetes are often found, associated with numerous factors: demographic, gender, psychological, medicinal, the presence of hyperglycemia, diabetic complications, including autonomic neuropathy. Depending on the nature of these complications, different classes of drugs are required: proton pump inhibitors, prokinetics, antibiotics, antidiarrheal and laxatives. However, the main condition for treatment is to achieve glycemic control in patients with diabetes

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