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Gastrointestinal Tract Disorders in Patients with Diabetes

In this issue of "Clinical Diabetology", Samak and colleagues from Iran [1] assessed prevalence of different gastrointestinal (GI) symptoms in 1364 patients with diabetes, comparing them with a group of 1305 control subjects. Although this paper suffers from some limitations, like use of non-validated questionnaire or probably not the best matching of the groups, and in spite of the fact that the authors did not find a significant difference between the groups (with overall prevalence of GI symptoms of 54.8% in patients with diabetes vs. 57.8% in the control group), it reminds of an important problem — gastrointestinal diseases in patients with diabetes.

Although they are not — at least directly — a cause of increased mortality, like cardiovascular diseases, they are common and often not easy to diagnose and treat not only for a diabetologist, but also for a gastroenterologist. Below, the reader will find a table that may facilitate a differential diagnosis of gastrointestinal signs and symptoms in diabetes (Tab. 1), and, because of limited space, description of only four most common and probably most important causes of gastrointestinal disorders related to diabetes.

Probably most known for the reader, at least for an endocrinologist or diabetologist, is diabetic gastroparesis, i.e., delayed gastric emptying with no detectable GI tract obstruction. Delayed gastric emptying may be present in up to 40% of patients with diabetes. Its prevalence depends possibly on disease duration and definitely on type of the disease as well as sex, and only part of these patients have clinical symptoms. From this reason the prevalence of diagnosed gastroparesis is assessed for about 5% in type 1 diabetes (T1D), and about

Table 1. Gastrointestinal Disorders Caused by or Often Coexisting with Diabetes (Based on [7])

Esophageal disorders
• Gastroesophageal reflux disease (GERD)
• Esophageal motility disorder
• Esophageal candidiasis
Gastric disorders
• Gastroparesis
• Accelerated gastric emptying
Small intestine disorders
• Celiac disease
• SIBO
• Diabetic diarrhea
Large intestine disorders
• Fecal incontinence
• Drugs-related adverse events
• Antidiabetic drugs (metformin, GLP-1 and GLP-1/GIP receptor agonists)
• Other drugs
Others
• Cholelithiasis and its complications
• Metabolic dysfunction — associated steatotic liver disease (MASLD, former NAFLD)
• Pancreatitis
• Pancreatic cancer

GIP — gastric inhibitory polypeptide; GLP-1 — glucagon-like peptide-1; MASLD — metabolic dysfunction-associated steatotic liver disease; NAFLD — non-alcoholic fatty liver disease; SIBO — small intestine bacterial overgrowth

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1% in type 2 diabetes (T2D) [2], being more frequent in women than in men. The most characteristic symptoms are early and prolonged satiety, nausea and vomiting, although different other symptoms may be also present. Treatment is only partially effective. Optimal control of diabetes may be beneficial, although drugs like amylin, GLP-1 (glucagon-like peptide-1) receptor agonists or double GLP-1/gastric inhibitory polypeptide (GIP) receptor agonists that may further delay gastric emptying should be avoided. Dietary treatment aims to decrease the volume and increase frequency of meals. In pharmacological treatment, metoclopramide may be used as a short term symptomatic treatment, and itopride or domperidone for longer periods. Other possible treatment method is gastric peroral endoscopic pyloromyotomy (G-POEM).

Small intestine bacterial overgrowth (SIBO) is a less known and relatively new, but probably a most frequent gastrointestinal disease in patients with diabetes. A recent meta-analysis assessed the odds ratio for SIBO for 4.18 (95% CI: 1.34–13.05). The frequency of the disease was slightly higher in T1D than in T2D (30 vs. 25%) [3]. It has, however, to be mentioned that the prevalence of SIBO depends on many risk factors, as practically all gastrointestinal and many other diseases may predispose to intestinal bacterial overgrowth [4], and therefore may vary in different studies and populations. Symptoms of SIBO may be variable, too. Abdominal distention, flatulence and bloating, usually with pain, and diarrhea, often after meals, are probably most characteristic.

Diagnosis is usually confirmed by the assessment of breath hydrogen, lactulose hydrogen or methane, gases that are produced by the excessive gut microbiota in SIBO (human cells do not produce them) and may be detected in exhaled air [5]. Regarding treatment, elimination of underlying disease or diseases may be important, but is only rarely possible. Dietary intervention may be helpful, but most effective is pharmacological treatment with rifaximin, which may improve symptoms in 33% to 92% of patients. The dose as well as time of treatment are, however, not well established. American College of Gastroenterology guidelines [6] suggests a dose of 550 mg t.i.d. (1650 mg daily) which may be more effective than lower doses, especially when treatment time is 14 days or longer. Systemic antibiotics may be also effective, but in general, treatment of SIBO only rarely results in complete eradication of SIBO and durable removal of all symptoms.

Celiac disease is the third important comorbidity of diabetes, limited mainly to autoimmunologic diabetes. Inflammatory reaction to wheat, rye or barley gluten is mediated by α-gliadin, gluten metabolite that crosses intestinal epithelium, and provokes immunologic reaction leading to destruction of enterocytes and villous atrophy. The prevalence of celiac disease in T1D is assessed for 3–8% [7]. In children the disease causes different gastrointestinal signs symptoms, like abdominal pain, diarrhea or vomiting after gluten-containing meals. Chronic exposure to gluten leads to weight loss and malabsorption syndrome and nutritional deficiencies. The latter, like iron, calcium and vitamin deficiencies, are also typical in adults with celiac disease, in whom GI symptoms are less frequent.

Diagnosis of celiac disease is usually made after testing for transglutaminase IgA or anti-endomysial antibodies, although histological assessment of duodenal tissue obtained during endoscopy remains golden diagnostic standard. Complete elimination of gluten from the diet is highly effective in treatment of celiac disease, although occasionally not easy to perform. A proper supply of deficient nutrients may be necessary.

Finally, some antidiabetic drugs may cause gastrointestinal symptoms. They are typical adverse events specifically for metformin and GLP-1 or GLP-1/GIP receptor agonists. The FDA-approved label for metformin [8] states that diarrhea, the most typical GI adverse event may occur in more than 50% treated patients, although only in 6% results in drug discontinuation. In clinical practice, however, metformin intolerance and adverse events seem to be less common. All GI adverse events (diarrhea, nausea, vomiting, flatulence, indigestion and abdominal discomfort) occur much less frequently after extended-release formulation of metformin.

Different GLP-1 receptor agonists have slightly different GI-adverse event profile. Because of delaying gastric emptying and intestinal motility, in some patients dyspepsia, loss of appetite and constipation may happen besides adverse events mentioned with metformin. In general, it seems that the more potent the drug and the higher dose, the more frequent are the GI adverse events, being most frequent in patients who used a dual GLP-1/GIP receptor agonist, tirzepatide [9].

In patients treated with GLP-1 or GLP-1/GIP receptor agonist, it is necessary to start treatment with lower dose, escalating it according to needs up to a maximal dose. If an adverse event occurs, de-escalation to previous dose often resolve the problem. In clinical practice, less than 10% of patients have persistent GI adverse events, and many tolerate them and may remain on drug.

In summary, the paper of Samak et al. published in this issue of "Clinical Diabetology" reminds that often neglected by endocrinologists gastrointestinal adverse events are frequent and may be caused by different diseases. Most frequent and important are diabetic

gastroparesis, SIBO, celiac disease and drug adverse events, but a proper diagnosis shall be made in every case, and proper treatment shall be introduced.

Conflict of interest

The authors declare that there is no conflict of interest.

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