Chapter 18
Diabetes Mellitus and Dyspepsia

Lea Smirčić-Duvnjak

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INTRODUCTION

The term dyspepsia has been widely used by health care professionals to describe different upper gastrointestinal symptoms related to organic disease or presumed to be functional if such causal pathology could not be identified [1]. The lack of clarity in terminology creates a lot of problems in everyday clinical practice as a large proportion of the population complains of symptoms that might be related to dyspepsia. As the prevalence of diabetes mellitus is estimated to be around 246 million people worldwide and is rapidly rising, diabetic patients represent a significant percentage of the affected population [2].

DEFINITION

Diabetes is a severe and life-threatening disease, associated with macrovascular and specific microvascular complications. It carries an increased cardiovascular risk and often leads to blindness, end-stage renal disease, and leg amputation. It is also very closely related to other cardiovascular risk factors such as obesity, hypertension, and dyslipidemia [3]. This picture of multiple vascular risk factors

L. Smirčić-Duvnjak (✉)
Vuk Vrhovac University Clinic for Diabetes,
Endocrinology and Metabolic Diseases, University of Zagreb,
School of Medicine, Dugidol 4a, Zagreb, Croatia
e-mail: lduvnjak@idb.hr

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and wide-ranging complications makes the approach to individual diabetic patient complaining of dyspeptic symptoms very complex. Furthermore, there is still no agreement about the symptoms that should be included in the definition of functional dyspepsia [1, 4]. The most widely used definition is the International Committee of Clinical Investigators revised definition (Rome III criteria) that includes one or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain, and epigastric burning with at least a 3-month history in the last year [1].

It appears that at some point in any diabetic patient's life, the chances of presenting with dyspeptic symptoms are extremely high.

EPIDEMIOLOGY

Literature data reporting on the prevalence of dyspepsia in diabetic patients are limited and conflicting. While some studies have confirmed the increased incidence of gastrointestinal (GI) symptoms in diabetic population compared with the nondiabetic one, others have failed to detect a difference in the prevalence rate of GI symptoms between the two groups [5–9]. The conflicting results can be explained by different populations and ethnic groups studied. In fact, investigations differed in study population comprising patients attending diabetes clinics who were unrepresentative of diabetic population in general or focused on selected subgroups of diabetic patients [6–8]. GI symptoms were also inconsistently defined, and some studies lacked an appropriately defined control group [7]. A large population-based survey has identified increased prevalence of both upper and lower GI symptoms in type 1 and type 2 diabetic patients compared with community controls. The authors have suggested that the effect may be associated with poor glycemic control but not with the duration of diabetes or the type of treatment. The study included a representative population of diabetic patients of all ages and grades of severity [10]. Recently published data documented an increased prevalence of upper GI symptoms in type 2 diabetic patients compared with age- and gender-matched nondiabetic controls, which are also associated with poor glycemic control [11].

CLINICAL PRESENTATION

Diabetes can affect the entire gastrointestinal tract, from the oral cavity to the anorectal region resulting in various symptoms whose severity and specificity depend not only on the composite of dysfunctional elements but also on diabetes itself [4,12].

Approximately 75% of patients referred to diabetes clinics have at least one gastrointestinal symptom. The most common symptoms related to dyspepsia are: heartburn, nausea, early satiety, bloating, and vomiting, while gastroesophageal reflux and gastroparesis represent the most frequent conditions associated with these symptoms [12].

Gastroparesis denotes delayed gastric emptying in the absence of mechanical obstruction of the stomach [1, 4, 12].

In type 1 diabetes, delayed emptying has been identified in 27% to 58% of cases, while in long standing type 2 diabetes, the prevalence rate is about 30% [13, 14]. A meta-analysis has documented delayed gastric emptying in 40% of patients with functional dyspepsia [15].

However, the presentations vary in individual patient and can often be clinically silent [16]. According to literature data, symptoms associated with gastroparesis occur only in 5% to 12% of diabetic patients [10]. It appears that in diabetic patients with delayed gastric emptying, a particular pattern of characteristic symptoms is missing [17].

Although a large spectrum of dyspeptic symptoms is strongly suggestive of slow gastric emptying, a significant correlation between the severity of these symptoms and the rate of gastric emptying has not been documented [17].

In diabetic patients, gastroparesis often develops after at least 10 years of diabetes duration and is typically associated with other microvascular complications – nephropathy, retinopathy, and neuropathy. Apart from suffering from impaired quality of life and glucose control, patients with gastroparesis are at risk of malnutrition, weight loss, and impaired drug absorption [12, 16].

PATHOGENESIS

To maintain a normal process of food digestion, absorption, and elimination, an interaction between the nerve endings embedding the muscle wall, neurotransmitters, hormones, and the muscle fibers is required. The natural history of dyspepsia and its pathogenesis in patients with diabetes remains poorly understood. Several mechanisms have been implicated in its development including autonomic neuropathy, microangiopathy, altered production of insulin and glucagon, increased susceptibility to gastrointestinal infections, and poor glycemic control. Diabetic autonomic neuropathy (DAN), involving the entire autonomic nervous system (ANS), has significant impact on morbidity and mortality in diabetic patients. Gastrointestinal dysfunction represents only one of its numerous

manifestations, including cardiovascular, genitourinary, sudomotor, or ocular complications. The widespread effects of DAN can be explained by ANS vasomotor, visceromotor, and sensory fibers innervating every organ in our body [16]. The pathogenesis of DAN is complex and includes metabolic, vascular, autoimmune, and neurohormonal factors. Hyperglycemia can cause direct neuronal damage activating the polyol pathway with subsequent sorbitol accumulation [18]. Formation of advanced glycosylation end products, reduction in neurotrophic growth factors, and increased oxidative stress have also been implicated in the process. These factors decrease nerve blood flow and damage the vascular endothelium and neurons [19–22]. An involvement of sympathetic and parasympathetic nerve antibodies in the pathogenesis of both types of diabetic patients has also been documented [23, 24]. GI manifestations of DAN have been classified, according to the affected section of the GI tract, into esophageal enteropathy, gastroparesis diabeticorum, diarrhea, constipation, fecal incontinence, gallbladder atony, and enlargement [17]. Besides gastroparesis, esophageal enteropathy can also be associated with dyspeptic symptoms. It includes disordered peristalsis and abnormal lower esophageal sphincter function, results at least in part from vagal neuropathy, and presents as heartburn and dysphagia for solids [17].

In diabetic gastroparesis, disturbances of the nervous system and of muscular and hormonal activities of the digestive system have been recognized [12, 16, 25].

DAN damages the vagus nerve, leads to reduction in the number of intrinsic inhibitory neurons critical for motor coordination and in the number of the interstitial cells of Cajal [26, 27]. Neurohormonal changes in diabetes such as increased glucagon levels retard gastric emptying and reduce the frequency of antral contractions [28].

Delayed gastric emptying can further worsen glycemic control by impairing the delivery of food to the intestines and the relation between glucose absorption and exogenous insulin administration. It can also alter the pharmacokinetics of orally administered hypoglycemic agents [12, 17].

It has to be emphasized that, although GI symptoms are commonly attributed to DAN, they may be caused by other factors as well. Studies have demonstrated an increased prevalence of GI symptoms in diabetic patients without signs of DAN, although in some of them, DAN was diagnosed using cardiovascular reflex test instead of specific test of GI autonomic function [10, 12, 25].

Poor glycemic control may in itself promote GI symptoms. Variations in blood glucose concentrations affect neuromuscular

function throughout the gut and perception of sensations arising from the gut [29–32].

Acute hyperglycemia can affect motor function and cause proximal gastric distension, leading to increased perception of nausea. Slow gastric emptying and reduced lower esophageal sphincter pressure have been described during acute hyperglycemia episodes in diabetic patients [10]. Many studies have confirmed the association of poor glycemic control and GI symptoms by comparing self-reported glycemic profile and the presence of GI symptoms [10]. In type 1 diabetic patients, the sensation of postprandial fullness was associated with blood glucose concentration [29]. Upper dysmotility-like symptoms were significantly more prevalent in individuals with self-reported poor glycemic control than in those reporting good or average glycemic control [10].

A significant correlation between higher glycated hemoglobin levels and the increased rate of GI symptoms has also been documented [16].

Evidently, the association between DAN, glycemic control, and GI symptoms is complex. Whether DAN or poor glycemic control **per se** represent a key player in the pathogenesis of dyspepsia remains unclarified, these factors obviously being interrelated. As they progress with time, it is not possible to determine which factor precedes the other.

Coexisting psychiatric disorders, alcohol intake, use of drugs apart from insulin, and oral hypoglycemic agents such as anticholinergics, antidepressants, and calcium-channel blockers may also contribute to dyspepsia [12, 16, 25].

As the prevalence of the metabolic syndrome in type 2 diabetic patients is increased, abdominal discomfort or pain can also be caused by nonalcoholic fatty liver disease (NAFLD). NAFLD represents a spectrum of several nonalcoholic-related steatotic liver diseases, ranging from benign fatty liver to nonalcoholic steatohepatitis (NASH), associated with cirrhosis and hepatocellular carcinoma. Increased prevalence of obesity, diabetes, hyperlipidemia, and insulin resistance in patients with NAFLD implicates a close link with the metabolic syndrome. The diagnosis can be confirmed with elevated liver enzyme tests, abdominal ultrasonography, and liver biopsy [32].

Dyspeptic symptoms associated with the use of diabetes medications represent a very important issue from the clinical point of view. Metformin and acarbose are often prescribed for type 2 diabetes.

Metformin is widely accepted as a first-line therapy in type 2 diabetes and a very effective insulin sensitizer. It also has some

side-effects, including gastrointestinal symptoms, among which nausea and diarrhea are the most prominent ones. About 10% to 15% of people taking metformin have significant gastrointestinal side effects and are unable to tolerate the drug [1, 4, 12, 25].

Glucagon-like peptide 1 (GLP-1) analogs, the recently introduced agents for type 2 diabetes treatment, have raised considerable interest because of their additional favorable effects [33]. GLP-1 agonists augment insulin secretion from the beta cells and inhibit glucagon secretion, leading to reduced hepatic glucose production, lower fasting glucose, and improved postprandial glucose profile. Binding to certain receptors in the appetite-regulating centers in the hypothalamus and the hindbrain, GLP-1 agonists lead to a decreased appetite and promote weight loss. There is evidence that on a long-term basis, these agents can preserve the beta-cell function [33].

Another important effect refers to the inhibition of gastrointestinal motility and delayed gastric emptying that slow the entry of carbohydrates into the systemic circulation, thus decreasing the rise in postprandial glucose [34–36].

Nausea represents the major side-effect, occurring in 20% to 30% of patients, which can be minimized by starting with lower doses of GLP-1 analogs. The fact that this inhibitory action contributes to dyspeptic symptoms had raised concerns that it could represent a problem in patients with gastroparesis. However, so far, not a single case has been reported [33].

DIAGNOSTIC APPROACH

Data concerning the duration of diabetes, glycemic control, and current diabetic medications should be obtained by careful history taking. Medication history includes the use of other agents, anticholinergic agents, ganglion blockers, and psychotropic drugs associated with dyspeptic symptoms. The presence of other related diabetic complications – retinopathy, nephropathy, and neuropathy should also be evaluated. History of pancreatitis and biliary stone disease should be considered. If celiac disease is suspected, laboratory tests including serum levels of celiac disease, gliadin, endomysial, gluten, and reticulin antibodies should be performed. Based on clinical signs, some of the alternative causes such as pregnancy and uremia can be easily excluded [12, 37, 38].

Physical examination findings might suggest autonomic dysfunction (abnormal pupil responses, abnormal sweating, urinary retention, or impotence) and reveal signs of peripheral neuropathy and epigastric distention. The absence of a splashing sound on

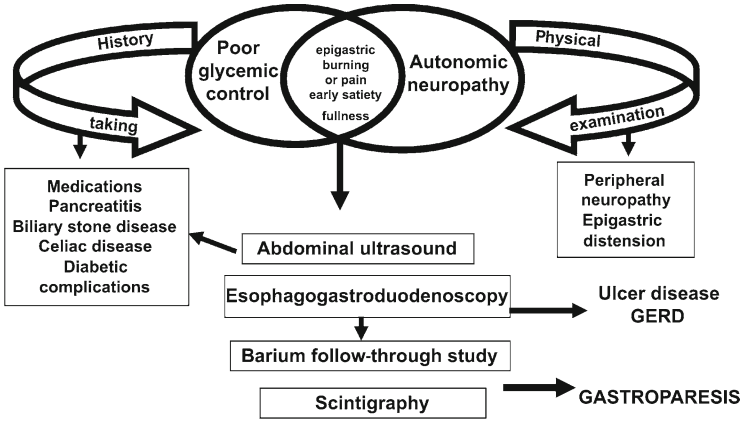

FIG. 18.1 Diagnostic approach to diabetic patients with dyspepsia.

abdominal succussion 1 hour after a meal suggests normal gastric emptying of liquids [17].

While patients complain of unexplained troublesome abdominal symptoms, diagnostic approach usually begins with a hepatobiliary ultrasound. Obstruction of the GI tract should be ruled out by esophagogastroduodenoscopy or a barium follow-through examination.

Endoscopy often reveals reflux esophagitis, ulcers, or food debris in severe gastroparesis. In the majority of patients with delayed gastric emptying, endoscopy findings are normal. To assess disorders of storage, grinding, and propulsion caused by gastric pump failure, it is essential to perform a summative measurement of these functions. Scintigraphy represents the gold standard for measuring gastric emptying. The test is not widely available, requiring special equipment and expertise, and involving exposure to radiation. Other specialized evaluations for the assessment of gastroparesis include manometry to detect antral hypomotility and/or pylorospasm and electrogastrography to detect abnormalities in GI pacemaking (Fig. 18.1) [12, 17, 38].

THERAPEUTIC APPROACH

Because of an incompletely understood and multifactorial pathogenesis, the management of dyspepsia in diabetes is less than optimal. Treatment strategies focus on normalization of glucose regulation and control of symptoms [38]. Dyspeptic symptoms can alter food intake, delivery, and absorption from the

intestines, impairing the effects of antidiabetic drugs and insulin administration. This can result in wide variations in 24-h glucose profile with sudden episodes of postprandial hypoglycemia [12, 17]. Consumption of frequent small meals while avoiding high-fiber and fatty foods, smoking cessation, and light postprandial exercise can improve gastric emptying. While consumption of frequent small meals provides symptomatic relief, during an exacerbation of gastroparesis, a liquid diet is recommended. To achieve an optimal glucose profile, insulin therapy is advisable for the majority of patients with severe symptoms. In those with brittle diabetes, the use of insulin pumps might be necessary [17, 25]. Pharmacological approach includes the use of prokinetic and antiemetic agents [16, 38]. As prokinetic drugs stimulate peristalsis and improve gastric pump function, they may be useful in the treatment of diabetic patients with dyspepsia. Metoclopropamide is a dopaminergic antagonist with antiemetic properties that enhances gastric emptying. Unfortunately, it crosses the blood–brain barrier causing neurological side effects that limit its use. Cisapride is a prokinetic agent that efficaciously facilitates gastric emptying. Due to its potential to cause cardiac dysrhythmias by prolonging QT interval, it was withdrawn from the market [16, 25]. A range of antiemetics might be useful in controlling nausea and vomiting, among them prochlorperazine and promethazine, and 5HT3 receptor antagonists such as ondansetron or dolastetron. If pain relief is required, the agents frequently used in clinical practice are low-dose tricyclics and pregabalin. Tramadol and opiates are not agents of choice because of their inhibiting effect on motility [12, 16, 25, 38]. Novel therapies, including implantable gastric pacemaker, are promising in patients with severe gastroparesis but are still subjects of ongoing investigations [16, 37, 38].

CONCLUSIONS

The global diabetes pandemic is likely to result in a heavy burden of diabetes complications that will pose a significant challenge to healthcare systems in the future.

The frequent association between dyspepsia and diabetes is more than a chance finding. Due to a poorly understood pathogenesis and the lack of a specific pattern of symptoms, many diabetic patients with dyspepsia remain undiagnosed and undertreated. Diagnostic strategies should be directed at excluding other disorders, particularly peptic ulcer and gastroesophageal reflux disease, and medication use. Strong consideration should be given to glucose regulation and ANS evaluation. Treatment strategies focus on the

normalization of blood glucose profile and the control of symptoms. It is important not only to diagnose and treat patients with diabetes and its comorbidities but also to prevent their development by promoting healthy lifestyle. In patients with diabetes and dyspepsia, a multitarget approach based on the assessment of the overall metabolic risk should be applied. Increased understanding of the mechanisms contributing to dyspepsia in diabetes needs to be obtained in future follow-up studies in order to develop a logical, evidence-based treatment strategy.

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