Mechanisms and factors associated with gastrointestinal symptoms in patients with diabetes mellitus

Mônica Loureiro Celino Rodrigues,1 Maria Eugênia Farias Almeida Motta2

Abstract

Objectives: To present the main mechanisms that cause gastrointestinal symptoms in patients with diabetes mellitus, their frequency, and controversies as to their occurrence in children and adolescents.

Sources: Non-systematic review of the literature conducted in the MEDLINE/PubMed and SciELo databases (1983-2011), as well as relevant book chapters. The most relevant and up-to-date articles on the topic were selected.

Summary of the findings: Prevalence of diabetes mellitus has been increasing over the years in many countries. The complications caused by this disease in the digestive system, such as gastrointestinal symptoms (nausea, vomiting, abdominal pain, heartburn, dysphagia, constipation, diarrhea, and fecal incontinence) are well known. The pathogenesis of changes in the gastrointestinal functions in patients with diabetes mellitus is still being investigated at the same time as the role of the enteric nervous system and its neurotransmitters has gained significance. As a consequence of the complications in the digestive system, which damage the enteric nervous system, patients with diabetes mellitus may have specific gastrointestinal motility disorders, some of which may be of great relevance, such as diabetic gastroparesis, constipation, and diarrhea. Gastrointestinal dysfunction increases the morbidity of diabetes mellitus and worsens the quality of life of diabetic individuals.

Conclusions: There are few studies addressing these problems in childhood and adolescence. Diabetes mellitus affects the digestive system over the years. Because this condition worsens the quality of life of diabetic individuals and leads to complications, attention must be paid to gastrointestinal symptoms when treating patients with diabetes mellitus.


Introduction

The term diabetes mellitus (DM) encompasses a group of metabolic diseases of different etiologies characterized by chronic hyperglycemia, with disturbances in the metabolism of carbohydrates, fats and proteins, resulting in defects in insulin secretion and/or action. Chronic hyperglycemia is associated with dysfunction, damage, and failure of several organs, especially eyes, kidneys, nervous system, heart, and blood vessels.1-3

The etiologic classification of DM includes three types: type 1 (T1DM), type 2 (T2DM), and other specific types. T1DM, which has immune-mediated or idiopathic etiology, is caused by the destruction of pancreatic beta cells, leading to an absolute deficiency of insulin. This type of DM accounts for 5-10% of DM cases, and patients with this clinical form of the disease need to use exogenous insulin.3 Its clinical signs are: polyuria, polydipsia, weight loss despite polyphagia,
hyperglycemia, glucosuria, acidosis, ketosis, and in more severe cases, coma.\textsuperscript{1} In children and adolescents, the first manifestation of the disease may be ketoacidosis.\textsuperscript{3} T1DM is considered one of the most prevalent chronic diseases in childhood. Currently, the incidence of T1DM has been increasing, particularly in the pediatric population younger than 5 years old.\textsuperscript{2,4}

The prevalence of DM in the general population, regardless of type, is estimated at 200 million people, 5% of the adult population.\textsuperscript{2} In the Americas, the number of people with DM was estimated at 3.5 million in 2000, and this number is expected to increase to 64 million by 2025.\textsuperscript{5} There is a big difference in the incidence of DM in different regions of the world. It can reach large amplitudes of different incidences, such as 0.1/100,000 per year in China and 45/100,000 a year in Finland, 0.1/100,000 in Venezuela (Caracas) 8/100,000 in Brazil (São Paulo).\textsuperscript{6,7} In one of the centers participating in the Brazilian Study on the Incidence of Insulin-Dependent Diabetes Mellitus, which is part of the Diabetes Mondiale study (DIAMOND Project), there was a mean incidence of 12.7/100,000 in Londrina (PR), which is higher than the 7.6/100,000 in São Paulo (SP) and well above the 1.8/100,000 in Campina Grande (PB).\textsuperscript{8}

The occurrence of DM complications in the digestive system is relatively well-known. These complications appear as gastrointestinal symptoms (nausea, vomiting, abdominal pain, heartburn, dysphagia, constipation, diarrhea, and fecal incontinence). These symptoms are caused by gastrointestinal motility disorders, changes in visceral sensitivity, alteration in the secretion of neurotransmitters, psychological and digestive comorbidities (such as celiac disease), mucosal inflammation, gallstone disease, and hepatic steatosis.\textsuperscript{9-11} The term diabetic gastroenteropathy refers to all gastrointestinal complications observed in patients with DM.\textsuperscript{9-11}

The pathogenesis of the changes in the gastrointestinal functions in DM is still being investigated, at the same time as the role of the enteric nervous system and its neurotransmitters has gained significance. As a consequence of the complications in the digestive canal, which damage in the enteric nervous system (ENS), patients with DM may have specific gastrointestinal motility disorders, some of which may be of great clinical relevance, such as diabetic gastroparesis, constipation, and diarrhea.\textsuperscript{10,12} Thus, diabetic enteropathy reflects widespread autonomic involvement.\textsuperscript{11,13,14}

Currently, it is known that the entire gastrointestinal tract (GIT) is affected by DM, from the mouth to the anorectal region, and dysfunction of this system contributes to the morbidity of this disease and worsens the quality of life of diabetic individuals. Thus, there is need of achieving better understanding of the gastrointestinal symptoms in patients with DM and joining efforts of pediatricians and pediatric endocrinologists and gastroenterologists for the proper management of patients.

**Gastrointestinal symptoms in DM**

Prevalence of gastrointestinal symptoms has been reported to be higher in patients with DM than in the general population. Although there is controversy, these symptoms are not considered important causes of mortality in patients with DM, but they can also have a negative influence on health status and quality of life.\textsuperscript{10,15,16}

Most studies have shown a variety of gastrointestinal symptoms in patients with DM, although many of these patients, particularly those with the T1DM, may present without gastrointestinal symptoms. The fact that there are few studies involving children and adolescents with T1DM is relevant, and, among patients with T2DM, the results are controversial.\textsuperscript{17-19} Among the symptoms most commonly found in DM patients, nausea, abdominal pain, vomiting, early satiety, bloating, dysphagia, regurgitation, heartburn, epigastric/abdominal pain, abdominal distension, constipation, diarrhea, and fecal incontinence.\textsuperscript{10,18,20-22}

In a study of frequency of gastrointestinal symptoms in outpatients with T2DM, the authors found that 76% had at least one clinical manifestation, and constipation was the most frequent complication (60% of cases).\textsuperscript{23} Another study found that 68% of patients with T1DM and T2DM reported at least one symptom, but the prevalence of constipation was low, only 16%.\textsuperscript{24} Symptoms of dyspepsia were reported in 7.2% of children and adolescents with T1DM and esophagitis and gastroduodenitis, but intestinal motility was not investigated.\textsuperscript{25}

A low prevalence of gastrointestinal symptoms has been observed in subjects with T1DM and T2DM.\textsuperscript{26} Abdominal pain (18%) and constipation (21%) were the most frequent symptoms, but this prevalence was also low in the control group.\textsuperscript{26} In another group of patients with T1DM and T2DM, the following gastrointestinal symptoms have been found: postprandial fullness (30.6%), pyrosis (30%), abdominal pain (19.6%), abdominal distension (18.9%), nausea (18.3%), constipation (16.9%), epigastric pain (15.6%), dysphagia (13%), vomiting (7.2%), diarrhea (7.2%), and fecal incontinence (4.5%).\textsuperscript{26} There was no significant difference between pyrosis and fecal incontinence in patients with T1DM and T2DM.\textsuperscript{10}

Children and adolescents with T1DM showed a higher frequency of gastrointestinal symptoms than the control group, with statistical difference (44.9% vs. 36%, respectively; p < 0.05).\textsuperscript{27}

A study conducted with patients with T1DM and T2DM followed up at outpatient clinics and in the community with the purpose of determining whether there was a relationship between gastrointestinal symptoms and glycemic control, as well as between gastrointestinal
symptoms and DM complications has suggested that 57% of patients reported at least one DM complication. These complications were associated with seven out of the eight groups of gastrointestinal symptoms. The authors concluded that gastrointestinal symptoms may be associated with DM complications of both types, particularly diabetic autonomic neuropathy and inadequate glycemic control.

Another study has demonstrated that 43% of patients with T2DM had symptoms of the upper GIT vs. 31% of subjects in the control group. Regarding lower GIT symptoms in the group with T2DM, 58% showed symptoms vs. 55% in the control group. This difference between the two groups was significant only for upper GIT symptoms. Factors of T2DM associated with gastrointestinal symptoms have also been investigated. Glycosylated hemoglobin (HbA1c) level was the only independent risk factor for upper GIT symptoms.

Based on the results of these studies, it is possible to conclude that there is a relationship between gastrointestinal symptoms and DM. However, there are a few studies investigating T1DM, and the results are controversial. Despite the evidence, the actual prevalence of gastrointestinal symptoms in patients with DM, particularly those with T1DM, has not been determined because the studies have shown different results. In addition, studies conducted in the general population with different groups of patients without DM have shown a high prevalence of gastrointestinal symptoms, suggesting a causal relationship for the occurrence of gastrointestinal symptoms in patients with DM.

However, due to the worldwide increase in the incidence and prevalence of T1DM and T2DM, special attention should be given to the presence of gastrointestinal symptoms in the population with DM, considering them as an indication of DM complication. These symptoms should also be used to understand the mechanisms that enable their occurrence because of their influence on the quality of life of these patients. Special attention should also be given to individuals with T1DM affected early in life and who will have to deal with the disease for a long period of time.

**Gastrointestinal symptoms in DM: how do they occur?**

Despite the controversy about the conditions that lead to the appearance of gastrointestinal symptoms in patients with DM, many factors have been implicated in the pathogenesis and causal relationship (Figure 1). We will discuss these factors below.

**Autoimmunity, inflammation and DM**

T1DM is caused by immune-mediated destruction of pancreatic beta cells. During this autoimmune process, the cells of the neuromuscular apparatus of the GIT may be damaged, particularly neurons. Currently, there is much interest in the role of autoimmune processes in the pathogenesis of neuromuscular disorders of the GIT. And some studies have suggested that autoantibodies can play a key role in other (paraneoplastic and idiopathic) motility changes, in spite of little evidence regarding the autoimmune pathogenesis of diabetic gastroparesis.

Studies have described lymphocyte infiltration into the myenteric region of the esophagus in patients with T1DM and T2DM, as well as infiltration of lymphocytes, macrophages, and plasma cells into the lymph nodes of nerve bundles of the autonomic nervous system of patients with prolonged disease, complicated with diarrhea and gastroparesis. However, inflammatory infiltrates or other infiltrating cells have not been found in specimens from the stomach of patients with difficult to treat severe diabetic gastroparesis.

Reports that prostaglandins are involved in mediating abnormal gastric electrical rhythm during hyperglycemia and that administration of indomethacin can prevent tachygastria in healthy subjects have suggested the probable inflammatory cause of motor alterations in the GIT associated with DM in general. This finding is reinforced by other studies that have demonstrated inflammation associated with neurodegeneration, which can lead to secondary alterations in motility. Other studies have revealed high serum concentration of interleukin 6 in patients with T1DM compared with a control group of 38 healthy individuals.

In addition, circulating complement-fixing antibodies directed against autonomic nerves are frequent findings in T1DM and rare in T2DM, which is usually considered a metabolic rather than an autoimmune disease. Because of the lack of follow-up studies, the meaning of these findings remains poorly understood, although it suggests the involvement of the inflammatory process in the origin of the gastrointestinal symptoms.

Autoantibodies directed against the calcium channels of the smooth muscle of the colon have been detected in patients with T1DM but not in controls, which leads to change in motility (impaired smooth muscle contraction) and, consequently, gastrointestinal symptoms, especially abdominal distension and sensation of postprandial fullness.

The presence of antibodies directed against gastric parietal cells is found in 15-21% of patients with T1DM. Compared with non-diabetic individuals, this percentage tends to fall to 2-10%. Another analysis has demonstrated that 20 to 40% of patients with antibodies directed against gastric parietal cells have T1DM. The positivity of these antibodies is found in the beginning of both types of DM, particularly in patients who have positive antithyroid peroxidase.
antibodies (antiTPO). Inhibition of autoantigen expression (H/K ATPase) by these antibodies results in hypochlorhydria or achlorhydria, which leads to high incidence of atrophic gastritis because of autoimmune damage to the mucosa. A small number of patients with T1DM (2.5 to 4%) have intrinsic antifactor antibodies, causing pernicious anemia.17 All these findings may suggest the autoimmune nature of the pathogenesis of the gastrointestinal symptoms in DMT1. It seems reasonable to assume that autoimmune and inflammatory processes are somehow related to the genesis of T1DM and, consequently, to the gastrointestinal symptoms in patients with this disease.

**How does hyperglycemia cause gastrointestinal symptoms in DM?**

Hyperglycemia is a condition linked to DM. The concept of the disease demonstrates this association in a specific manner.3,4,41 It is responsible for many complications, both in T1DM and T2DM, including diabetic neuropathy and involvement of the GIT. Digestive tract dysfunction in DM is secondary to inadequate glycemic control and consequent diabetic autonomic neuropathy, which has great influence on the sensory and motor functions of the digestive tract from the stomach to its terminal portion.12 Diabetic angiopathy and vascular complications are also secondary to chronic hyperglycemia and are related to the pathogenesis of intestinal ischemia and impaired nerve and muscle function in diabetic gastroenteropathy.14,42

The hypothesis that inadequate glycemic control is the major cause of gastrointestinal symptoms has been raised in some studies.17,43,44 It has been proved by associations between acute changes in glucose levels and motility.12,31,43 Acute variations in serum glucose, even within the limits of standard rates, may have great influence on the sensory and motor function of the digestive tract.17,42 Lack of glycemic control affects gastric motility, and delayed gastric emptying makes it difficult to control glucose levels, leading to gastrointestinal symptoms (early satiety, postprandial fullness, epigastric pain, nausea, and vomiting) in a vicious cycle process.17,35,42,25-48 Glycemic imbalance associates immediate postprandial hypoglycemia with hyperglycemia long after meals due
to delayed absorption of the bolus, a consequence of delayed gastric emptying.\textsuperscript{35,49} Moreover, it can result in desynchronization after administration of insulin and emptying of nutrients from the stomach into the small intestine.\textsuperscript{35,49} In patients with T1DM and gastroparesis, normal glucose level is maintained with less insulin, unlike those with normal gastric emptying.\textsuperscript{17} A study evaluating delayed gastric emptying caused by hyperglycemia as a physiological response to minimized postprandial hyperglycemia concluded that, in patients with T1DM, this defense mechanism is impaired and contributes to high rates of glucose derived from meals.\textsuperscript{50}

Hyperglycemia relaxes the gastric fundus, causing retrograde pyloric flow, with consequent stagnation of bolus and impaired absorption, contributing to symptoms in the high GIT and glycemic control difficulties.\textsuperscript{35,49} It also activates oxidative stress pathways (imbalance between pro- and antioxidant systems), which causes apoptosis of enteric neurons and changes in their chemical code, resulting in motility changes.\textsuperscript{12} A study has shown that increased oxidative stress in the stomach and liver in laboratory animals was influenced by DM duration and increased glycemia.\textsuperscript{1} The increased sensitivity of the colonic tissue to oxidative stress may be due to the reduction in the antioxidants that occurs in the colon of patients with any type of DM and it is related to high concentrations of HbA1c and prolonged duration of DM. Antioxidants, such as lipoic acid, reverse this effect.\textsuperscript{12}

Although some studies have concluded that diabetic autonomic neuropathy is not an etiological factor for gastrointestinal symptoms in children and adolescents,\textsuperscript{31} other studies have reported that diabetic autonomic neuropathy, when involving the ENS, plays a significant role in the pathogenesis of the GIT of patients with any type of DM. Structural and functional changes in the enteric neurons, such as: a) degeneration and decreased number and size of neurons; b) significant decrease in the colonic lymph nodes; c) loss of inhibitory neurons; d) activation of oxidative stress pathways; e) remodeling of the neurons in the ENS; f) decrease and selective loss of subtypes of inhibitory neurons that synthesize antioxidant substances (nitric oxide and neuropeptide Y); and g) reduction of neuronal markers and antioxidants in the colons of patients with DM, are caused by hyperglycemia and explain the gastrointestinal changes.\textsuperscript{12,37,51}

**Motility and changes in cellular components of GIT tissues: role in the gastrointestinal symptoms of patients with DM**

Approximately 75\% of diabetic patients with any type of DM experience dysfunctions, probably as a result of motility alteration.\textsuperscript{12,35} The prevalence of symptoms related to the upper GIT, such as nausea and early satiety, is higher in both types of DM patients with impaired glycemic control and motor dysfunctions. This reinforces the concept that the effects of glucose concentration in the perception of the upper GIT stimuli are clinically important.\textsuperscript{35,42,49}

Changes in the GIT motility manifested by delayed gastric emptying in patients with long-term T1DM and T2DM are usually associated with gastroparesis, a consequence of diabetic autonomic neuropathy.\textsuperscript{20,52} Weak contractions of the antral phase, increasing the diameter of the postprandial gastric antrum, weak fundic contractions, pyloric spasms, and slow arrhythmic waves are some of the findings demonstrating these changes and associated with symptoms in the upper GIT.\textsuperscript{20,52}

Studies have shown that individuals with any type of DM have several abnormalities of gastric motility: there is meal-induced impaired gastric fundus relaxation, there may be arrhythmic slow waves, such as bradycardia and tachygastria, flattened pattern waves, absence of postprandial increase in the forces of slow waves, reduced amplitude and frequency of antral contractions, reduced amplitude of fundic contractions, absence of antral interdigestive migrating motor complex, among others.\textsuperscript{14,17,49,53} Impaired relaxation of gastric fundus also leads to inhibited frequency of propagation of antral contractions, promotion of retrograde pyloric flow, with consequent stagnation of the bolus and impaired absorption, contributing to gastrointestinal symptoms and the formation of bezoar (unabsorbed food) that occurs in DM.\textsuperscript{14,17,49} Another mechanism through which hyperglycemia affects gastric motility is reduced secretion and, consequently, decreased serum concentration of motility regulatory peptides, such as motilin.\textsuperscript{31}

Although it has been little investigated in terms of esophageal motility, some patients with T1DM and T2DM have abnormalities of the esophageal sphincter and increased prevalence of symptoms of gastroesophageal reflux disease over time.\textsuperscript{11,14,42}

Interstitial cells of Cajal (ICC), together with innervation and smooth muscles, play an important role in the regulation of motility. Such circular muscle cells retransmit information from enteric neurons to smooth muscle cells, whereas in the myenteric plexus, circular muscle cells generate rhythmic electrical depolarization (slow waves), which control the frequency and duration of muscle contractions. Histopathological studies of gastric specimens in patients with T1DM revealed: a) depletion of ICC in the myenteric plexus and smooth muscles and b) loss of neurons and reduced staining of various neurotransmitters and markers of ICC, resulting in impaired function of gastric motility.\textsuperscript{20} It is possible that similar changes are present in other portions of the GIT, causing symptoms. ICC depletion has been demonstrated both in patients with DM and in laboratory animal models. In a well-designed mice model with human T1DM, there was constipation 6-8 weeks after the onset of DM, and ICC
depletion extended from distal GIT to the gastric body.\textsuperscript{35} Dysfunction was evidenced with delayed gastric emptying for solids, and electrical arrhythmia also occurred.\textsuperscript{35}

ICC depletion is more often focal than diffuse and both can be detected in the myenteric region or within the muscle layers of the GIT. Lesions may lead to very severe clinical forms of dysmotility.\textsuperscript{54,55}

In the distal colon, the loss of ICC is associated with loss of excitatory and inhibitory neuromuscular transmission. However, paradoxically in the proximal colon, the authors detected phases of activity and hyperexcitability, which were interpreted as compensatory changes developed in response to distal hypomotility that occurs as a response to severe constipation in patients with T1DM and T2DM.\textsuperscript{35}

Therefore, studies have strongly demonstrated that the loss of ICC is common in long-term T1DM and T2DM with inadequate glycemic control, and that this loss does not occur in isolation, but combined with dystrophy of intrinsic and extrinsic nerves of the smooth muscle.\textsuperscript{35} Intensive changes in the cellular content of GIT tissues of patients with T1DM and T2DM are preceded by subtle abnormalities that can only be detected at the molecular level.\textsuperscript{35} These early abnormalities, combined with other factors, such as infections, stress, acute hyperglycemia and psychogenic factors, can lead to severe clinical forms of dysmotility.\textsuperscript{35}

Colonic motility disorders in T1DM and T2DM are manifested by diarrhea or constipation. Information available on electrical activity and colonic motility is still limited. Changes in motility in the colon have not been fully understood so far, but they lead to delayed intestinal transit, impaired gastrocolic reflex, abnormalities of the internal anal sphincter tone, impaired rectal sensation and compliance, and delayed postprandial colonic motility.\textsuperscript{14,17,35} These changes may be attributed to the loss of nitrergic innervation (motor neurons of the CNS circular muscles, which are sensitive to the action of nitric oxide – an inhibitory neurotransmitter) of the gastric fundus, which impairs receptive relaxation and accommodation reflexes.\textsuperscript{14}

Sensory changes and gastrointestinal symptoms in DM

Some studies have shown that changes in sensitivity are present in the esophagus, stomach, small intestine, and colons in the presence of marked hyperglycemia both in healthy subjects and patients with T1DM and T2DM, and it is likely that this represents a relationship with increased visceral sensation.\textsuperscript{14,42}

Many patients with any type of DM have symptoms of gastropathy without associated delayed gastric emptying and without evidence of autonomic neuropathy. The symptoms of this group of patients did not distinguish them from those with delayed gastric emptying and can be attributed to the loss of nitric innervation (motor neurons of the CNS circular muscles, which are sensitive to the action of nitric oxide – an inhibitory neurotransmitter) of the gastric fundus, which impairs receptive relaxation and accommodation reflexes.\textsuperscript{14}

Healthy patients undergoing severe hyperglycemia have showed increased awareness of sensations that arise in the upper GIT, such as nausea and bloating during proximal gastric distension at fasting and during slow duodenal lipid infusion.\textsuperscript{56,57} Both healthy subjects and those with T1DM can also have changes in the rectal distension perception (increased or decreased) in the presence of hyperglycemia.\textsuperscript{56,57}
Fecal incontinence is relatively common in patients with T1DM and T2DM. Its severity is related to the duration of DM and the onset of angiopathy and neuropathy. Most patients with T1DM and T2DM and fecal incontinence have multiple abnormalities of anorectal sensory and motor functions, which are not found in continent patients with DM. Patients with any type of DM with fecal incontinence have decreased resting anal pressure and compression pressure, decreased perception of rectal distension, increased threshold for the reflection of the external anal sphincter, and impaired anal cutaneous reflex. Abnormal rectal sensation in these patients is assumed to be a manifestation of sensory neuropathy secondary to hyperglycemia, and it is not found in patients with fecal incontinence related to other disorders. The instability of the external anal sphincter in some patients with T1DM and T2DM is one of the major causes of fecal incontinence.

Functional gastrointestinal changes and medications for DM

Controversial data regarding the frequency of gastrointestinal symptoms in both types of diabetic patients may be linked not only to the pathophysiological changes in the GIT, but also to the occurrence of functional disorders such as irritable bowel syndrome and functional dyspepsia. In addition, other studies in patients with T1DM and T2DM have found that symptoms suggestive of upper GIT diseases, as well as changes in bowel habits, were more significantly associated with psycho-emotional disorders than with the presence of peripheral neuropathy. The presence of a chronic disease may be an important factor in the production of psychosomatic gastrointestinal symptoms unrelated to organic impairment of the GIT.

The medications recommended for the treatment of patients with T2DM, who do not achieve glycemic control after 4 to 6 weeks of diet and exercise, contribute to gastrointestinal symptoms in these patients. The main drugs used to treat these patients are metformin (group of biguanides) and sulfonylureas. The most frequent symptoms caused by these medications are diarrhea and vomiting, which lead to poorer quality of life with T2DM and may result in lack of compliance to treatment.

The greater predisposition of patients with T1DM and T2DM to infections and stress, in addition to the above mentioned conditions, are situations that, when associated with different pathophysiological mechanisms responsible for the onset of gastrointestinal symptoms, contribute to the emergence and worsening of these symptoms.

Final comments

The presence of gastrointestinal symptoms in both types of DM is mentioned in several medical publications. Because DM is a disease that worsens the quality of life of patients and may lead to complications, it should receive special attention during follow-up and treatment.

There are few studies addressing this problem in childhood and adolescence, and their results are controversial. We believe that gastrointestinal symptoms should be thoroughly investigated for early detection, considering therapeutic measures aimed at improving the quality of life and prognosis in the medium and long term.

References


