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PRACTICAL APPROACH

A Practical Approach to Gastrointestinal Complications of Diabetes

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ABSTRACT

Gastrointestinal symptoms occur frequently among people with diabetes mellitus and are associated with considerable morbidity. Enteropathy, or large bowel dysfunction, includes constipation, diarrhea and fecal incontinence, and is particularly disturbing for many patients. The pathogenesis of diabetic enteropathy is complex, primarily related to gastrointestinal autonomic dysfunction and etiologically associated with chronic hyperglycemia and diabetes duration. Since there are many other non-iatrogenic and iatrogenic causes of the cardinal symptoms of large bowel dysfunction, patients suspected of having diabetic enteropathy require detailed evaluation. The management of patients with diabetic enteropathy is challenging, and often requires a multidisciplinary approach focusing on a combination of symptom mitigation and glycemic control.

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INTRODUCTION

The gastrointestinal (GI) complications of diabetes have become increasingly prevalent as the rate of diabetes has increased [1]. The GI tract manifestations of diabetes include gastroparesis and enteropathy, and their symptoms are classically caused by abnormal GI motility, which is a consequence of diabetic autonomic neuropathy involving the GI tract [2]. Up to 75% of people with diabetes may experience GI symptoms, leading to both a significant decrement in patient quality of life and an increase in health care costs. The classic GI symptoms of diabetes include post-prandial fullness with nausea, bloating, abdominal pain, diarrhea, and/or constipation [1].

Gastroparesis is a well-recognized GI manifestation of diabetes and is more common in women. Delayed gastric emptying has been demonstrated in between 27% and 65% of patients with type 1 diabetes mellitus

(T1DM) and in up to 30% of patients with type 2 diabetes mellitus (T2DM) [3, 4]. Of note, obesity appears to independently predict symptoms of gastroparesis patients with T2DM with comorbid sensory motor neuropathy [5].

There are multiple clinical features which may be attributable to gastroparesis, includeing nausea and vomiting as well as early satiety, often combined with bloating and upper abdominal pain. Deteriorating glycemic control coupled with increased glucose variability consequent upon mismatched insulin action and nutrient absorption may also suggest underlying gastroparesis. Up to 53% of patients may experience weight loss, while as many as 24% of patients may actually gain weight [4]. Symptom presentation can be either acute or insidious, with a third of cases having chronic symptoms with periodic exacerbations, while a further third will experience chronic progressive symptoms [4].

The diagnosis of gastroparesis is typically one of exclusion, when other potential causes of presenting symptoms have been evaluated and postprandial gastric stasis is confirmed [6]. Whenever possible, patients should discontinue medications that exacerbate gastric dysmotility, in particular glucagon-like peptide-1 (GLP-1)-receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and metformin. Other simple therapeutic approaches include improving blood glucose control, increasing dietary liquid content, consuming smaller meals, and discontinuing the use of tobacco and alcohol. Qualitative dietary changes should also be made, namely, reducing the intake of insoluble dietary fiber, foods high in fat, and alcohol. Prokinetic agents (e.g., metoclopramide, erythromycin) may also be helpful in managing the symptoms of gastroparesis [6].

Enteropathy is a less well-recognized GI manifestation of diabetes and can be considered to be symptoms that affect the large bowel. Clinical presentation includes diarrhea, constipation, and fecal incontinence, which can often be nocturnal [1], while overt steatorrhea has been reported in a minority of patients [7]. The nature of the symptoms associated with diabetic enteropathy can by definition be both distressing and often multifaceted. Furthermore, many commonly used drugs in diabetes, such as metformin, statins, and the incretin-based therapies [7–9], are associated with intestinal side effects, which may confuse the issue with respect to identifying and managing diabetic enteropathy.

Based on such considerations, this article focuses on the pathophysiology, clinical presentation, epidemiology, and management of diabetic enteropathy, aiming to provide a practical approach to this often under-recognized and challenging complication of diabetes.

PATHOPHYSIOLOGY

GI autonomic nerve dysfunction is the key pathological factor with respect to enteropathy in people with diabetes, including abnormalities of motor function and visceral hypersensitivity [10]. Additional factors thought to play a role in the pathogenesis of diabetic enteropathy include altered GI hormone secretion and a proinflammatory diathesis combined with a genetic predisposition [10]. All these are enhanced in the presence of acute or chronic hyperglycemia, the latter exerting a particularly noxious effect on the interstitial Cajal cells, ultimately leading to impaired intestinal motility.

While enteropathy can affect people with T1DM and T2DM, it occurs more commonly in people with T1DM [11]. There does not, however, appear to be any differential mechanism, with the relatively higher risk in T1DM being potentially attributable to the longer duration of hyperglycemia, which, in turn, aggravates intestinal motility.

In both T1DM and T2DM, insulin-growth factor I (IGF-I) are reduced, which may result in smooth muscle atrophy, contributing to impaired GI function [10]. Diabetes duration and the level of glucose control are both factors that are related to reduced IGF-1 expression in diabetes, and this process may partly explain the epidemiological associations between diabetes duration and glycemic control with diabetic enteropathy.

Other candidate mechanisms involved in the pathogenesis of enteropathy in diabetes include an impaired synthesis of neuronal nitric oxide, which is an important neurotransmitter within the bowel. Enhanced oxidative stress, an autoimmune diathesis, and imbalance between inhibitory and excitatory enteric neuropeptide ratios have also been implicated as potential contributory factors [10].

The diarrhea of diabetic enteropathy reflects perturbations in small bowel motility and is often associated with bacterial overgrowth [10]. Hyperglycemia and in particular glucose variability may influence sphincter function. Indeed, acute hyperglycemia inhibits external anal sphincter function and decreases rectal compliance, potentially leading to fecal incontinence [12]. Furthermore, depression rather than glycemic control may also be linked with the development of GI symptoms in diabetes, suggesting that emotional status may be a factor, which many clinicians may under-recognize, in the development of diabetic enteropathy [10].

EPIDEMIOLOGY, CLINICAL PRESENTATION, AND DIAGNOSIS

Epidemiology and Clinical Presentation

Constipation is a common presentation of diabetic enteropathy, affecting up to 60% of people with long-standing diabetes [13]. Complications arising from severe constipation such as perforation and overflow diarrhea are, however, relatively rare. Based on studies with radio-opaque markers, there is evidence for a generalized slowing in transit constipation in the diabetic population [14]. However, there does not appear to be a difference between subjects with and without autonomic neuropathy [15].

Diarrhea is an important and often debilitating feature of diabetic enteropathy occurring in up to 20% of patients [16]. It may happen at any time of the day, but it is typically nocturnal. Characteristically, it is seen in patients with poorly controlled diabetes with co-existing peripheral and autonomic neuropathy.

Fecal incontinence, particularly nocturnal, related to internal and external sphincter dysfunction is a particularly troublesome symptom. Acute hyperglycemia and glucose excursions have been shown to inhibit rectal sphincter function, decreasing rectal compliance and thus leading to fecal incontinence [12, 17].

Enteropathic symptoms, in particular diarrhea and constipation, occur with many commonly used drugs in diabetes. Metformin is the most commonly recognized drug in terms of GI side effects, including abdominal discomfort, bloating, nausea, anorexia, diarrhea, and constipation. Up to 10% of people receiving metformin have been reported to experience one or more of these

symptoms [7]; however, the incidence and severity of such symptoms may be reduced by slow dose titration, while dose reduction may also be required in some individuals to mitigate such symptoms and ensure therapy persistence.

Other blood-glucose-lowering therapies with a mechanism of action involving the modulation of intestinal physiology, such as the incretin-based therapies and the alpha-glucosidase inhibitors [17], are associated with a variety of GI side effects, with altered bowel function (either diarrhea or constipation) occurring in up to 20% of people receiving GLP-1 receptor agonist therapy and in 1–10% of people taking DPP-4 inhibitor therapy [9].

GI side effects also occur in up to 5% of people receiving statins, while fibrate therapy may also be associated with GI adverse events, including diarrhea and constipation in as many as 10% of patients [18].

Due to the often debilitating nature of the symptoms of diabetic enteropathy, patients can often experience social isolation, relationship difficulties, and employment and work problems. Consequently, many patients—particularly those with severe symptoms—may become depressed and require psychological support.

Investigation and Diagnosis

Given the high prevalence of enteropathic symptoms, particularly in relation to many drugs frequently prescribed for diabetes, prior to embarking on any investigations [19] (see Table 1) or making a presumptive diagnosis of diabetic enteropathy, attention should be focused on potential treatment changes. These may include discontinuing, reducing the dose of metformin, or switching to the modified release preparation, which has been suggested to induce fewer GI side effects [7]. The GLP-1 receptor agonists are commonly associated with GI side effects, and switching between agents within a class, reducing dose, or discontinuing therapy are all potential considerations. Furthermore, a trial in which any other medications typically associated with GI adverse effects are discontinued should also be adopted. In addition, some diabetic foods may exert a laxative effect, and as such should also be discontinued in the setting of persistent diarrhea.

In the presence of persisting symptoms, despite appropriate therapeutic modifications as outlined above, investigations such as endoscopy, stool culture, and computed tomography should be initiated to exclude other causes (see Table 1).

Pancreatic exocrine insufficiency also needs to be excluded as a potential cause of enteropathy in diabetes. This is particularly pertinent since pancreatitis occurs 2–4 times more commonly in people with diabetes than in the nondiabetic population [20]. Risk factors for pancreatitis tend to cluster in diabetes, including an increase in gall stone disease consequent upon gall bladder dysmotility [21], obesity, and the use of many medications such as angiotensin-converting enzyme inhibitors and diuretics that are associated with an increase in the risk of pancreatitis [22]. Based on such considerations, measurement of fecal elastase should be one of the initial investigations conducted when evaluating a patient with potential diabetic enteropathy (see Table 1).

Other causes of diarrhea also need to be excluded, e.g., infectious diarrhea, celiac disease, bile salt diarrhea, and the concomitant use of drugs that may cause

Table 1 Diagnostic approach to diabetic enteropathy

Differential diagnosis	Features and diagnostic approach
Bacterial overgrowth in the small bowel	Response to antibiotics
Celiac sprue	Flat biopsy of the small bowel
	Improved biopsy findings after GFD
	Clinical response to GFD
Bile acid catharsis	Increase in stool bile acids
	Response to cholestyramine
Anorectal dysfunction	Resting pressure or abnormal rectal sensation on anorectal manometry[a]
	Fecal incontinence
Intestinal motility or secretory disorder	Abnormal results on GI manometry or transit study
	Response to opioids or clonidine
Lactose intolerance	Abnormal results of lactose-hydrogen breath test
	Response to lactose-free diet
Iatrogenic	Intake of medication known to cause diarrhea
	Response to withdrawal

GFD gluten-free diet, *GI* gastrointestinal

[a] Anorectal manometry is a test performed to evaluate patients with constipation or fecal incontinence. This test measures anal sphincter muscle pressure, the sensation in the rectum, and the neural reflexes that are needed for normal bowel movements

diarrhea such as metformin, GLP-1 receptor agonists, DPP-4 inhibitors, proton pump inhibitors, and statins (see Table 2).

Investigating colonic transit time may be useful in terms of confirming a diagnosis of enteropathy, using noninvasive radio-opaque marker methods. The demonstration of reduced anal sphincter tone, by barostat or manometry, may also be useful with respect to confirming a diagnosis of enteropathy [12, 13].

Patient questionnaires, such as the Diabetes Bowel Symptom Questionnaire (DBSQ), provide a specific measure of GI symptoms and glycemic control in patients with diabetes [23] and as such may be useful in quantifying the impact on quality of life or the enteropathic symptoms in people with diabetes.

Management of Diabetic Enteropathy

The management of enteropathy in diabetes represents a considerable challenge and is generally suboptimal, thus undoubtedly prevention is better than cure. The fundamental objectives of managing diabetic enteropathy revolve around symptom relief and glycemic control.

It is important to assess patients' nutritional status, especially in cases of combined gastroparesis and diarrhea. The recognition of dehydration, weight loss, and electrolyte imbalance is particularly important and may necessitate acute hospitalization and enteral feeding, particularly in patients with >5% weight loss in 3 months.

Table 2 Potential management algorithm for patients presenting with suspected enteropathy

1. Patient presenting with suspected enteropathy
2. Clinical evaluation (e.g., type and nature of symptoms, acute/chronic/duration, presence of other GI symptoms, presence of other neuropathic symptoms/signs)
3. Investigate to exclude alternative causes (e.g., other bowel pathology, pancreatic insufficiency, functional infection)
4. Diagnosis of diabetic enteropathy confirmed
5. Initiate stepwise therapeutic strategy:
Step 1: Ensure adequate hydration and commence antidiarrheal agents (e.g., loperamide, codeine)
Step 2: Improve metabolic control.
Step 3: If symptoms persist despite implementing steps 1 and 2, therapeutic trial of antibiotic therapy (e.g., rifaximin)
Step 4: If symptoms persist despite implementing steps 1, 2, and 3, add somatostatin analogue (e.g., octreotide/lanreotide). Be aware these agents may influence blood glucose levels
Step 5: If pain is a major feature, then amitriptyline or pregabalin may provide benefit

Nutritional counseling with specialist dietetic input is an important component of the management of diabetic enteropathy, with dietary manipulation (low fat/fiber, small-portion meals) often providing symptomatic benefit [10].

Bacterial overgrowth is found in up to 40% of diabetic patients with diarrhea [11]. Consequently, the treatment of enteropathic symptoms should include intermittent and even potentially long-term administration of selective antibiotics. Rifaximin is the most extensively studied agent in this context, improving symptoms in between 33% and 92% of patients while eradicating bacterial overgrowth in up to 80% of patients [11].

Symptomatic benefit may also be achieved with the use of opioid-based agents and, in the event of severe refractory diarrhea, somatostatin analogues may be useful [24], while loperamide may provide benefit in the management of fecal incontinence. In terms of somatostatin analogue therapy, octreotide and lanreotide are useful in a variety of diarrhea states, while there is a suggestion that the longer half-life of lanreotide may result in greater symptomatic benefit [25].

Management of constipation revolves around the use of traditional laxatives, and is still primarily aimed at symptom relief. In patients where abdominal pain is the main symptomatic manifestation of enteropathy, medications such as tricyclic and tetracyclic antidepressants, gabapentin, and pregabalin can be used with varying degrees of benefit [26].

Improving overall glucose control and, in particular, limiting glucose variability are important considerations in the management of patients exhibiting diabetic enteropathy, particularly in those in whom diarrhea is the main symptomatic manifestation. The use of multiple daily dosing insulin regimens, insulin pump therapy, and continuous glucose monitoring may be considered as therapeutic options in such cases.

SUMMARY

Enteropathy or large bowel dysfunction represents a major morbidity for many people

with diabetes and can go unrecognized for a long time. Thus, a high index of suspicion is required in the case of persistent GI symptoms, especially in patients with long-standing diabetes and other chronic microvascular complications, particularly neuropathy. Diagnosis requires careful clinical evaluation and exclusion of other potential causes, both iatrogenic and non-iatrogenic. The management of enteropathy remains challenging, revolving around symptom mitigation and optimization of glucose control.

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