



DAVID L. LONGWORTH, MD, EDITOR  
 JAMES K. STOLLER, MD, EDITOR

WIAM I. HUSSEIN, MD

Dr. Hussein is a senior endocrinology fellow at the Cleveland Clinic, with research interests in quality of diabetes care and in hypothyroidism.

S. SETHU K. REDDY, MD

Dr. Reddy is a staff physician in the Department of Endocrinology at the Cleveland Clinic, and has research interests in diabetes and its complications.

# Chronic diarrhea in a 57-year-old woman with diabetes

**A** 57-year-old woman with a 20-year history of diabetes and poorly controlled blood glucose levels despite a twice-a-day regimen of NPH and regular insulin has had diarrhea of 3 months' duration. The diarrhea is episodic (lasting days to weeks) and usually occurs at night. The stool is watery, but never bloody, mucousy, or greasy. Between episodes, the patient has normal bowel habits or mild constipation.

The patient has had stool cultures and upper and lower endoscopies with biopsies; the results were all normal. She also has undergone multiple courses of empiric antibiotic treatment, with no improvement. She takes Imodium (loperamide) every day, which relieves the symptoms. She also has hypertension, diabetic nephropathy, retinopathy, and peripheral neuropathy.

On physical examination, her pulse is 88 and regular, and her blood pressure is 130/60 mm Hg supine and 105/50 mm Hg standing. Her lung and heart sounds are normal. Examination of the abdomen reveals no organomegaly, no tenderness, and normal bowel sounds. Neurologic examination reveals an absent sense of vibration in both lower extremities, decreased sense of touch, and diminished ankle reflexes.

**1** What is the most likely cause of diarrhea in this patient?

- Small-bowel bacterial overgrowth

- Celiac sprue
- Pancreatic insufficiency
- Autonomic neuropathy ("true diabetic diarrhea")

Small-bowel bacterial overgrowth results in bile-salt deconjugation, causing fat malabsorption and diarrhea. This condition is usually diagnosed by quantitative culture of jejunal aspirates; more than 100 000 aerobes or >1000 anaerobes per mL is diagnostic. This type of diarrhea usually improves with a 14-day course of antibiotics. However, it is unlikely in this patient because it is uncommon in persons with diabetes.

Patients with type I diabetes have an increased prevalence of celiac sprue, probably because the histocompatibility antigens HLA-B8 and HLA-DR3 occur in both diseases. Celiac sprue should always be excluded in diabetic patients with gastrointestinal problems because specific treatment for it is available (ie, a gluten-free diet). It is diagnosed by serologic testing for antiendomysial or antigliadin antibodies and by small-bowel biopsy. This patient had normal small-bowel biopsy results, excluding celiac sprue as a possibility.

Impaired exocrine pancreatic function does occur in diabetes; the causes are pancreatic atrophy, disruption of cholinergic enteropancreatic reflexes, and elevated serum levels of glucagon, somatostatin, and pancreatic polypeptide, all of which reduce pancreatic enzyme secretion. However in one study, only

20% of patients with diabetes had impaired exocrine pancreatic function, and only 20% of these had steatorrhea. This patient has no evidence suggestive of malabsorption.

Diabetic patients with autonomic neuropathic diarrhea have a history of longstanding, poorly controlled diabetes with evidence of peripheral and autonomic neuropathy. The pattern is episodic, with attacks lasting for days to weeks, and normal bowel habits or constipation between attacks. The diarrhea is usually severe, with frequent watery stools, characteristic nocturnal diarrhea, and, sometimes, incontinence.

All these reasons make autonomic neuropathy the most likely cause of this patient's symptoms. However, this diagnosis should be made only after other organic causes of diarrhea have been excluded.

- 2 Which of the following is *not* a manifestation of autonomic neuropathy in diabetes?
- Resting tachycardia
  - Urinary bladder dysfunction and impotence
  - Gastroparesis and diarrhea
  - Argyll Robertson pupils
  - Resting bradycardia

Autonomic neuropathy in diabetes manifests itself as impairment of both sympathetic and parasympathetic nerves. Its cardiovascular signs are resting tachycardia and postural hypotension. A lack of R-R variation on electrocardiography with deep breathing, Valsalva maneuver, or squatting confirms the diagnosis. A common symptom is postural dizziness or presyncope.

Another possible manifestation is urinary bladder dysfunction causing incontinence or urinary retention. Impotence is a common manifestation of autonomic neuropathy in diabetic men.

The gastrointestinal symptoms of autonomic neuropathy result from lack of peristalsis in the stomach and intestine. Symptoms include early satiety, bloating, nausea, belching, abdominal distension, and constipation or diarrhea. (Constipation is often an early sign.)

Argyll Robertson pupils are seen occasionally in patients with diabetes.

Resting bradycardia is not a sign of diabetic autonomic neuropathy.

3 Which of these agents can be used in diabetic diarrhea?

- Antidiarrheal agents (loperamide, diphenoxylate, codeine)
- Clonidine
- Verapamil
- Octreotide

All of these agents have been used in diabetic diarrhea, with variable results.

Antidiarrheal agents can reduce the number of stools, particularly if the diarrhea is associated with rapid intestinal transit. Retardation of motility can promote stasis and aggravate bacterial overgrowth; hence, it is important to exclude bacterial overgrowth before using antidiarrheal agents.

Clonidine 0.1 to 0.5 mg twice daily by mouth reduces the number and volume of stools, but can slow gastric emptying and occasionally causes postural hypotension.

Verapamil 40 mg twice daily may help control diarrhea, probably by globally slowing colonic transit.

The long-acting somatostatin analogue octreotide inhibits water secretion, increases the gut's absorptive capacity, and suppresses gastrointestinal hormones that can cause diarrhea. It is given as a subcutaneous injection of 50 to 75  $\mu$ g twice daily. However, at higher doses, octreotide inhibits pancreatic secretion and may aggravate malabsorption.

This patient was started on clonidine 0.1 mg twice daily. The diarrhea almost completely resolved over 2 to 3 weeks, with no aggravation of her postural hypotension. Clonidine has been used for up to 24 months, and drug holidays may be attempted. It is important, however, to taper the dosage slowly to avoid withdrawal symptoms.

#### ■ SUGGESTED READING

Camilleri M. Gastrointestinal problems in diabetes. *Endocrinol Metab Clin North Am* June 1996; 25(2):364–375.

Ewing D. Autonomic neuropathy. In Pickup J, Williams G, eds. *Textbook of diabetes*. Oxford: Blackwell, 1991:635–647.

Fedorak RN, Field M, Chang EB. Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985; 102:197–199.

Feldman M, Schiller IR. Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983; 94:378–384.