Journal of Pediatric Gastroenterology and Nutrition
38:4–6 © January 2004 Lippincott Williams & Wilkins, Inc., Philadelphia

Editorial

Diabetes and Gastrointestinal Tract: The Intrigue Continues

Salvatore Cucchiara and Osvaldo Borrelli

Department of Pediatrics, Division of Pediatric Gastroenterology, University of Rome "La Sapienza," Rome, Italy.

The term "diabetic enteropathy" usually refers to all the gastrointestinal complications encountered in patients with diabetes mellitus, such as dysphagia, heartburn, nausea and vomiting, abdominal pain, constipation, diarrhea, and fecal incontinence (1). The entire gastrointestinal tract can be affected by diabetes, from the oral cavity and esophagus to the large bowel and anorectal region. Although gastrointestinal symptoms in diabetes are commonly thought to be a result of disordered gastrointestinal motility, other variables can underlie them: altered visceral sensitivity, altered secretion of neurotransmitters, psychiatry comorbidity, and mucosal inflammation (2).

The true prevalence of gastrointestinal symptoms among community patients with diabetes is not clearly defined because epidemiologic studies have yielded conflicting results; furthermore, most studies have focused on patients with diabetes attending tertiary hospitals, which are unlikely to be representative of the general diabetic population. Whereas studies from Feldman and Schiller (3) and from Clouse and Lustman (4) indicate that two thirds of adult patients with diabetes have at least one gastrointestinal symptom, other reports in adults, such as the Rochester Diabetic Neuropathy Study (5) and the Pittsburgh Epidemiology of Complications Study (6), reveal that gastrointestinal disturbances in patients with diabetes observed in tertiary settings are rare.

The prevalence of gastrointestinal disturbances in children with diabetes is also poorly defined. A study in 118 consecutive children and adolescents with insulin-dependent diabetes mellitus (IDDM) revealed a prevalence of gastrointestinal symptoms statistically similar to 171 control children and adolescents (44.9% *v* 36.8%); furthermore, gastrointestinal symptoms did not have any impact on the metabolic control of the disease (7). Previously, dyspeptic symptoms were reported in 7.2% of 31 children and adolescents with IDDM: symptoms were related to macroscopic or microscopic esophagitis or unspecific gastroduodenitis, whereas gut motility was not studied (8).

In this issue of the *Journal of Pediatric Gastroenterology and Nutrition*, Vazeou et al. (9) have studied 33 consecutive children with IDDM and gastrointestinal symptoms of functional type (dyspepsia in 14, constipation in 19) in comparison with 48 non-IDDM children with either chronic dyspepsia or chronic constipation. Aims of the study were to assess some variables of gastrointestinal motility, such as gastric emptying (GE) time (measured by scintigraphy) and mouth-to-anus transit time (MATT; measured by carmine red), and to evaluate if autonomic neuropathy played a role in gastrointestinal symptoms and dysmotility. Motility studies were not performed in 36 healthy children, who were selected only for comparison of autonomic cardiovascular tests. The main results of the study can be summarized as follows: motility variables did not differ between IDDM patients and non-IDDM gastrointestinal symptomatic subjects; no features of autonomic neuropathy, as evaluated by cardiovascular tests, were observed; lower serum motilin values were detected in patients with IDDM than in healthy control subjects, mainly in those with higher blood glucose concentration. Although the study claims to address several issues regarding the relationship between diabetes and the gastrointestinal tract, several questions on this topic remain unanswered.

Of great practical importance are the questions if gastrointestinal symptoms in patients with diabetes arise from disordered gastrointestinal motility and if the latter has a serious effect on metabolic control of diabetes. Dyspeptic symptoms usually observed in patients with diabetes include a large spectrum of features, ranging from early satiety, bloating, and fullness to nausea, abdominal pain, and vomiting. These symptoms are strongly suggestive of slow GE; however, clinical observations in patients with and without diabetes who have dyspepsia indicate a poor correlation between symptom severity and the rate of GE (10). It also is known that severe gastroparesis can be asymptomatic and that dyspeptic symptoms can occur because of abnormalities in functional variables of the stomach other than GE, such as visceral sensitivity and receptive relaxation (2). Increased gastric sensitivity lowers the threshold for perception of symptoms, such as discomfort after eating, bloating, and pain, whereas defective postprandial ac-

commodation may cause early antral distension that results in early satiety and nausea (1). These parameters have not been measured in the study of Vazeou et al.

Recently, a consensus has emerged that functional disorders of the stomach should be managed by taking into account different pathogenetic variables: contractile activity of antropyloric region, receptive relaxation of the fundus, visceral sensitivity, gastric electrical activity that originates by the interstitial cells of Cajal, and neuropeptides involved in triggering and modulating neuromuscular interactions (11). Therefore, if only the GE time is measured in patients with dyspepsia, a limited and partial interpretation of gastric function ensues.

Whether or not diabetic gastropathy affects and deteriorates glycemic control is a question that has not been addressed in depth by Vazeou et al. It is conceivable that a delay in GE can contribute to poor glycemic control by determining a mismatch between the onset of insulin action and the delivery of nutrients into the small bowel. Delay in GE and gastric electrical abnormalities previously have been reported in 26 of 40 consecutive children with IDDM observed in a tertiary center: these subjects had significantly higher levels of both HbA_{1c} and blood glucose measured 180 minutes after feeding than did those with normal GE times; in these patients, a strong correlation between disordered gastric motility and variables of deranged glycemic control also was found (12). On the other hand, abnormal GE may result from high blood glucose levels that usually are encountered in patients with diabetes who have poor metabolic control. However, this aspect deserves additional evaluation.

Bytzer et al. (13) observed in adult patients with diabetes that gastrointestinal symptoms were not correlated to blood glucose and HbA_{1c} levels, whereas another study showed an association between self-reported poor glycemic control and gastrointestinal complaints (14). Data from the group of Frank et al. (15) indicate that in adults with noninsulin dependent diabetes, GE of solid was normal, despite high levels of blood glucose and HbA_{1c}. In contrast, during acute experimental hyperglycemia, gastric electrical and motor abnormalities and GE delay have been documented, and endogenous prostaglandins have been suggested to play a role (16).

The relationship between gastrointestinal motility and blood glycemic levels is also made complex by the notion that abnormal glucose control may alter delivery of glucose counterregulatory peptides, most of which influence gastrointestinal motility. Vazeou et al. have detected lower serum motilin concentrations in their patients with diabetes than in healthy control subjects, mainly in those with higher blood glucose concentrations. Measuring blood levels of this peptide without relation to the gastrointestinal motility patterns seems to be a costly whim because it does not help in highlighting pathogenesis of diabetic gastropathy. Plasma levels of motilin are known to fluctuate in synchrony with interdigestive migrating motor complex, and it is agreed that peaks of motilin occur during the passage of phase III of the interdigestive motor complex at the level of the antrum (17). However, a clear role of motilin during the period after feeding has not been stated. In contrast to the findings of Vazeou, previous reports in patients with diabetes have shown elevated levels of serum motilin, which have been interpreted as a compensatory reaction to reduced incidence of interdigestive migrating motor complexes (2); interestingly, when these patients were treated with prokinetics, levels of motilin decreased (18).

Vazeou et al. also investigated their patients' cardiovascular autonomic function and looked for a relationship between autonomic neuropathy and GI dysmotility. No features of disturbed autonomic function were observed. Autonomic neuropathy is one of the most critical factors in the pathogenesis of gastrointestinal symptoms in patients with diabetes and may involve different sites of the gastrointestinal tract (1). In particular, it has been pathogenetically related to esophageal motor dysfunction, gastroesophageal reflux, GE delay and altered intragastric meal distribution, disturbed small bowel transit, and constipation. As Vazeou et al. comment, diabetic autonomic neuropathy did not play any role in gastrointestinal disturbances of the studied population: this is in accordance with previously reported data in children with IDDM showing that the development of autonomic neuropathy depends on duration and pediatric age (puberty seems to be the critical period for the development of autonomic neuropathy) (19). Interestingly, in adult patients with diabetes, impaired GE, and abnormal intragastric meal distribution, dyspeptic symptoms were not more common in those with delayed GE time and neuropathy than in those without neuropathy and normal GE time: these data show that symptoms are not a reliable indication of neuropathy and delayed GE time and suggest that in patients with diabetes who have autonomic neuropathy, gastric motor studies should be planned, regardless of gastrointestinal symptoms (20).

The paper of Vazeou et al. again proposes the possibility of a relationship between diabetes mellitus and gastrointestinal symptoms and motility. Gastrointestinal problems encountered in patients with diabetes are protean and sustained by diverse pathophysiologic events. The pathophysiologic heterogeneity affects clinical presentation, the impact on metabolic control of diabetes, and treatment options. Many obvious and important questions are awaiting answers from appropriately designed studies in pediatric patients with IDDM: Which is the true prevalence of gastrointestinal disturbances in children with diabetes? Are different clinical complaints underlain by different pathogenetic variables? When should children with IDDM be investigated for disturbances of the gastrointestinal function? What kind of investigative tools should be applied? Does the patho-

physiologic investigation help in selecting therapeutic options? Should we expect improved metabolic control of diabetes by treating gastrointestinal disturbances? Overall, studies of the gastrointestinal functional disorders in diabetes are a good and fecund opportunity for an interaction between clinical and basic researchers of different extraction.

REFERENCES

1. Camilleri M. Advances in diabetic gastroparesis. Reviews in *Gastroenterological Disorders* 2002;2:47–56.
2. Chandran M, Chu NV, Edelman S. Gastrointestinal disturbances in diabetes. *Curr Diab Rep* 2003;3:43–8.
3. Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983;98: 378–84.
4. Clouse RE, Lustman PJ. Gastrointestinal symptoms in diabetic patients: lack of association with neuropathy. *Am J Gastroenterol* 1989;84:868–72.
5. Dyck PJ, Karnes JL, O'Brien PC, et al. The Rochester Diabetic Neuropathy Study: reassessment of tests of criteria for diagnosis and staged severity. *Neurology* 1992;42:1164–70.
6. Maser RE, Pfeifer MA, Dorman JS, et al. Diabetic autonomic neuropathy and cardiovascular risk. *Arch Intern Med* 1990;150: 1218–22.
7. Vazeou A, Papadopoulou A, Booth IW, et al. Prevalence of gastrointestinal symptoms in children and adolescents with type 1 diabetes. *Diabetes Care* 2001;24:962–4.
8. Burghen GA, Murrell LR, Whitington GL, et al. Acid peptic disease in children with type 1 diabetes mellitus: a complicated relationship. *Am J Dis Child* 1992;146:718–22.
9. Vazeou A, Papadopoulou A, Papadimitriou A, et al. Autonomic neuropathy and gastrointestinal motility disorders in children and adolescents with type 1 diabetes mellitus. *J Pediatr Gastroenterol Nutr* 2003;37:61–65.
10. Talley NJ. Diabetic gastropathy and prokinetics. *Am J Gastroenterol* 2003;98:264–71.
11. Koch KL. Diabetic gastropathy: gastric neuromuscular dysfunction in diabetes mellitus. *Dig Dis Sci* 1999;44:1061–75.
12. Cucchiara S, Franzese A, Salvia G, et al. Gastric emptying delay and gastric electrical derangement in IDDM. *Diabetes Care* 1998; 21:438–43.
13. Bytzer P, Hammer J, Talley NJ, et al. Gastrointestinal symptoms in diabetes mellitus are associated with diabetic complications but not with current diabetic control. *Gastroenterology* 2000;118:A468.
14. Bytzer P, Talley NJ, Leemon M, et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 2001;161: 1989–96.
15. Frank JW, Saslow SB, Camilleri M, et al. Mechanisms of accelerated gastric emptying of liquids and hyperglycemia in patients with type II diabetes mellitus. *Gastroenterology* 1995;109:755–65.
16. Hasler WL, Soudah HC, Dulai G, et al. Mediation of hyperglycemia-evoked gastric slow-wave dysrhythmias by endogenous prostaglandins. *Gastroenterology* 1995;108:727–36.
17. Tack J. George Brohee Prize 1994. Motilin and the enteric nervous system in the control of interdigestive and postprandial gastric motility. *Acta Gastroenterol Belg* 1995;58:21–30.
18. Achem-Karam SR, Funakoshi A, Vinik AI, et al. Plasma motilin concentration and interdigestive migrating motor complex in diabetic gastroparesis. Effect of metoclopramide. *Gastroenterology* 1985;88:492–5.
19. Massin MM, Derkenne B, Tallsund M, et al. Cardiac autonomic dysfunction in diabetic children. *Diabetes Care* 1999;22:1845–50.
20. Stacher G, Lenglinger J, Bergmann H, et al. Impaired gastric emptying and altered intragastric meal distribution in diabetes mellitus related to autonomic neuropathy? *Dig Dis Sci* 2003;48:1027–34.