Gastro Intestinal Manifestations of Diabetes Mellitus

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ABSTRACT

Dysfunction of the autonomic nervous system is a well established long term complication of diabetes mellitus. Moreover, autonomic innervations is essential for appropriate functioning of the gastrointestinal tract, (GI), including the synchronicity between the motility induced peristaltic movement and the sphincters as well as the secretary capacity of the GI glands, i.e. salivary glands, pancreas, gallbladder. Therefore, several patients with diabetes mellitus of prolonged duration manifest chronic and recurrent clinical features related to the disordered motility of almost the whole GI tract including esophageal as well as epipharyngeal dysphagia, gastroparesis, constipation, diarrhoea, and fecal incontinence. Finally, acute cholecystitis secondary to biliary calculi or sometimes even in the absence of calculi, i.e. acalculus cholecystitis secondary to atonic gallbladder and dysfunction of the sphincter of Oddie, pancreatic maldigestion due to decreased secretion of pancreatic enzymes are also known to occur more frequently in subjects with diabetes when compared to the normal population. Alternatively, transient reversible disorders of gastrointestinal motility also occur during acute metabolic complications such as diabetic ketoacidosis and the hyperglycemic hyperosmolar state and are attributed to dehydration, altered acidbase status as well as imbalance of serum electrolytes secondary to urinary losses induced by osmotic diuresis. Therapeutic strategies in the management of chronic recurrent manifestations secondary to autonomic dysfunction include dietary manipulations, and several drugs including dopamine antagonists, antibiotics as well as hormones facilitating peristalsis. On the other hand, the gastrointestinal manifestations that occur during acute metabolic complications are self limited and respond promptly following restoration of a normal metabolic milieu.

INTRODUCTION

Gastrointestinal manifestations are frequently observed in diabetes mellitus and may occur in up to 76% of all diabetes patients [1]. They may be noted at the onset of diabetes mellitus, during an acute critical presentation such as ketoacidosis or may manifest after the diabetes has been present for several years. All organs of the GI tract from the mouth to the anus as well as the gallbladder, liver and pancreas may be involved [2]. Autonomic dysfunction secondary to neuropathy may lead to recurrent and permanent manifestations whereas metabolic aberrations such as ketoacidosis may cause transient clinical manifestations including nausea, abdominal pain and distention.

Oral Disorders

The clinical features of involvement of the mouth include epipharyngeal dysphagia secondary to decreased salivary flow which induces impaired bolus formation. There is also an associated defective epiglottic mobility, defective closure of the laryngeal vestibule and weakness of the pharyngeal musculature. The syndrome of gustatory sweating is also an another relatively frequent disorder seen in some patients caused by autonomic dysfunction. This syndrome consists of inappropriate and untimely facial sweating substituting salivary secretions in response to chewing of food. Finally, premature teeth loss may also occur because of loss of supporting bony tissue secondary to osteoporosis and periodontal disease. Loss of teeth further disrupts the chewing mechanism with progressive worsening of the dysphagia. Gustatory sweating frequently poses a therapeutic dilemma while epipharyngeal dysphagia could be managed with appropriate physical therapy in order to assist swallowing.

Dysphagia and Heartburn

Esophageal symptoms are common, and when present vary from heartburn, chest pain, chest discomfort ultimately leading to dysphagia [3]. The first step should always be to search for the more common causes such as gastro esophageal reflux and peptic ulcer disease before attributing these symptoms to diabetes. In a patient complaining of dysphagia upper gastrointestinal endoscopy and cineradiography are among the obligatory tests that should be offered to the patient. Motility abnormalities associated with diabetes include delayed esophageal emptying, esophageal dilatation, and spontaneous tertiary contractions [4-6]. Upper GI endoscopy may reveal reflux, candidiasis, or other forms of infectious, inflammatory or neoplatsic lesions. Although esophageal dysfunction is often asymptomatic, the patients who present with dysphagia may respond to small frequent feedings

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as well as drugs such as metoclopramide. However, esophageal dilations may be rarely required. The relatively high incidence of coronary heart disease in diabetics should always be borne in mind during the evaluation of chest pain and upper GI symptoms in diabetic patients and therefore mandate an appropriate testing to exclude refractory angina pectoris and occasionally even a myocardial infarction.

Gastroparesis

Gastric retention in diabetes mellitus was first described in detail by Rundles in 1945. Subsequently, Kassender in 1958 coined the term "gastroparesis diabetecorum" to describe gastric atony and delayed emptying. Vagal neuropathy as a complication of diabetes leads to impaired neural control of the myoelectric activity of the stomach and therefore, delays gastric emptying and impaires the gastric acid response to sham feeding [7, 8]. Gastroparesis may contribute to instability of blood sugar levels because of both the unpredictable oral intake and the variable timing of absorption of nutrients as a result of delayed gastric emptying. These patients frequently manifest anorexia, early satiety, postprandial abdominal fullness and discomfort. However, the relationship between gastroparesis on one aspect and vomiting on the other is more complex. In some patients, delayed gastric emptying is the primary process which initiates nausea and vomiting by stimulating the vomiting center in the brainstem through the gastric afferent nerves [9]. In order diabetic patients, episodes of pyloric spasm or intense disorganized antral contractions lead to nausea and vomiting [10, 11]. The lack of a normal antral interdigestive migratory motor complex, (IMMC), may contribute to abnormal emptying especially of dietary fiber, debris and bacteria which in turn renders the patient susceptible to bacterial overgrowth in the stomach and the upper intestine. These complexes, (IMMC), are stimulated by motilin [12] and suppressed by somatostatin [13]. The elevated motilin level in the presence of decreased or absent interdigestive migratory motor complexes in gastroparesis may indicate a compensatory motilin response to end organ insensitivity [14, 15]. The high levels of somatostatin seen in insulin deficiency may also contribute to the inhibition of these complexes [16].

Treatment of gastroparesis includes restoration of optimal metabolic control of diabetes mellitus as well as correction of associated fluid and electrolyte abnormalities. Small, frequent, soft and liquid meals are helpful in ameliorating the symptoms. Occasionally, in a patient with refractory symptoms, a naso-gastric suction may be required to decompress the dilated stomach. Pharmacologic therapy is the next logical choice in the therapeutic strategy. The drug of choice is metoclopramide, a central and peripheral dopamine antagonist known to increase gastric emptying [17]. The usual tolerated and therapeutic dose is 10 mg before each meal and again at bed time. In the presence of severe and disabling symptoms, the patient may require hospitalization and metoclopramide may be administered intravenously or as a rectal suppository. Domperidone, a second generation pro-kinetic dopamine antagonist, does not cross the blood brain barrier and can be given in higher doses with significantly less neurological adverse effects [18]. Cisapride, another agent which is a serotonin antagonist, stimulates acetylcholine release and enhances motility of the esophagus, stomach and intestine [19]. Cisapride used either orally or intravenously has been documented to be an effective treatment for gastroparesis [20]. Erythromycin has also been shown to mimic the action of motilin by competitive binding to motilin receptors and stimulate phase III, (intense motor activity), contractions of the stomach and improves gastric emptying [21]. However, despite its proven efficacy in the acute management of symptomatic gastroparesis, its prolonged use is not recommended because of the lack of adequate data in terms of its efficacy.

Diabetic Diarrhoea

Diabetic diarrhoea is usually chronic and intermittent and is defined as a stool volume of more than 20 g/day and usually occurs in patients with poorly controlled, long standing diabetes. It occurs more often in men with a male to female ratio of 3 : 2 [22]. The overall prevalence of diabetic diarrhoea has been reported to vary from 8 to 22% [1, 23]. The exact pathophysiology of diabetic diarrhoea is not well defined. Several mechanisms are deemed to be responsible for the development of this disorder. Autonomic neuropathy of the bowel [24, 25] with resultant dysmotility promoting bacterial overgrowth in the small bowel [26, 27] is thought to be the major contributing factor. However, pancreatic insufficiency [28], bile acid malaborption [29], gluten induced enteropathy and altered regulation of secretions of gut hormones [30, 31] are also documented to occur more frequently in diabetics as compared to the general population. Therefore, these factors are also thought to contribute to diarrhoea in subjects with long standing diabetes mellitus. Thus, visceral autonomic neuropathy appears to play a major role in diabetic diarrhoea. Patients with diabetic diarrhoea have

abnormal motility of the small bowel [32, 33] which may be due to impaired propagation of myoelectric activity in the small intestine. However, there is no conclusive evidence implicating either the rapid or the slow transit in the small bowel for induction of diabetic diarrhoea. Change and associates [34] have demonstrated that diarrhoea in streptozocin induced diabetic rats was due to increased net secretion of fluid and electrolyte by the intestine initiated by faulty adrenergic regulation of mucosal ion transport caused by reduced a -2 adrenergic tone in enterocytes. This was effectively reversed by clonidine. Bacterial overgrowth can lead to bile acid deconjugation, fat malabsorption and diarrhoea. However, only a small percentage of patients with diabetic diarrhoea actually exhibited bacterial overgrowth in some studies [27, 35]. Excessive consumption of dietetic foods that contain sorbitol, an artificial sweetener, may also cause osmotic diarrhoea. Some patients with diabetes mellitus have myoelectrical abnormality of the colon [36] and colonic dysfunction has been reported in nocturnal diarrhoea associated with diabetes mellitus [37]. Anorectal dysfunction is relatively common and fecal incontinence is experienced by approximately 20% of patients with long standing diabetes [1]. The majority of patients with fecal incontinence, on anorectal testing demonstrate a decreased rectal sensation [38] and hypotonia [39] of the anal canal probably caused by autonomic dysfunction of the internal anal sphincter. Anorectal manometry and rectal sensory testing can reliably differentiate between sympathetic and pudendal neuropathy. Wald and Tunuguntla have demonstrated significant improvement of this abnormality with biofeedback training [38]. In a review of causes of chronic diarrhoea in 33 patients with diabetes, Valdovinos and his associates [40] documented the presence of one or more of the aforementioned causes in almost all the patients suggesting multifactorial induction of diarrhoea in these patients. The management of diarrhoea includes primarily the determination of the cause followed by the appropriate therapeutic intevention. Thus, replacement of the pancreatic enzymes is an appropriate therapy if pancreatic maldigestion is determined to be the cause. Oral cholestryramine may also relieve diarrhoea in a situation involving altered biliary secretion and function. Finally, if these measures fail to remit the diarrhoea, an oral or a dermal clonidine administration, oral antibiotic therapy or as the last resort parenteral somatostatin administration may be attempted. Fortunately, in several patients the diarrhoea is self limited in duration and may, therefore, remit itself for a prolonged period before recurrence. Occasionally usage of diapers may be required in the presence of an embarrassing fecal incontinence.

Constipation

Constipation is the most common gastrointestinal symptom in diabetic patients [1]. The exact pathogenesis of constipation in diabetes is not well understood. Autonomic dysfunction with a lack of synchronicity between the gut musculature and the sphincters is thought to be the major contributing factor. Battle et al, in their study of colonic myoelectric and motor activity, demonstrated that diabetic patients with severe constipation had a totally absent gastrocolic response to feeding, with variable consequences resulting in mild to moderate constipation [36]. Diabetic constipation may be associated occasionally, with a marked sigmoid dilation simulating megacolon along with overflow diarrhoea and incontinence [41]. Thus, this pattern may be indistinguishable from intestinal pseudo-obstruction [20]. Some diabetic patients with constipation may benefit from a trial of metoclopramide or Cisapride [9]. Dietary manipulations with soluble forms of fiber 20 to 30 g per day, sometimes in combination with bulk or osmotic laxatives may be helpful in relief of constipation although, it still remains an empiric management. However, a solid diet containing undigestible high fiber should be avoided, since this maneuver may aggravates symptoms of gastroparesis or precipitate bezoar formation.

Cholelithiasis

The prevalence of gallstones in the diabetic population varies with different studies suggested increased occurrence of gallstones in diabetics. However, these studies failed to differentiate the effects of obesity and hyperlipidaemia from those of diabetes itself. Nevertheless, the increased prevalence is partly attributed to altered gallbladder contractility and mesenteric ischaemia. The routine use of surgery in diabetics with asymtomatic gallstones remains controvertial. However, many studies have concluded that the outcome of biliary surgery via transabdominal procedure in the diabetic population especially in terms of both morbidity and mortality is determined primarily by the presence of preoperative concurrent medical disorders [46, 47] and is not significantly different when compared with the non-diabetic population. Moreover, laparoscopic cholecystectomy does not appear to pose an increased difficulty in the diabetic population. However, current data does not support prophylactic cholecystectomy by either procedure in diabetic patients with asymptomatic gallstones.

Finally, even in subjects with symptomatic gallstones, lithotripsy may supersede cholecystectomy. However, cholecysteoctomy must be performed in diabetic subjects with onset of acute cholecystitis which may be secondary to either gallstones or atonic gallbladder as a result of autonomic dysfunction.

Pancreatic Disease

A direct relationship between diabetes mellitus and pancreatitis has not been established. However, a higher incidence of gallstones associated pancreatitis is reported in Type 2 diabetics in comparison to the general population and is related to obesity [48] and the presence of lithogenic bile [49]. Similarly, exocrine pancreatic insufficiency apparently occurs more frequently in diabetics when compared to normal population. Finally, hyperamylasemia occurs in 46 to 79% of patients with diabetic ketoacidosis, (DKA). In the vast majority of these patients with DKA and hyperamylasemia, the major contributor to this elevation is the salivary isoamylase. In most instances, therefore, the elevation is insignificant and no further evaluation is required. Occasionally, in a young subject with ketoacidosis, an elevated serum amylase may pose a diagnostic dilemma regarding the presence of acute pancreatitis especially when abdominal pain, nausea and vomiting are the presenting clinical features. Chronic pancreatitis with maldigestion can be easily managed with replacement of pancreatic enzymes.

Liver

Fatty liver is produced by either micro vascular or macro vascular deposition of fat without significant hepatic necrosis in the presence of a prolonged lapse of metabolic control and hyperglycemia. The incidence of diabetic fatty liver ranges from 4 to 17% in Type 1 diabetes, and 21 to 78% in Type 2 diabetes [50]. The majority of these patients have asymptomatic hepatomegaly, with few if any symptoms, and normal liver function studies. Mild elevation of liver enzymes, mainly the alkaline phosphatase and Gamma - glutamyltranspeptidase (GGT), have been documented to occur in up to 18% of patients with or without a significant hepatic enlargement. Fatty metamorphosis in the liver is usually reversible on achieving and maintaining optimal metabolic control.

Summary

It is apparent that several syndromes involving the gastrointestinal tract itself and other para GI organ systems occur frequently in subjects with diabetes mellitus as a consequence of autonomic dysfunction, an established long-term neuropathic complication of diabetes mellitus. Moreover, we believe that the microangiopathic and the macro vascular involvement of these organ systems play a contributory role in the onset and recurrence of clinical manifestations affecting these organ systems, occasionally leading to ongoing disabiling symptomatology.

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