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Progress report

Diabetes and the gut

The pathophysiology of impaired gastrointestinal function in both chronic diabetes[1,2], and acute ketoacidosis[3], remains undefined, although several mechanisms have been implicated. These include autonomic neuropathy[4], microangiopathy[5], changes in insulin and glucagon release, and acute metabolic disturbance. In recent years various new gastrointestinal hormones have been described[6,7], although their physiological importance remains to be determined[8]. It is likely that both the chronic, and acute, metabolic changes found in diabetes will modify the release of these hormones and alter their effects on the gut. However, at the present time there are no studies of gut hormone levels in diabetics with gastrointestinal complications and the pathophysiological significance of these substances remains ill-defined.

This review will consider both the acute and chronic effects of diabetes mellitus on the gastrointestinal tract alone and will largely be confined to human data.

Acute manifestations

Anorexia, nausea, and vomiting are common presenting features of diabetic ketoacidosis[3,9]. The aetiology of these symptoms is frequently attributed to acute gastric stasis and nasogastric suction has been advocated as a routine procedure in the emergency treatment of these patients[10,11], although there is no general agreement on this[12]. The frequency of clinically significant gastric dilatation in such patients is unknown and there is no detailed study of gastric emptying during ketoacidosis.

The aetiology of acute gastric dilatation during ketoacidosis is unknown, although acute metabolic changes including glucagon and insulin release have been implicated[13,14]. It has also been suggested that gastric atony results from an acute, reversible, autonomic disturbance[15]. The effects of local gastrointestinal hormones on gastric motility have been incompletely studied and, to date, only motilin has been found to increase gastric emptying[6,16], but has not been implicated in this context. Possibly the acute electrolyte changes of ketoacidosis, especially intracellular hypokalaemia, affect gastric motility. Acute gastroparesis has also been described in recent onset diabetics after sudden stress in whom there was no acute metabolic disturbance[17].

Haematemesis as a complication of diabetic ketoacidosis is usually secondary to either acute erosive, or haemorrhagic, gastritis. It has been suggested that this results from an increased concentration of urea in the retained gastric fluid[18]. The incidence of duodenal ulceration is thought to be reduced among diabetics[19,20], although there is some conflicting evidence for this[21], and it is rarely responsible for haematemesis in these subjects.

Acute abdominal pain, in the absence of intra-abdominal disease, may occur in these patients and can be of sufficient severity to mimic an acute

abdomen. This can present a difficult diagnostic problem, as many of these patients have both a leucocytosis[3,22] and raised serum amylase[23]. The diagnosis of acute pancreatitis is especially difficult in this condition and is probably frequently under-diagnosed[24]. Persistent abdominal pain in diabetics may also occur as a result of diabetic radiculopathy affecting the thoracic nerve roots[25]. This condition may be diagnosed by electromyography and probably explains earlier reports of 'tabetic pains' in diabetics[1].

Chronic manifestations

Although chronic gastrointestinal symptoms in association with diabetes had been recognised previously, it was the report by Rundles in 1945[4] that first drew attention to the effects of diabetes on the gut. It was later suggested that these effects were a manifestation of autonomic neuropathy[26]. Subsequent series have stressed the frequent association with neuropathy in these patients, although histological evidence of autonomic denervation to the gut is incomplete.

OESOPHAGUS

Clinical manifestations of oesophageal dysfunction as a complication of diabetes are rare, although dysphagia and diffuse ulceration have been described[27,28]. Evidence for altered oesophageal motor function in diabetics was first reported in 1967[29]. Fourteen patients were studied by means of a ciné-radiographic technique. All had gastrointestinal symptoms and clinical evidence of autonomic neuropathy. Twelve of these patients had diminished, or absent, oesophageal peristalsis and oesophageal emptying in the supine position was delayed. Tertiary (non-peristaltic) or spastic contractions were frequently observed but only three of these subjects described oesophageal symptoms. Eight of these patients subsequently underwent oesophageal manometry[30], which demonstrated a reduction in the resting lower oesophageal sphincter pressure (LOSP) and confirmed the reduction of amplitude of peristaltic contraction together with the high incidence of tertiary contractions. These observations have been confirmed in a combined radiological —manometric study[31] in which loss of tone of LOSP was found to result in gastro-oesophageal reflux. In contrast with the observed hypersensitivity of the oesophageal muscle to cholinergic agents in conditions such as achalasia and Chagas disease, where there is degeneration of the myenteric plexus[32,33], no increase in LOSP was produced after bethanechol in diabetic subjects[31]. This indirect evidence suggests that the myenteric plexus is functionally intact in the diabetic.

Studies of the neuropathology of the oesophagus are few. In one series[34] abnormalities were found in 18 of twenty unselected diabetics without clinically significant dysphagia or neuropathy. Abnormalities were found predominantly in the axons of the extrinsic and intrinsic parasympathetic fibres while the neurones were normal.

Although it appears that most diabetics with oesophageal dysfunction also have peripheral neuropathy, it is not clear whether altered motor function also occurs in uncomplicated diabetics. In a comparative study of oesophageal motility in neuropathic and non-complicated diabetics the amplitude of pharyngeal contractions and the resting LOSP showed increased responsiveness to normal stimuli in diabetics without neuropathy[35]. The authors

suggested that the transient hypersensitivity to normal stimuli might be an early manifestation of diabetic neuropathy affecting the oesophagus. In a series of 50 diabetics peripheral neuropathy was found to precede oesophageal dysfunction[36].

STOMACH

Gastric retention as a late complication of diabetes was described in 1945[4]. In a subsequent study[26] delayed gastric emptying was again observed in a series of patients with severe neuropathy and it was suggested that it resulted from autonomic dysfunction. In 1958, Kassander[37] described the condition as 'gastroparesis diabeticorum', emphasising that such patients were frequently asymptomatic, and attributed it to autonomic neuropathy. Later series have stressed the frequent association with generalised diabetic neuropathy and also the similar condition found after vagotomy[38].

In these, and other, series[1,39,40] gastric emptying was assessed by barium radiology. Gastric emptying in diabetics has also been studied by a dye-dilution method[41]. By this means, delayed emptying of saline[42], and water[43], have been described, although the results were conflicting with regard to the effect of diabetic neuropathy.

Although these techniques provide a simple method of estimating gastric emptying it is likely that the response to normal food is very different. Measurement of the rate of gastric emptying of solid meals using isotopically labelled food has been described[44]. A recent study of the gastric emptying of solid meals in diabetics[45] showed no significant difference in the rate of emptying between non-complicated diabetics, diabetics with autonomic neuropathy, and healthy controls. However, the results were more variable in the diabetic groups, which emphasises the difficulty of interpreting single observations. Similarly, in an earlier study of gastric emptying in diabetics using hypertonic glucose solution[46] a few subjects were found with very slow emptying, although the overall mean rate was no different from that of controls.

The differential rates of gastric emptying of both the solid, and liquid components of a standard meal have been compared in a small series of diabetics using a double-isotope technique[47]. The normal differentiation between solid and liquid emptying was impaired in the diabetics compared with controls, which, it was suggested, might be due to abnormal antral peristalsis not attributable to vagal denervation.

The aetiology of gastric stasis in the diabetic remains unresolved. In view of the frequent association with peripheral and autonomic neuropathy, as well as the similar condition found after vagotomy, it is likely that visceral neuropathy is important in the aetiology. Unfortunately, there are no detailed neuropathological studies available. Other mechanisms may also contribute to the aetiology. Hyperglycaemia, and also glucagon, have been shown to reduce gastric emptying in non-diabetics with duodenal ulceration[13], although the concentrations of glucagon required to affect emptying are much higher than the physiological range[7]. Furthermore, in diabetics a similar effect of hyperglycaemia could not be demonstrated[43]. It has also been suggested[48] that diminished gastric acid production after vagal neuropathy might affect the emptying rate. The importance of gastrointestinal hormones in chronic gastric stasis remains to be established.

Symptomatically the effects of gastric stasis are very variable. Many

patients are entirely asymptomatic, while some describe vague abdominal pain, fullness, nausea, and vomiting. Treatment is generally disappointing and various anticholinesterase preparations have been tried without much success[37,39,40]. Antiemetics can provide temporary relief and, recently, metoclopramide has been used successfully in some patients[49]. Various surgical drainage procedures have been performed[38], mostly with little benefit probably, as there is no structural lesion of the gastric outlet.

Studies of gastric acid secretion in diabetics are conflicting. Some authors have found diminished acid secretion[48,50,51], while others have reported no significant difference from non-diabetic controls[43,52,53]. Gastric acid secretion after pentagastrin was measured in a series of diabetics with autonomic neuropathy and compared with the effect of insulin-induced hypoglycaemia[54]. Secretion was reduced during hypoglycaemia but was normal after pentagastrin, which suggests vagal neuropathy with normally functioning gastric mucosa. However, gastrin release during insulin hypoglycaemia is enhanced after vagal section in man[7], and the reduced response to hypoglycaemia might reflect diminished vagal sensitivity as a result of poor diabetic control, although there is no evidence to support this hypothesis. The gastric mucosa has been found to be more frequently atrophic than in age-matched controls[1,55] and impaired gastric secretion may be associated with histological changes[56]. Corresponding with the increased incidence of gastric mucosal atrophy there is an increased incidence of pernicious anaemia[57–59] and gastric parietal cell antibodies among diabetics[60,61].

Other factors may also influence acid secretion including hyperglycaemia, which has been found to have an inhibiting effect, and increased glucagon secretion[62,63].

SMALL BOWEL

In addition to all the usual causes of diarrhoea the specific condition of diabetic diarrhoea is recognised. The term 'diarrhoea of diabetes' was first used in 1936[64] to describe unexplained diarrhoea associated with severe diabetes. The authors observed no improvement during treatment with pancreatic juice. Later reports have emphasised that such patients are usually poorly controlled, complicated, diabetics with evidence of generalised neuropathy. In a series of 125 cases of diabetic neuropathy, 27 were found to have watery diarrhoea[4]. Subsequently in 1946, a series of 40 cases of diabetic diarrhoea were reported[65]. The average of these subjects was 42 years and the diabetes, which was poorly controlled, averaged nine years in duration. Neuropathy was found in 23 of these cases. Symptomatically they complained of intermittent, watery, diarrhoea, frequently worse nocturnally and associated with faecal incontinence. Later series have stressed the frequent association with neuropathy and especially autonomic disturbance, while pancreatic exocrine function studies and small intestinal mucosal biopsy have been normal[53,66–70].

Steatorrhoea has also been described in diabetic subjects in whom there was no evidence of either pancreatic exocrine insufficiency or coeliac disease[71–73]. Several authors have described patients with diabetes and associated coeliac disease[73,74], although the nature of this association is not yet clear. Recently the histocompatibility antigen HLA B8 has been shown to be positively associated with juvenile-onset diabetes[75] and also coeliac disease[76].

The pathogenesis of diabetic diarrhoea and, also, steatorrhoea remains

undefined. It has commonly been attributed to visceral neuropathy in view of the frequent coexistence with symptoms of generalised autonomic dysfunction, including neurogenic bladder, orthostatic hypotension, impotence, and gustatory sweating. In addition, similar intermittent diarrhoea is found after vagotomy or ganglion blocking agents.

Despite this well-recognised clinical association, histological findings are inconclusive. Abnormalities of the myenteric plexus have been reported in one case[77], but in a controlled study[71] no specific lesions were observed in the enteric ganglia, mucosa, muscle, or microvasculature. There is no substantial evidence of histological abnormalities affecting the intestinal sympathetic or parasympathetic nerves, the submucosal or myenteric plexus, and the thoracolumbar and presacral nerves[67,68,71,78]. However, lesions of the dendritic processes of the pre- and paravertebral sympathetic ganglia have been reported[79] which may result in altered sympathetic function. It has been suggested that afferent sympathetic innervation is impaired, while the efferent pathways are uninterrupted[53].

Malins and French first reported symptomatic relief in 16 of 22 patients with diabetic diarrhoea treated with chlortetracycline[67]. Since then there have been a number of other reports of clinical improvement after broad-spectrum antibiotics[80,81,84]. This indirect evidence suggests that such patients have clinically significant bacterial overgrowth in the small bowel, and that the condition may be considered as a variant of the blind-loop syndrome[82,83]. However, there is no controlled trial of antibiotics in diabetic diarrhoea and direct evidence of upper small bowel bacterial overgrowth has been obtained in only a few patients[53,80,84]. Evidence of bile acid deconjugation in patients with diabetic diarrhoea has been obtained by means of the ^{14}C-glycocholate (^{14}C-GCA) test[85], which provides further, indirect, evidence of small bowel overgrowth[70]. Of the seven patients studied, four had increased breath $^{14}CO_2$ and normal faecal ^{14}C excretion and responded to antibiotics. After treatment the ^{14}C-GCA test became normal. This test may be used to predict the likely response to antibiotics in patients with diabetic diarrhoea[70].

Bile acid malabsorption has also been implicated in the aetiology of diabetic diarrhoea after a report of symptomatic improvement with cholestyramine[86]. The authors drew attention to the similar clinical improvement with cholestyramine seen in post-vagotomy diarrhoea, where bile acid malabsorption has been demonstrated[87,88]. However, in the series already described[70] evidence for bile acid malabsorption was found in only one patient with diabetic diarrhoea and treatment with cholestyramine was not successful. This contrasts with a report of the ^{14}C-glycocholate test in post-vagotomy diarrhoea in which bile acid malabsorption was observed in five patients, all of whom improved with cholestyramine[89]. Increased deconjugation of ^{14}C-glycocholic acid has also been reported in a series of patients treated with biguanide oral hypoglycaemic agents, none of whom had symptoms of gastrointestinal or liver disease[90]. After antibiotics breath $^{14}CO_2$ excretion was normalised. Thus small intestinal bacterial overgrowth may explain the previously observed malabsorption of vitamin B_{12} in patients taking biguanides[91–93], although these results contrast with an earlier study in which oral tetracycline for seven days only marginally improved B_{12} absorption in four out of five patients taking metformin[92].

Results of small bowel transit studies in these subjects are contradictory. Measurements using balloon kymography have shown reduced motility in

diabetics with autonomic neuropathy compared with controls[94], while radiological studies using barium have been reported as showing both increased and decreased transit[26,53,67,80,95]. Dye-marker methods have also been used with variable results[68,95]. More recently, the measurement of the breath hydrogen appearance time after ingestion of a non-absorbable carbohydrate has been found to provide a simple, non-invasive, method of estimating small bowel transit[96]. By means of this technique small bowel transit has been found to be delayed in diabetics with autonomic neuropathy compared with non-complicated diabetics and controls[97]. Unfortunately, it is not possible to study transit in this way when there is small bowel bacterial overgrowth, as premature hydrogen production will often occur[97].

In summary, it is likely that small bowel transit is reduced in patients with autonomic neuropathy affecting the bowel and that this may result in the development of bacterial overgrowth in some patients. Where small bowel bacterial overgrowth occurs bile acids may be deconjugated which, in turn, can result in diarrhoea. Treatment in these patients would normally be successful with antibiotics, although there remain some patients with diabetic diarrhoea in whom bile acid deconjugation cannot be demonstrated, and in these subjects treatment with antibiotics is unlikely to be effective. Treatment has also been described with cholinergic drugs[68] and sympathomimetic agents[67] with marginal therapeutic effect. Otherwise treatment is largely symptomatic, including careful diabetic control. Loperamide may also prove effective in some antibiotic resistant cases (Scarpello, J. H. B., unpublished observations).

ABSORPTION

There are only a few detailed reports of perfusion studies in the human diabetic[53,98–100], in contrast with the large number of investigations in the experimental animal when diabetes has been chemically induced[101]. In man the results are conflicting with reports that duodenal glucose absorption is both increased[100] and normal[98]. In a recent study[102] the effects of serum insulin and glucose concentrations on jejunal absorption of glucose, sodium and water were compared in insulin-requiring diabetics and healthy controls. Normal absorption was found in the diabetics and no significant alteration in absorption was observed in the controls during periods of increased serum insulin or glucose concentration. The authors speculate that the different results in animal studies, where glucose absorption has usually been found to be increased, may reflect differences in the severity and duration of insulin deprivation. The enzymatic activities of disaccharidases, alkaline phosphatase, and peptide hydrolases, have been measured in small bowel biopsies of maturity- and juvenile-type diabetes[103]. Normal hydrolysis of disaccharides and oligopeptides was found in contrast to the increased digestive enzymatic activities observed in experimental diabetes[104–107]. Absorption studies in patients with diabetic diarrhoea are even fewer. In the most detailed series[53] the jejunal absorption of sodium and water was similar to that of non-diabetic controls.

LARGE BOWEL

Constipation has been reported as a common feature of diabetic neuropathy[4,108], although it is difficult to compare its incidence with that of the normal population. It can be very severe and result in colonic dilatation with

faecal impaction[109]. The aetiology of constipation in these subjects is unclear. It has been suggested that colonic neuropathy occurs as part of the overall diabetic neuropathy[2]. To date there are no studies of colonic motility in diabetes.

Summary

In conclusion, most gastrointestinal complications of diabetes do not produce symptoms. However, in a minority there may be severe nausea, vomiting, diarrhoea, or faecal impaction, associated with considerable morbidity. More research is required into the effects of diabetes on the gut, which should, in turn, result in a better understanding of normal gastrointestinal function. Although at present most symptoms are attributed to the effects of visceral neuropathy, their intermittent nature is difficult to understand and suggests that transient metabolic or hormonal disturbances may be responsible.

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