REVIEW ARTICLE

"Complications of Gastrointestinal System in Diabetes Mellitus"- Neglected Part of Diabetic Management

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Abstract

The incidence and prevalence of diabetes mellitus and its complications are increasing. Like other complications, most of the diabetes patients have gastrointestinal (GI) symptoms but in majority of cases GI complications are under diagnosed and not treated properly, resulting in impairment of the quality of daily life.

GI system including liver and pancreas are involved in diabetes mellitus. These GI complications of diabetes mellitus need proper diagnosis and treatment to get a quality of life and clinician needs clinical suspicion to identify and proper knowledge to treat.

Keywords: Diabetes, Gastrointestinal complications, Diabetic gastroparesis, NAFLD, Pancreatic steatosis, Oral complications, Esophageal complications, Intestinal complications.

Introduction

Diabetes mellitus (DM) is a systemic disease which can affect any part of human body including gastrointestinal (GI) system. More than 70% of diabetes patients attending clinics usually have significant GI symptoms (1,2). The entire GI system can be affected by diabetes including oral cavity, oesophagus, stomach, intestine, liver and pancreas (Figure1). Duration of diabetes, severity and poor gycemic control usually are associated with more severe GI complications. Diabetic patients who have retinopathy, nephropathy and / or neuropathy should be presumed to have GI complications until proven otherwise. Early detection and tight blood sugar control can reduce incidence and prevalence of GI complications of diabetes.

Oral manifestations

The prevalence of xerostomia (dryness of mouth) in diabetic patients ranges between 34% and 51% (3,4) and hyposalivation in diabetes can cause difficulty in eating, swallowing, and speaking. Sialosis (non-inflammatory, asymptomatic, non-neoplastic,

bilateral chronic diffuse swelling of salivary glands mainly affecting the parotid) has been found to be more common in diabetic patients (5). Diabetic patients have taste dysfunction more frequently than healthy individuals (6) due to neuropathy, and inhibiting to maintain a good diet (7). Oral Candidiasis is the most common fungal infection in diabetes patients compared to non-diabetics (8,9). Multiple studies showed that deep neck bacterial infection is more common in patients with diabetes compared to patient without diabetes (10,11). Recurrent apthous stomatitis and oral lichen planus are more common in patients with diabetes than non-diabetic (12). Xerostomia, oral infection, periodontal and sensory disorders could increase the likelihood of developing new and recurrent dental caries and tooth loss (3) in diabetic patients. So it is importance to provide tight glycemic control and good oral care to minimize complications, prevent morbidity in diabetic individuals and to improve the quality of life. (13)

Oesophageal complications of diabetes

Oesophageal candidiasis: Patients with diabetes have an increased risk of oesophageal candidiasis, which may present with painful swallowing and / or difficulty in swallowing. Oesophageal candidiasis is usually diagnosed by endoscopy and/ or biopsy, and treated by tight blood sugar control and anti-fungal medication.

Oesophageal dysmotility: Among diabetic patients, prevalence of esophageal dysmotility is 63% (14). Failed peristalsis or non-conducting waves are more common in diabetic patients who have neuropathy as

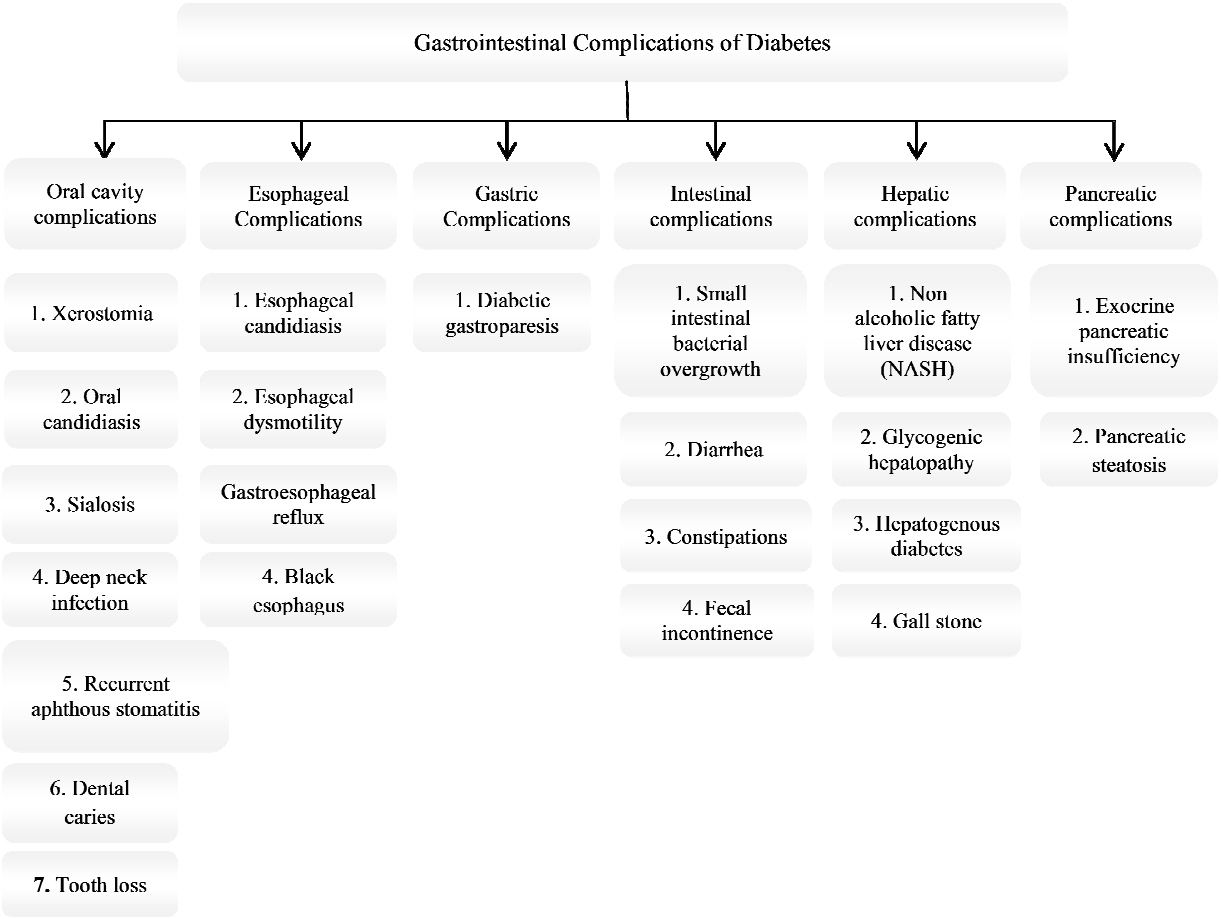

Figure 1. Gastrointestinal complications of diabetes mellitus

compared to those without neuropathy, while high amplitude and broad waves in high resolution manometry were more common in patients who do not have diabetic neuropathy (15). Oesophageal dysfunction in diabetic patients usually asymptomatic but may cause regurgitation of food particle, difficulty in swallowing, and pill-induced esophagitis. It can be diagnosed by manometry and symptomatic cases usually treated by diet modification and advised to drink adequate fluid immediately after taking medications to avoid pill-induced esophagitis.

Gastroesophageal reflux (GERD): Prevalence of gastroesophageal reflux disease in type 2 diabetic patients is higher than non-diabetic patients (16). Prevalence of typical GERD symptoms is similar in both groups with and without peripheral neuropathy but erosive esophagitis is more frequent seen in diabetic patients having neuropathy (17). GERD can be diagnosed by presence of typical symptoms and/ or endoscopy, and treated by acid suppressing agents (Proton pump inhibitor or H2 blocker) and lifestyle modification.

Black oesophagus: Acute oesophageal necrosis (black oesophagus) is a rare oesophageal complication of diabetic ketoacidosis (18) and may be complicated by oesophageal perforation and stricture. Acute oesophageal necrosis has poor prognosis, needs supportive care like oesophageal rest, gastric acid suppression and treatment of underlying disease (19).

Gastric complications

Diabetic gastroparesis: Population-based study (20) reported that incidence of gastroparesis over 10 years in type I DM patients is 5.2% and 1.0% in patients in type 2 diabetes mellitus patients, and higher than non-diabetic individuals (0.2%). Obesity is a significant independent predictor of gastroparesis in patients with diabetic (21). Higher prevalence of gastroparesis is seen in women than in men (22) but other study showed no gender differentiation (23).

Multiple factors including vagus nerve dysfunction, glycemic excursions, diminution of expression neuronal nitric oxide synthase with in the myenteric plexus on the enteric nervous system, disturbance/ loss of interstitial cell of Cajal (specialized pacemaker cells), and proinflammatory state due to excessive oxidative stress might be responsible for gastroparesis in diabetic gastroparesis (24,25). Some drugs used in DM to control blood sugar, such as GLP1 receptor agonists and amylin analog (pramlinitide) can cause delayed gastric emptying (26).

Diabetic gastroparesis patients are usually presented with nausea and vomiting, early satiety, abdominal pain, bloating, postprandial fullness, belching, and weight loss (27).

When diabetes gastroparesis is suspected, first step is to exclude mechanical gastric outlet obstruction by Upper GI endoscopy. Barium meal may be an alternative but inferior to endoscopy.

Technetium- labelled gastric emptying scintigraphy test with low-fat, egg-white, albumin-based meal is the gold standard for diagnosis of diabetic gastroparesis (28,29). Delayed gastric emptying is diagnosed if there is greater than 60% retention at 2 h or 10% retention at 4 h after food intake (30). It is recommended that fasting glucose level should be < 275 mg/dl before the test and prokinetic agents (such as metoclopramide, erythromycin, domperidone, etc), opiate medications, and anticholinergic agents should be stopped at least 2 days prior (31).

The wireless motility capsule which detects changes in pH and temperature in addition to whole gut transit time can be used to identify delayed gastric emptying in DM (32). Normal emptying of the capsule from stomach to oesophagus (identified by changing of PH) should occur within 5 h of ingestion and if it takes > 6 hours (a maximum gastric emptying time value is 6 hours), indicates gastroparesis (32). This test is contraindicated in children and in adult patients having oesophageal stricture.

$^{13}CO_2$ breath test using octanoic acid can be used to detect gastroparesis in diabetes. This investigation may be as accurate as gastric-emptying scintigraphy (34). It is also less expensive and easier to perform than gastric emptying scintigraphy.

The standard treatment of symptomatic diabetic gastroparesis is tight blood sugar control (to maintain glucose levels < 180 mg/dl to avoid inhibiting effect of blood sugar on gastric myoelectric control and motility), diet modification, prokinetic drugs, anti-emetics, and in severe cases gastric pacemaker implantation and surgical procedures.

Intestinal complications in diabetes

In patients with diabetes, small intestinal transit often is abnormal such as slow or rapid and up to 80% patients with diabetic gastroparesis patients have abnormal small intestinal motility (35).

Diarrhoea: Diarrhoea is seen in up to 20% of patients with diabetes due to diabetic enteropathy (36). Due to involvement of enteric nerves of the small intestine in diabetes, there is abnormal motility, secretion, or absorption in the small intestine which leads to delayed emptying and stagnation of fluids, resulting in bacterial overgrowth syndromes (SIBO), bloating, diarrhea and abdominal pain. Small intestinal bacterial overgrowth is found in up to 40% of diabetic patients with diarrhea (37). Though the diagnostic test requires small-bowel intubation, aspiration of small intestinal fluid and quantitative cultures of fluid, Breath hydrogen testing and the ($_{14}$C)-D-xylose test may be helpful in diagnosis of SIBO as well. SIBO is treated by short term or intermittent (in case of recurrent SIBO) use of antibiotics. Rifaximin is the most extensively studied agent in SIBO treatment.

Other causes of diarrhoea in diabetes are hyper motility caused by decreased sympathetic inhibition, pancreatic insufficiency, steatorrhea, and drugs used in diabetes (Metformin, Acarbose, Voglibose, etc).

Diarrhoea (other than SIBO) in diabetic patients is mainly treated empirically such as correcting fluid and electrolyte imbalances, improving nutrition and blood glucose control, managing any underlying cause and Ant diarrheal agents.

Constipation: In long standing diabetes mellitus, constipation is one of the most common complications affecting up to 60% patients (38) due to myenteric neuronal loss and evidence of increased oxidative stress (39). The frequency of constipation is higher in patients with diabetes than in the general population. Patients whose glycated hemoglobin (HbA1c) levels are >7, has a greater association with constipation than diabetic patients with HgA1c values within the normal range. Prevalence of constipation is usually 22% in patients with diabetes with autonomic neuropathy, and is significantly more common than in diabetic patients without neuropathy (40). Constipation in diabetes is initially treated by tight glycemic control and life style modification (Diet modification + plus Exercise). For patients who are not responding to above measures, laxatives should be the next step of treatment. Treatment should begin with bulking agents followed by osmotic laxatives if response is poor. Lactulose, polyethylene glycols are the most frequently used osmotic agents. Chloride-channel activators (Lubiprostone) and 5-HT4 agonist (Pruclopride) can be used for severe or resistant cases (41). Linaclotide (guanylate cyclase C agonist) is approved for the management of constipation variant of irritable bowel syndrome and chronic constipation without known cause but has not been evaluated in diabetes.

Fecal incontinence: It can also be seen in acute hyperglycaemia and glucose excursions due to inhibition of rectal sphincter function and decreasing rectal sensation to distension (42,43). Diagnostic approach to fecal incontinence in diabetic patients is similar to that for the general population. Loperamide can be useful in fecal incontinence.

Pancreatic involvement in diabetes

Pancreatic exocrine insufficiency: Twenty percent insulin independent patients and 30-50% insulin dependent patients are suffering from pancreatic exocrine insufficiency (44,45). One study showed that benefit of fecal elastase-1 estimation (surrogate marker of exocrine pancreatic insufficiency) in subclinical patients (46). However, pancreatic function tests are not routinely used to diagnose PEI.

The proposed explanations for development of PEI in diabetes patients are: 1) regulatory properties (stimulating-inhibitory balance) of islet cell for exocrine tissue functions changes in diabetic patients (47), 2) In insulin deficiency trophic effect of insulin on pancreatic acinar cell is reduced, results in pancreatic acinar atrophy (48), 3) Decrease in the enteropancreatic reflex and exocrine functions due to autonomic neuropathy and gastroparesis in diabetes (49), 4) antibodies against pancreatic islet cells may cross-react against the acinar cell and/ or antibodies against exocrine pancreatic tissue (anti-cytokeratin antibodies) may cause pancreatic insufficiency (50,51), 5) blood supply to the pancreas is impaired due to microvascular complications, resulting in pancreatic fibrosis and exocrine pancreatic insufficiency (52,53), 6) inhibitory effect on pancreatic external secretion of diabetic acidosis, 7) impaired excretion of gastrointestinal regulatory mediators.

Symptoms of exocrine pancreatic insufficiency are clinically manifested when duodenal lipase concentration is below 5-10% of normal postprandial level. PEI causes interruption in fat absorption resulting in steatorrhea and weight loss.

After exclusion of other causes, PEI is diagnosed by measuring elastase-1 level in a stool specimen. Stool faecal elastase-1 level in between 100 µg/g and 200 µg/g indicate mild PEI, while level < 100 µg/g indicates severe PEI.

Pancreatic enzyme replacement therapy (PERT) can be used in PEI patients with clinical manifestations. A cumulative quantity of 25 000–50 000 U of exogenous lipase is required intraduodenally for digestion of a regular meal, so higher doses of lipase supplements are need probably because of partial acidic destruction of orally administered pancreatic enzymes (54). The minimum recommended dose of exogenous lipase is 25 000 - 40 000 IU per meal and then titrated depending on the clinical response (55).

Pancreatic steatosis: Radiologically normal individuals have up to 6.2% fatty infiltration in pancreas. Excess ectopic fat infiltration has been linked to insulin resistance (56), and there is negative association between pancreatic fat content and insulin secretion (57). Patients with type II diabetes have higher pancreatic fat content than normal individuals (58).

Pancreatic steatosis (PS) is can be diagnosed by using different imaging techniques such as abdominal ultrasonography, CT scan abdomen, MRI abdomen and or Endoscopic ultrasonography.

Pancreatic steatosis has several clinical significances because it can be responsible for post-operative pancreatic fistula formation, carotid atherosclerosis, severity of acute pancreatitis, development of subclinical chronic pancreatitis, development of pancreatic cancer and pancreatic exocrine deficiency. (59)

Till now there are no approved drugs for management of pancreatic steatosis and its treatment depends upon the underlying cause.

Hepato-biliary injury in diabetes

Serum alanine aminotransferases (ALT) elevation is common in patients with type 2 diabetes but uncommon (0.5%) in apparently normal subjects (60) and the most common cause of mild elevation of ALT is non-alcoholic fatty liver disease (NAFLD) (61).

Non-alcoholic fatty liver disease:

The prevalence of NAFLD in diabetes is 34–74% (62,63) and when diabetes is associated with obesity, it is around 100% (64). 69% of

patients with type II Diabetes have NAFLD during abdominal ultrasonographic examination (65). Strong association has been observed between NASH, insulin resistance and increased level of free fatty acids in the liver (66,67). Although the majority of NAFLD patients are asymptomatic, it may lead to tender hepatomegally, elevated serum alanine aminotransferases, and right upper abdominal pain-discomfort, and this may progress to fibrosis and cirrhosis of the liver in less than 20% cases. Mortality due to liver problems is higher in this group of patients than in the general population.

American Association for the Study of Liver Diseases (AASLD) guideline is used to detect NAFLD which includes presence of hepatic steatosis by imaging or histology, absence of significant alcohol intake (According to Asia-Pacific Guidelines: significant alcohol intake is considered when > 7 standard alcoholic drinks/week (70 g ethanol) in women and > 14 (140 g) in men; according to AASLD: significant alcohol consumption indicates > 21 standard drink on average per week in men and > 14 in women; according to EASL guideline: significant alcohol consumption is considered when > 30 g/d in men and > 20 g/d in women), exclusion of other aetiologies of hepatic steatosis. To assess the presence of steatosis, all above guidelines mentioned following scoring index, such as Fatty Liver Index (calculated from serum triglyceride, body mass index, waist circumference, and gamma-glutamyltransferase) (68) and NAFLD liver fat score (calculated by evaluating the presence/absence of metabolic syndrome and type 2 diabetes, fasting serum insulin, and aminotransferases) (69).

Liver biopsy is gold standard to detect presence of steatohepatitis and fibrosis in patients with NAFLD but now a day's several noninvasive measures are available to identify hepatic steatosis (Controlled attenuation parameter or CAP value from fibroscan and measurement of circulating levels of cytokeratin-18 fragments level) (70-72) and fibrosis (NAFLD fibrosis score (NFS), Fibrosis 4 calculator (FIB-4), aspartate aminotransferases (AST) to platelet ratio index (APRI), Fibrometer, FibroTest, transient elastography, magnetic resonance elastography (MRE) and shear wave elastography) (73-76).

Median cut-off value of fibroscan (Transient elastography) to identify advanced fibrosis in patients with NAFLD has been established to 9.9 kpa with 95% sensitivity and 77% specificity (77). Liver stiffness value of < 5.6 kpa is considered as no fibrosis or mild fibrosis and a cut-off value ≥ 17 kpa is considered to be optimal for discrimination of liver fibrosis from liver cirrhosis in NAFLD patients (78).

Management of NAFLD includes treatment of underline disease (in diabetic patient: tight blood sugar control), Lifestyle modification which includes diet modification, exercise and weight reduction in obese patients. Lifestyle modification (LM) is an effective treatment to reduce hepatic injury in NAFLD patients and serial Fibroscan (transient elastography) can be used to assess the treatment response in NAFLD patients (79). LM reduces fatty infiltration in liver, and controlled attenuation parameter (CAP) can be used to detect the improvement of hepatic steatosis during follow-up (80).

According to AASLD guideline vitamin E (α-tocopherol) can be used at a daily dose of 800 IU/day and/ or Pioglitazone in adults with biopsy-proven non-alcoholic steatohepatitis (NASH). AASLD guideline recommends foregut bariatric surgery in otherwise eligible obese individuals with NAFLD or NASH.

Glycogenic hepatopathy: Glycogenic hepatopathy is characterised by pathological overloading of hepatocytes with glycogen and is usually seen in patients with longstanding poorly controlled type I diabetes mellitus, and manifested by poorly controlled diabetes, hepatic enlargement, altered lipid profile, short stature, cushingoid features and delayed puberty (81). Rapid improvement is seen within 4 wk with tight diabetes control by insulin treatment in these patients (82).

Hepatogenous diabetes: Here diabetes develops in patients with cirrhosis and clinically different from type II diabetes: 1) less frequently associated with microangiopathy and 2) suffer from complications of cirrhosis more frequently (83,84).

Diabetic patients have an increased incidence of gallstones and gall bladder problems, and primarily related to the obesity associated with type 2 diabetes and not to the diabetes itself.

Conclusions

As diabetes is a systemic disease, like other organs (such as kidney, heart, eyes, nerves, etc) GI tract is also involved and this involvement has substantial impact on quality of life in people with diabetes. Complications of GI tract are common but less frequently recognized in clinical practice. Severity of GI complications depends on duration of diabetes, severity of diabetes and the degree of glycemic control. The entire GI tract can be affected, including the oral cavity, esophagus, stomach, intestine, liver and pancreas. Usually asymptomatic when it involves pancreas and / or liver but produces symptoms when esophagus, oral cavity, stomach and / or intestine are involved. Most of the complications are managed by tight glycemic control, diet modification, exercise and treatment of specific complication if present, and improve quality of life.

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Conflict of Interest

Nil.

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