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REVIEW

Gastrointestinal complications of diabetes mellitus

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Abstract

Diabetes mellitus affects virtually every organ system in the body and the degree of organ involvement depends on the duration and severity of the disease, and other co-morbidities. Gastrointestinal (GI) involvement can present with esophageal dysmotility, gastro-esophageal reflux disease (GERD), gastroparesis, enteropathy, non alcoholic fatty liver disease (NAFLD) and glycogenic hepatopathy. Severity of GERD is inversely related to glycemic control and management is with prokinetics and proton pump inhibitors. Diabetic gastroparesis manifests as early satiety, bloating, vomiting, abdominal pain and erratic glycemic control. Gastric emptying scintigraphy is considered the gold standard test for diagnosis. Management includes dietary modifications, maintaining euglycemia, prokinetics, endoscopic and surgical treatments. Diabetic enteropathy is also common and management involves glycemic control and symptomatic measures. NAFLD is considered a hepatic manifestation of metabolic syndrome and treatment is mainly lifestyle measures, with diabetes and dyslipidemia management when coexistent. Glycogenic hepatopathy is a manifestation of poorly controlled type 1 diabetes and is managed by prompt insulin treatment. Though GI complications of diabetes are relatively common, awareness about its manifestations and treatment options are low among physicians. Optimal management of GI complications is important for appropriate metabolic control of diabetes and improvement in quality of life of the patient. This review is an update on the GI complications of diabetes, their pathophysiology, diagnostic evaluation and management.

Key words: Gastrointestinal complications; Diabetes mellitus; Esophageal complications; Nonalcoholic fatty liver disease; Diabetic gastroparesis; Diabetic enteropathy; Glycogenic hepatopathy

Core tip: Although relatively common, gastrointestinal (GI) complications of diabetes mellitus are underrecognized by most physicians. Early identification and prompt management of GI complications are of paramount importance as they are associated with significant morbidity. Common GI complications are esophageal dysmotility, gastro-esophageal reflux disease, gastroparesis, enteropathy, non alcoholic fatty liver disease (NAFLD) and glycogenic hepatopathy. Damage to the myenteric neurons due to longstanding diabetes causes esophageal, gastric and enteric disease. NAFLD is a hepatic manifestation of metabolic syndrome and is commonly seen in type 2 diabetes while glycogenic hepatopathy is due to poor glycemic control in type 1 diabetes. Clinical manifestations, pathogenesis, diagnostic evaluation and management of GI complications of diabetes are discussed in this article.

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INTRODUCTION

The prevalence of diabetes mellitus has now reached epidemic proportions in both developed and developing countries, affecting more than 366 million people worldwide[1]. This number is likely to increase in the coming years as a result of an ageing global population, urbanization, rising prevalence of obesity and sedentary lifestyles. Diabetes affects virtually every organ system in the body and the duration and severity of the disease may have a direct impact on organ involvement. Though gastrointestinal (GI) complications are common in longstanding diabetes, the awareness of these complications is low among physicians. Early identification and appropriate management of GI complications are important for improving both diabetic care and quality of life of the affected patient. This review aims to outline the GI complications of diabetes and the latest management options.

ESOPHAGEAL COMPLICATIONS

The thoracic esophagus and lower esophageal sphincter (LES) are composed of smooth muscle fibres innervated by myenteric plexus, and these autonomic nerves can be affected by diabetic neuropathy in patients with longstanding diabetes. Autonomic neuropathy and structural remodeling of the esophageal musculature in diabetes results in abnormal peristalsis, spontaneous contractions and reduced LES tone[2]. Morphological and biomechanical properties of the esophagus have been found to be altered significantly in animal models of diabetes[3]. The prevalence of esophageal dysmotility in diabetes has been reported to be as high as 63%[4]. The same study also found that there was no difference in dysmotility between patients with type 1 and type 2 diabetes or between genders and there was a strong association with retinopathy. Patients with dysmotility had longer duration of diabetes compared with those without dysmotility. Although the prevalence of esophageal dysmotility is high among patients with diabetes, only a minority present with the classical symptoms of dysphagia and heartburn[5].

The prevalence of gastroesophageal reflux symptoms in diabetes could be as high as 41%[6]. Erosive esophagitis (EE) was more frequent (66.7%) in diabetic patients with neuropathy than those without neuropathy (33.3%); also asymptomatic EE was significantly more frequent in the same group. In patients with type 2 diabetes, peripheral neuropathy is an independent risk factor for EE; however patients may be asymptomatic and a gastroscopy may be recommended in these patients[7]. Circulating levels of adiponectin, a potential anti-inflammatory adipocytokine is inversely related to visceral fat accumulation and it has been shown that the prevalence of gastroesophageal reflux disease is higher in type 2 diabetic patients with metabolic syndrome and low levels of serum adiponectin[8].

Diagnosis of reflux and dysmotility has relied on esophageal pH monitoring and conventional manometry for many years. The use of the wireless Bravo pH capsule, which allows catheter-free monitoring and impedance-pH measurement, a catheter-based technique which allows detection of acid and non-acid reflux have been major developments in the diagnostic field recently[9]. Two new procedures are available to assess esophageal motility: high resolution manometry which uses many pressure sensors and provides spatiotemporal plots of esophageal pressure changes; and impedance manometry, a test that directly measures bolus transit and provides conventional manometric data[9].

Gastroesophageal reflux disease was found to be inversely related to glycemic control and better glycemic control may improve esophageal dysmotility and reflux[10]. Management of reflux disease involves prokinetic drugs, such as metoclopramide and proton pump inhibitors. A two-week course of erythromycin has been shown to reduce mean esophageal transit time and gastric emptying time in type 2 diabetics[11]. Patients are also advised to drink fluids immediately after taking medications to avoid pill-induced esophagitis.

GASTROPARESIS

Gastroparesis, one of the commonest GI complications of diabetes mellitus, produces symptoms of gastric retention in the absence of physical obstruction[12]. The incidence of gastroparesis in a population with diabetes is reportedly low (5.2% over 10 years in type 1 and 1% in type 2 diabetes), but greater than in the general population (0.2%)[13]. Delayed gastric emptying can be demonstrated in 27%-65% of patients with type 1 diabetes and about 30% of patients with type 2 diabetes[14]. The incidence of gastroparesis is higher in women[15]. A recent study has reported obesity as a significant independent predictor of symptoms suggestive of gastroparesis in patients with type 2 diabetes mellitus (T2DM) and neuropathy[16].

Pathogenesis

The pathogenesis of diabetic gastroparesis is multifactorial and currently poorly understood. Delayed gastric emptying may be the first indication of gastroparesis in diabetes[15]. Elevated glycated hemoglobin level, duration of diabetes in excess of 10 years and the presence of macro- and microvascular complications are all accepted risk factors for the development of diabetic gastroparesis. Delayed gastric emptying contributes to poor glycemic control and may be the first indication that the patient is developing gastroparesis. Loss of the normal Migrating Motor Complexes, blunted antral contractions, spasm of the pylorus and small intestine and poor meal accommodation in the stomach are all demonstrable in diabetes[12]. Other factors that may have a role in the pathogenesis includes impaired inhibitory nitric oxide containing nerves, absent or dysmorphic interstitial cells of Cajal, smooth muscle fibrosis and abnormal macrophage- containing immune infiltrates[17,18]. Bezoar formation can contribute to the development of gastroparesis in some individuals. Endoscopic biopsies from diabetic gastroparesis demonstrate abnormal mucosal nerve density and morphology, reflecting possible potential for endoscopic diagnosis

of enteric neuropathy[19]. Neurohumoral factors including glucagon-like peptide-1 (GLP-1) can play a role in gastroparesis and the use of GLP-1 agonists Exenatide and Liraglutide can lead to symptoms of gastroparesis. A recent study showed that deficiency of apolipoprotein E can be a risk factor in diabetic gastroparesis in an animal model[20]. Extrinsic factors such as medications as well as concomitant disorders such as anxiety and depression may result in increased reporting of symptoms.

Clinical features

Symptoms of gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating and upper abdominal pain. Worsening glycemic control along with frequent hypoglycemic episodes or unexplained alternating hyper- and hypoglycemia due to a mismatch between insulin action and carbohydrate absorption should prompt the clinician to evaluate the patient for diabetic gastroparesis. About 53% of patients may experience weight loss but 18%-24% may experience weight gain[14]. More than half of affected individuals present with acute onset of symptoms and the others insidiously. One third of cases have chronic symptoms with periodic exacerbations and one third have chronic worsening symptoms[14]. Epigastric distention and succussion splash may be observed in some patients but physical examination may not be always helpful.

Evaluation

A technical review from the American Gastroenterological Association recommends performing an initial evaluation consisting of careful history taking and physical examination, followed by complete blood count, thyroid stimulating hormone test, metabolic panel and optional amylase and pregnancy test[21]. History taking should particularly focus on macro- and micro-vascular complications of diabetes, although gastroparesis may occur in their absence. Additionally rumination syndrome should be excluded. Physical examination should focus on looking for evidence of peripheral and autonomic neuropathy, epigastric distension and the presence of succussion splash one hour post mealtimes. This is followed by upper GI endoscopy to rule out mechanical obstruction. Alternatively, an upper GI series with small bowel follow-through or small bowel magnetic resonance imaging can be performed. In the presence of significant abdominal pain, an abdominal ultrasound scan should be carried out to rule out biliary colic[16]. Presence of food in the stomach at endoscopy following a 12-h fast, in the absence of gastric outlet obstruction, is strongly suggestive of gastroparesis.

The diagnosis of gastroparesis is made by gastric emptying scintigraphy using ^{99m}Tc sulphur colloid bound to solid food[21]. This noninvasive, quantitative method is considered the gold standard test for diagnosing gastroparesis. The patient ingests a technetium-labeled egg meal and gastric emptying is then measured by scintiscanning at 15-min intervals for 4 h. However this test lacks standardization. A newer four image simplified scanning method has also shown comparable results[22]. The American Neurogastroenterology and Motility Society recommended a test meal of two slices of bread with jam plus two large eggs labeled with technetium-99m sulphur colloid and scintigraphy carried out at 0, 1, 2 and 4 h post prandially. A diagnosis of gastroparesis can be made if there is > 90% retention at 1 h, > 60% at 2 h and > 10% at 4 h[23].

An alternative method for gastric emptying study uses an indigestible wireless motility capsule (WMC), which senses intraluminal pH, temperatures and pressures as it traverses the gastrointestinal tract. The capsule wirelessly transmits the data to a receiver worn by the patient until it is excreted. WMC gastric emptying times greater than 5 h are said to be delayed, and this correlates with scintigraphic measurements[24]. Non-radioactive ^{13}C-breath tests quantify exhaled $^{13}CO_2$ after duodenal assimilation of a standardized substrate (octanoate, spirulina platensis) and are an alternative to scintigraphy[25]. The main advantage of these newer technologies is the lack of radiation exposure; however their general availability is limited.

Selected patients can be offered additional testing to exclude other contributions to the symptoms. Antroduodenal manometry excludes small bowel dysmotility, found in 17%-85% of gastroparetics[12]. Electrogastrography (EGG) can be used to detect rhythm disruptions and blunted postprandial responses. However a recent study has demonstrated the relative insensitivity of clinical EGG methodologies[26].

Treatment

Gastroparesis treatments include general measures, dietary modifications, medications that enhance emptying or lessen vomiting, non-medication interventions, psychological therapies and consideration of more invasive surgical treatment[12]. A grading system for assessing severity and guiding the management of gastroparesis has been suggested (Table 1)[27].

General approaches and dietary modifications

General approaches to management of gastroparesis include ensuring good hydration, correcting electrolyte imbalances, management of glycemic control and symptom reduction with pharmacotherapeutic agents. Any medications that can delay gastric emptying should be discontinued if possible. Dietary modifications include increasing liquid-based meals (as the rate of emptying liquid from the stomach is usually the same in diabetic gastroparesis), reducing fat and non-digestible fibre intake, avoiding large meals with high calorie contents and ensuring small frequent meals spread throughout the day.

Maintaining euglycemia has been one of the main principles of managing diabetic gastroparesis. Prolonged postprandial hyperglycemia has been observed in patients with diabetic gastroparesis compared to those with normal gastric emptying[28]. Another study observed a reduction of 1.8% in hemoglobin A_{1C} after initiating insulin

Table 1 Classification of severity of gastroparesis

Grade 1: Mild	Symptoms easily controlled Regular diet/minor dietary modifications helps to maintain normal nutritional status
Grade 2: Compensated	Moderate symptoms that are reasonably controlled with prokinetics and anti-emetics Maintenance of nutrition with diet/lifestyle changes Hospitalizations-infrequent
Grade 3: Gastric failure	Refractory symptoms Inadequate nutrition Needing hospitalization for therapy and nutritional supplementation (either enteral or parenteral) May need surgical or endoscopic intervention or gastric "pacemaker"

Originated from Abell *et al*[27].

Table 2 Drugs useful in treatment of diabetic gastroparesis

Drug/drug group	Mechanism of action	Common side effects	Efficacy
Metoclopramide 10 mg 4 times/d	Anti-emetic, reduces nausea and post-prandial fullness, increases gastro-esophageal sphincter tone and improves antro-pyloro-duodenal coordination	Tardive dyskinesia, drowsiness, irritability, extrapyramidal symptoms and dystonic reactions	Symptom control in 1/3 to 2/3 of patients
Domperidone 10 -20 mg 3 times/d	Similar to metoclopramide with fewer CNS side effects due to a predominant peripheral mechanism of action	May prolong QTc interval in ECG; in turn may provoke cardiac arrhythmia	Effective in up to 60% of cases; tachyphylaxis develops in a few weeks requiring discontinuation
Erythromycin 50-250 mg thrice daily	Motilin receptor agonist. Reduces gastric emptying time	Nausea and vomiting at high doses	Modest symptom control Intravenous form can be useful in refractory vomiting
Promethazine, prochlorperazine and chlorpromazine	Mechanism of antiemesis poorly understood	Drowsiness, liver injury and extrapyramidal effects	Marginal improvement of symptoms Intramuscular chlorpromazine is very effective in refractory vomiting
Ondansetron	Central serotonin receptor (5-HT3) antagonist Inhibits vagus nerve	Extrapyramidal effect	Modest efficacy

Originated from Hasler[12]. CNS: Central nervous system; ECG: Electrocardiogram; QTc: Corrected QT interval.

pump therapy[29]. This eventually reduced the number and length of hospitalizations for diabetic gastroparetics.

Prokinetics

Prokinetics are medications that augment gastrointestinal motility. In general these increase gastric motility and enhance stomach emptying. Medications commonly used in treatment are shown in Table 2.

Mosapride is a selective 5-HT$_4$ agonist that accelerates gastric emptying. Orally administered mosapride citrate has been associated with significantly increased food intake in ob/ob obese mice, with a tendency to decrease fasting blood glucose and fructosamine concentrations compared with controls[30]. A recent study reported symptom reductions in interferon induced gastroparesis in hepatitis C patients, treated with mosapride[31]. Other agents with gastric stimulating effects in gastroparesis include the new 5-HT$_4$ agonists prucalopride, velusetrag, naronapride and the acetycholinesterase inhibitor acotiamide, although their benefits are yet to be proven[12].

Ghrelin is peptide hormone secreted by the gastric fundic mucosa and pancreas. It is the first identified circulating hormone that controls hunger. One important physiological action of ghrelin is regulation of gastric motility[32]. Intravenous use of the ghrelin agonist TZP-101 was reported to reduce nausea and vomiting in patients with diabetic gastroparesis when compared to placebo[33]. Another study with the oral ghrelin analog TZP-102 also reported overall and individual reduction in the symptoms of diabetic gastroparetics[34].

Some published case reports have also claimed efficacy for the dopamine antagonist thiethylpeazine, the neurokinin NK1 antagonist aprepitant and the antidepressant mirtazapine. A retrospective study reported decreased symptoms in 88% of diabetics with tricyclic antidepressants. The herbal extract STW5 (iberogast) is also reported to be beneficial in functional dyspepsia and gastroparesis[12].

Endoscopic and surgical treatments

Mearin *et al*[35] proposed pyloric spasmodic contractions as one of the factors delaying gastric emptying. Endoscopic pyloric injections of botulinum toxin have been tried in the management of gastroparesis. This neurotoxin inhibits the release of acetylcholine at the neuromuscular junction, causing paralysis of the pylorus. Improved symptoms and accelerated gastric emptying persisting up to 3-6 mo were reported with pyloric botulinum toxin injections, especially in women and those with idiopathic gastroparesis[36]. It was also observed to be more beneficial in older men with vomiting[37]. However, small underpowered placebo-controlled trials did not show superior

responses for botulinum toxins *vs* placebo.

Gastric electrical stimulator implantations have also been shown to have benefits extending for more than 10 years and giving up to 80% reductions in nausea and vomiting. Additionally, there are reported improvements in nutritional and metabolic status, quality of life and health care utilizations[38]. Despite this, most studies show no effect on measured gastric emptying. One recent study showed improved symptoms in gastroparetics with gastric stimulators due to reduced gastric retention in diabetic patients[39]. Other newer technology in this field includes use of miniature wireless gastric stimulators inserted during endoscopy[40]. More studies are needed to ascertain the efficacy compared to other procedures.

Surgical treatments are rarely performed and are mainly reserved for patients with refractory gastroparetic symptoms who have failed to improve with other measures. A recent study demonstrated about 83% symptom reduction in gastroparetics after Heineke-Mikulicz pyloroplasty[41]. Completion gastrectomy was shown to give long-term symptom relief in some patients with post surgical gastroparesis, but data on patients with diabetic gastroparesis are limited. The possible benefits of pancreatic transplants for diabetic gastroparesis have not been proved[12].

Other measures include jejunostomy feeding and total parenteral nutrition. Jejunostomy feeding improves overall health and shows trends towards reduced healthcare utilization in diabetic gastroparesis[42]. The role of venting percutaneous gastrostomy in refractory idiopathic gastroparesis is controversial. One study reported symptom improvement as well as improvement in nutritional and functional status in patients with idiopathic gastroparesis[43]. Total parenteral nutrition can reverse rapid weight loss and ensure adequate sustenance and is usually used in patients with associated intestinal dysmotility[12].

ENTEROPATHY

Small intestinal and colorectal dysfunctions are common in patients with longstanding diabetes, especially in those with gastroparesis[44]. Diabetes-related enteropathy may present with diarrhea, constipation or fecal incontinence. The mechanism of development of enteropathy is similar to that of upper GI involvement in diabetes[45]. Advanced glycation end products (AGEs) cause damage to cellular DNA and tissues in diabetes. AGEs and their receptors are increased in the ganglia, crypt and brush border of diabetic jejunum and ileum as well as in the ganglia of diabetic colon in animal models[46]. Damage to the myenteric nerve plexus due to autonomic neuropathy and fibrosis of the intestinal muscular layers result in stasis of the intestinal contents. Reduced bowel motility results in constipation that may sometimes lead to overflow incontinence. Small intestinal bacterial overgrowth (SIBO), which can result in diarrhea, is usually a consequence of intestinal stasis.

Constipation alternating with diarrhea is one of the most common symptoms of diabetic enteropathy. The diarrhea is typically painless, may be associated with fecal incontinence and occurs during the day but more often at night[47]. Characteristically, it is seen in patients with poorly controlled diabetes who have peripheral and autonomic neuropathy[48]. Other causes of diarrhea in diabetics include pancreatic insufficiency, bile salt malabsorption, steatorrhea and drugs (Metformin). These should be excluded by appropriate investigations before making a diagnosis of diabetic enteropathy.

Constipation is a common problem affecting up to 60% of patients with long-standing diabetes mellitus[49]. Severe constipation leading to megacolon or colonic intestinal pseudo-obstruction occurs rarely. Stercoral ulcer, perforation and overflow diarrhea are encountered infrequently.

Fecal incontinence, particularly nocturnal, due to internal and external sphincter dysfunction secondary to autonomic neuropathy is a troublesome symptom. Acute hyperglycemia has been shown to inhibit external anal sphincter function and decrease rectal compliance, potentially increasing the risk of fecal incontinence[50].

Patients should undergo endoscopic examination, ultrasound or computed tomography to exclude other diagnosis. Although aspiration and direct culture of jejunal contents are regarded by many as the gold standards for the diagnosis of SIBO[51], these methods have several limitations, including the potential for contamination by oropharyngeal bacteria during intubation, and the fact that bacterial overgrowth may be patchy and may be missed by a single aspiration. Non-invasive diagnostic tests for SIBO are largely based on excretion of hydrogen in exhaled breath, following metabolism of carbohydrate by luminal bacteria. These tests have a specificity of 80%, but lack sensitivity (40%) and have their own limitations[52]. A radio opaque marker test is useful for excluding possible slow transit constipation. Tests for fecal incontinence include endoanal ultrasound and anorectal manometry.

Treatment of diabetic diarrhea mainly involves symptom relief, correction of fluid and electrolyte deficits, improvement of nutrition and glycemic control, and management of underlying causes[53]. Anti-diarrheal agents should be used with caution as there is a risk of toxic megacolon. Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract, has broad spectrum *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria, and has low risk of inducing bacterial resistance[54,55]. It has been shown to eradicate bacterial overgrowth in up to 84% of patients[56]. Other antibiotics used to treat this condition include amoxicillin-clavulanic acid, doxycycline, ciprofloxacin, metronidazole, neomycin and norfloxacin. There are anecdotal reports of successful treatment with somatostatin analogues of otherwise intractable secretory diarrhea in diabetic patients with autonomic neuropathy[57,58].

Loperamide may prove useful in fecal incontinence. Constipation may be treated with prompt hydration, reg-

ular exercise and increased intake of dietary fibre. Lactulose and osmotic laxatives may be necessary in more severe cases. Newer drugs for treatment of chronic constipation include prucalopride, a selective 5-HT$_4$ receptor agonist that enhances colonic transit and lubiprostone, which stimulates colonic water and electrolyte secretion through activation of type 2 chloride channels in enterocytes. They may prove useful in the future for treatment of chronic constipation in diabetes mellitus due to autonomic neuropathy and slow transit.

NONALCOHOLIC FATTY LIVER DISEASE

The definition of nonalcoholic fatty liver disease (NAFLD) requires that there is evidence of hepatic steatosis, either by imaging or by histology, and that there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders[59]. NAFLD is considered to be the hepatic manifestation of metabolic syndrome[60]. Metabolic syndrome encompasses the clinical tetrad of hyperinsulinemia with insulin resistance, visceral obesity, dyslipidemia and hypertension. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity (60%-95%), diabetes mellitus (28%-55%) and dyslipidemia (27%-92%) and, less clearly, with raised arterial pressure[61]. Histologically, NAFLD is further subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH).

Data from various studies indicate that the prevalence of NAFLD in the general population ranges from 6.3% to 33%. NAFLD is now the most common cause of chronic liver disease in North America, and it is estimated that 30% of the population of the United States has NAFLD[62]. In an ultrasonographic study, 69% of patients with T2DM had NAFLD[63]. Another study showed a prevalence of 62.3% (127 of the 204 diabetes patients had a fatty infiltration on ultrasound) and 87% of these patients with fatty infiltration who consented to biopsy had histological confirmation of the condition[64].

Clinical features, course and prognosis

Although the majority of patients with NAFLD are asymptomatic, some may present with nonspecific symptoms such as malaise and right upper quadrant pain. Clinical disease in NAFLD ranges from mild elevation of liver enzymes to severe liver disease with fibrosis and nodular degeneration. A recent study identified that approximately 30% of NAFLD cases with isolated steatosis will progress to NASH and, of these, approximately 20% will develop cirrhosis. About 40% of these cirrhotic patients develop decompensated liver disease[65].

Patients with simple fatty change had no increase in mortality, whereas patients with NASH had reduced survival and more cases died from cardiovascular disease (15.5% *vs* 7.5%) than liver related disease (2.8% *vs* 0.2%)[66]. Another long term study, conducted in Minnesota United States, of 420 patients in the community with NAFLD showed higher mortality in patients with impaired fasting glucose and cirrhosis, when compared with the general population. Liver-related mortality was also higher in this group than in the general population (13% *vs* < 1%)[67].

Hepatocellular carcinoma (HCC) is a well recognized complication of cirrhosis due to NAFLD[68-71]. Diabetes, obesity and cirrhosis-associated carcinogenic factors may have roles in the development of HCC in patients with NAFLD[68,70,72]. Presence of diabetes, elevated body mass index and liver fibrosis were identified as risk factors for progression to HCC among NAFLD cases[73]. Recent evidence from animal models shows that metabolic syndrome itself is high risk state for the development of NASH and HCC[74].

Pathogenesis

The development of NAFLD involves complex mechanisms and the relationship between T2DM and NAFLD is depicted in the Figure 1. Obesity, insulin resistance and metabolic syndrome are linked to the development of NAFLD[75]. It is now postulated that a combination of "multi hits" leads to development of steatohepatitis. This concept has replaced the earlier two hit hypothesis[76,77]. There is strong association between NASH, insulin resistance and increased level of free fatty acids in the liver[78,79]. Several factors including tumor necrosis factor alpha, oxidative stress, adiponectin, leptin, apoptosis and genetic factors are believed to have a role in the pathogenesis of NAFLD and NASH.

Evaluation

According to guidelines from the American Association for the Study of Liver Diseases (AASLD), the diagnosis of NAFLD requires that there is hepatic steatosis by imaging or histology, there is no significant alcohol overconsumption, there are no competing etiologies for hepatic steatosis, and there are no co-existing causes for chronic liver disease[59].

The following conditions should be excluded: history of alcohol intake > 20 g/d, nutritional causes (*e.g.,* total parenteral nutrition and rapid weight loss), metabolic disorders (glycogen storage disorders), chronic hepatitis C (particularly genotype 3), other causes of chronic liver diseases (autoimmune liver disease, Wilson's disease and hemochromatosis) and endocrine disorders such as polycystic ovary syndrome, hypopituitarism and hypothyroidism. Drug-induced steatosis can be caused by a number of agents including glucocorticoids, synthetic estrogens, amiodarone, methotrexate and highly active antiretroviral drugs. NAFL is considered benign whereas NASH can progress to cirrhosis, liver failure, and liver cancer.

Liver biopsy is considered the most reliable approach for identifying the presence of steatohepatitis and fibrosis in patients with NAFLD, but its limitations include cost, sampling error, and procedure-related morbidity and mortality. Features of the metabolic syndrome can predict the presence of steatohepatitis in patients with

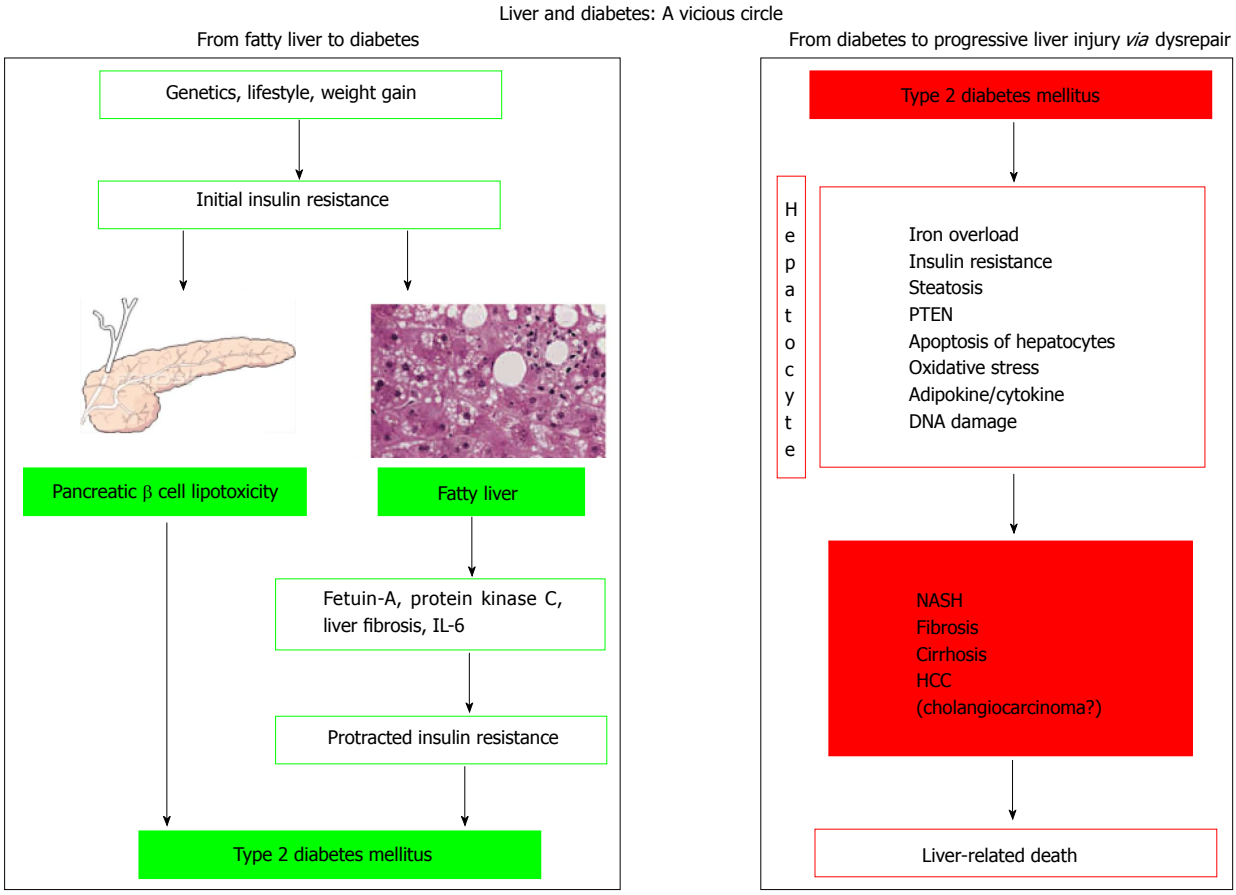

Figure 1 Molecular mechanisms involved in the vicious circle linking fatty liver to diabetes and diabetes to progressive liver injury. Left: The first part of the journey, leading from initial insulin resistance to fatty liver and eventually to the development of type 2 diabetes mellitus (T2DM) in those predisposed individuals in whom pancreatic lipotoxicity occurs; Right: The mechanism that (triggered by long-lasting/decompensated T2DM) may be conducive to progressive liver disease including primary liver cancer in predisposed individuals. HCC: Hepatocellular carcinoma; IL: Interleukin; NASH: Non-alcoholic steatohepatitis; PTEN: Phosphatase and tensin homolog. Reproduced from Loria *et al*[121].

NAFLD. Hence, liver biopsy is recommended in patients with NAFLD who have the metabolic syndrome[80-84]. There has been increasing interest in developing non-invasive methods to identify fibrosis in patients with NAFLD. NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis. In a meta-analysis of 13 studies consisting of 3064 patients, it was shown that NAFLD Fibrosis Score has a 90% sensitivity and 60% specificity to exclude advanced fibrosis and 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis[83]. The NAFLD Fibrosis Score is based on six variables [age, body mass index (BMI), hyperglycemia, platelet count, albumin, aspartate aminotransferase/alanine aminotransferase ratio] and it is calculated using the published formula (http://nafldscore.com).

A novel biomarker that has been investigated for the presence of steatohepatitis in patients with NAFLD is circulating levels of cytokeratin-18 fragments[85,86]. This has a sensitivity of 78% and specificity of 87% for identifying steatohepatitis in patients with NAFLD. Transient elastography (TE), which measures liver stiffness non-invasively, showed high sensitivity and specificity for identifying fibrosis in NAFLD in a recent meta-analysis[85]. However, TE has a high failure rate in individuals with a higher BMI. There is some evidence that the Enhanced Liver Fibrosis test which uses the fibrosis markers hyaluronic acid, amino-terminal propeptide-of-type-Ⅲ-collagen and tissue-inhibitor of matrix-metalloproteinase-1, compares favourably with the use of TE[87].

Management

The management of patients with NAFLD consists of treating liver disease and the associated metabolic co-morbidities such as obesity, hyperlipidemia, insulin resistance and T2DM.

Lifestyle modification and weight reduction: Modifications in diet and lifestyle along with weight reduction and exercise are the cornerstones of treatment of NAFLD, as it is a disease related to excess weight and sedentary lifestyle. Many studies have shown that lifestyle modification can reduce aminotransferase levels and improve hepatic steatosis when measured either by ultrasound[88-91] or MR imaging and spectroscopy[92-95]. A randomized study of 31 obese persons with NASH who

underwent intensive lifestyle changes (diet, behaviour modification and 200 min a week of moderate physical activity for 48 wk) *vs* structured basic education alone showed improvement in steatosis, necrosis and inflammation in the obese group and participants with 7% weight loss had significant improvement in steatosis, lobular inflammation, ballooning, and NAFLD Activity Score[96].

Insulin sensitizing agents: Insulin resistance plays a key role in the pathogenesis of NAFLD. The two main classes of insulin-sensitizing drugs used in the management of patients with NAFLD/NASH are biguanides (metformin) and the thiazolidinediones (pioglitazone).

Metformin increases insulin sensitivity by decreasing hepatic gluconeogenesis and decreasing triglyceride production[97]. Early small, open-label studies showed a reduction in insulin resistance and serum levels of aminotransferases[98-100] but no significant improvement in liver histology[99,100]. A recent meta-analysis examining effects of medical treatment and/or lifestyle intervention did not show significant benefit of metformin in NAFLD[101]. Metformin showed no effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH.

Pioglitazone has been available for over a decade for the treatment of T2DM. It acts by promoting peripheral and hepatic insulin sensitivity and increasing circulating levels of adiponectin[102]. A recent meta-analysis showed that pioglitazone improved histological disease activity, glucose, lipid and inflammatory variables and delayed fibrosis progression in patients with NAFLD[101]. The current recommendation by AASLD is that Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH, although the long term safety and efficacy of pioglitazone in patients with NASH is unknown.

Vitamin E: The antioxidants vitamin E and betaine were investigated as potential therapeutic agents in NASH[103,104]. When administered for 2 years vitamin E improved liver histology, but increased insulin resistance and plasma triacylglycerols[101]. Therefore, the current recommendation by the AASLD is that vitamin E (α-tocopherol), administered at a daily dose of 800 IU/d should be considered as first-line pharmacotherapy for non-diabetic adults with biopsy-proven NASH. However, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis or cryptogenic cirrhosis due to lack of supporting evidence.

Incretin mimetics: Incretins are a group of gastrointestinal hormones released after food intake that enhance insulin release from pancreatic beta cells. The most studied among these hormones is GLP-1. The role of the GLP-1 analogues exenatide and liraglutide in the management of T2DM in obesity is well established. These drugs may emerge as new options in management of NAFLD because of similar mechanisms in its pathogenesis.

Dipeptidyl-peptidase Ⅳ (DPP4) inhibitors were introduced as an alternative means to increase GLP-1 activity. There is increased serum DPP4 activity in patients with NASH, and this has a positive correlation with the histological grade and degree of liver steatosis[105] DPP4 inhibitors are already established oral treatments for type 2 diabetes[106], and data from experimental studies suggest that they may also reduce liver inflammation and steatosis[107]. Incretin mimetics may, in the future, represent a novel therapeutic option for slowing the progression of NAFLD.

Omega-3 fatty acids: So far, there is no clear evidence for the use of omega-3 fatty acids for the specific treatment NAFLD and NASH[108]. A large multicenter study of omega-3 fatty acid (eicosapentanoic acid) for treatment of NASH is ongoing in the United States.

Other agents: Orlistat, Sibutramine and Rimonabant (a cannabinoid receptor antagonist) have all been investigated for their potential as weight loss medications in NAFLD/NASH, although Sibutramine and Rimonabant have been withdrawn due to their side effects[109]. A single large multicenter randomized controlled trial showed that ursodeoxycholic acid offers no histological benefit over placebo in patients with NASH[110]. Recent data from animal models showed that consumption of hydrogen-rich water may be an effective treatment for NASH by reducing hepatic oxidative stress, apoptosis, inflammation, and hepatocarcinogenesis[111].

Bariatric surgery: AASLD recommends that foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH. In a study of 381 adult obese patients by Mathurin *et al*[112] there was a significant improvement in the prevalence and severity of steatosis and ballooning at 1 and 5 years following bariatric surgery. A recently published Cochrane review concluded that lack of randomized clinical trials or quasi-randomized clinical studies precludes definitive assessment of the benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH[113].

GLYCOGENIC HEPATOPATHY

Glycogenic hepatopathy is defined as pathological overloading of hepatocytes with glycogen leading to hepatic enlargement and/or derangement of liver enzymes and is usually seen in patients with longstanding poorly-controlled type 1 diabetes mellitus (T1DM)[114]. Glycogen accumulation in the liver was first described in 1930 as a component of Mauriac's Syndrome. This syndrome was characterized by unstable diabetes, hepatomegaly, hyperlipidemia, dwarfism, cushingoid features and delayed sexual maturity. It is now recognized that glycogen accumulation within hepatocytes can be present without all the findings described in Mauriac's Syndrome. Inadequate

control of T1DM results in concomitant presence of insulin and excess glucose that increases glycogen storage in the liver. Insulin activates the enzyme glycogen synthase phosphatase which dephosphorylates and activates glycogen synthase, another enzyme that is required for the conversion of glucose-1-phosphate to glycogen[115]. This results in increased glycogen storage in the liver and blocks glycogenolysis. The histological picture is characterized by pale appearance of the hepatocytes with compression of the sinusoids, glycogenated nuclei and giant mitochondria. Steatosis may be present, usually mild, or absent. Glycogen accumulation, the hallmark of this condition is demonstrated by PAS-diastase staining[114].

The disease is under-recognized and usually presents with abdominal pain, nausea, vomiting and abnormalities in liver function tests. While hepatic dysfunction is usually due to NAFLD in T2DM, liver dysfunction in T1DM usually results from glycogenic hepatopathy. It cannot be distinguished from NAFLD clinically or by ultrasound and confirmation requires a liver biopsy. The disorder should be suspected when liver dysfunction occurs in patients with T1DM, especially when viral, autoimmune and metabolic liver diseases are excluded by laboratory investigations. The hallmark of this condition is its reversibility with improved glycemic control. Unlike hepatic steatosis, glycogen overload is not known to progress to fibrosis distinct from fatty liver disease[116]. Prompt improvement with optimal diabetes control by insulin treatment within 4 wk is usually seen in these patients[117,118].

HEPATOGENOUS DIABETES

Up to 79% of cirrhotic subjects can have abnormalities of glucose metabolism[119]. T2DM is usually associated with metabolic syndrome that can lead to NAFLD and cirrhosis. The term "hepatogenous diabetes" (HD) is used to describe diabetes developing in patients with cirrhosis[119]. Numerous factors, including reduced insulin clearance, peripheral hyperinsulinemia and down-regulation of insulin receptors, lead to development of diabetes in cirrhosis[120]. HD is clinically different from T2DM in that it is less frequently associated with microangiopathy and patients suffer from complications of cirrhosis more frequently. However, HD is not yet recognized by the American Diabetes Association and the World Health Organization.

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