

# Fatty liver disease in diabetes mellitus

Harikrashna B. Bhatt, Robert J. Smith

The Warren Alpert School of Medicine, Brown University, Providence, RI 02906, USA

Correspondence to: Robert J. Smith, MD. The Warren Alpert School of Medicine, Brown University, 14 Arnold Street, Providence, RI 02906, USA.

Email: robert\_j\_smith@brown.edu.

**Abstract:** Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in type 2 diabetes mellitus (T2DM), likely reflecting the frequent occurrence of obesity and insulin resistance in T2DM. NAFLD also can occur in type 1 DM (T1DM), but must be distinguished from the more common glycogen hepatopathy as a cause of hepatomegaly and liver function abnormalities in T1DM. Weight reduction achieved by diet and exercise is effective in preventing and treating NAFLD in obese diabetic subjects. Bariatric surgery also has been shown to reverse NAFLD in T2DM, and recently approved weight loss medications should be evaluated for their impact on the development and progression of NAFLD. There is limited evidence suggesting that specific drugs used for blood glucose control in T2DM [thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) analogs, and dipeptidyl peptidase-4 (DPP-4) inhibitors] and also statins may have a role in preventing or treating NAFLD in patients with diabetes.

**Keywords:** Diabetes mellitus (DM); fatty liver; hepatic steatosis; non-alcoholic fatty liver disease (NAFLD); steatohepatitis

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## Non-alcoholic fatty liver disease (NAFLD)

The focus of this review is NAFLD as it relates to diabetes mellitus (DM). As the disease name suggests, NAFLD involves the presence of hepatic steatosis not caused by alcohol intake. When examined histologically, e.g., in a liver biopsy specimen, excess accumulation of lipids (representing predominantly triglycerides) is evident within hepatocytes. In some cases, NAFLD may progress from steatosis to steatohepatitis (with evidence of inflammation and cell injury), cirrhosis (hepatic fibrosis), and ultimately liver failure.

In assessing disease severity and risk of progression to cirrhosis, it is useful to divide NAFLD into two categories: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The difference between the two entities is histologic. In NASH, there is the presence of hepatic inflammation in contrast to NAFL, which involves only steatosis. NAFL and NASH occur as part of a continuum in which the histology often is not exclusively

steatosis or steatohepatitis. As one approach to defining the extent and severity of disease, an NAFLD activity score (NAS) has been developed, which assigns numerical values to various histologic measures of steatosis, inflammation, cell injury, and fibrosis (1). The resulting cumulative score then can be used to classify patients as having NAFL, borderline NASH, or fully developed NASH. The distinction between NAFL and NASH is important, since patients with NASH are much more likely to progress to clinically significant cirrhosis, portal hypertension, and liver failure (2). When cirrhosis develops in the context of NAFLD, there also is a several-fold increased risk of hepatocellular carcinoma (3).

Most patients with NAFLD are asymptomatic and typically identified when abnormal liver studies are noted on routine laboratory assessment. In particular, the liver enzymes alanine aminotransferase and aspartate aminotransferase are elevated. However, these enzymes may not be elevated in all cases of NAFLD, and the level of aminotransferases does not reliably predict the extent of

inflammation and cirrhosis (4). Imaging techniques, such as hepatic ultrasound or MRI can give insight into the extent of liver involvement in NAFLD, but also do not distinguish effectively between NAFL and NASH. Additional noninvasive measures of liver inflammation and fibrosis are under investigation, including levels of circulating cytokeratin-18 fragments (5), measures of a pool of fibrosis markers (6), and transient elastography as a measure of liver stiffness (5). However, a firm diagnosis of NAFLD with categorization of the extent of liver inflammation and fibrosis currently requires histological analysis of tissue obtained by biopsy.

### **Association of NAFLD with diabetes mellitus (DM)**

NAFLD is a very common disorder that has been increasing in prevalence worldwide. A population based analysis through the United States National Health and Nutrition Examination Survey indicates that the percentage of the US population with NAFLD has steadily increased over the past 20 years (7). The numbers vary across epidemiologic studies, but the median prevalence in the US and worldwide is in the range of 20% (7) and likely even higher in Asia (8). Hepatic steatosis and steatohepatitis can occur in association with multiple diseases affecting the liver, including hepatitis A, B and C, autoimmune hepatitis, hemochromatosis, and hypothyroidism. However, much of the increase in prevalence of NAFLD is driven by its epidemiologic and pathophysiologic links to type 2 DM (T2DM) and obesity. The prevalence of NAFLD in obese adults with T2DM has been estimated to be greater than 70% (9). Alanine aminotransferase has been noted to be more than twice normal in 20% of children with T2DM, and this is attributed in most cases to NAFLD (10).

T2DM in most affected individuals is characterized by the co-occurrence of resistance to the actions of insulin in its target tissues throughout the body and a failure of the beta cells in the pancreatic islets to secrete enough insulin to overcome this resistance. These abnormalities are believed to result from a combination of genetic and environmental factors. There appear to be multiple genetic factors predisposing to T2DM, with more than 40 associated gene variants thus far identified, each of which individually has a small impact on diabetes risk. While the molecular events linking most of these genes to the development of T2DM are not understood, many of the associated genes are involved in pathways linked to beta cell development or function. The most significant environmental determinants

are increased calorie intake and decreased physical activity, both of which contribute to the development of obesity and insulin resistance.

Changes in food intake and exercise patterns in many populations around the world, often associated with increasing urbanization, have driven an epidemic increase in obesity and T2DM over the past several decades. According to International Diabetes Federation data, close to 400 million people have diabetes worldwide, with the vast majority of these individuals (approximately 90%) having T2DM (11). An additional 316 million people have pre-diabetes (characterized by mildly elevated fasting or postprandial glucose), which places them at high risk for developing T2DM. There is an increased prevalence of NAFLD in individuals with pre-diabetes as well as overt T2DM.

In addition to the association with disordered glucose metabolism, most patients with NAFLD have other clinical characteristics that qualify them for the diagnosis of metabolic syndrome. A common operative definition of the metabolic syndrome is the presence of any three of the five abnormalities: abdominal obesity (increased waist size or waist/hip ratio), impaired glucose tolerance or overt diabetes, elevated triglycerides, low high-density lipoprotein cholesterol, and elevated blood pressure (12). In a study examining 304 individuals with NAFLD, 88% of those with steatohepatitis had metabolic syndrome (13). The multiple features that define the metabolic syndrome, in addition to disordered glucose metabolism, represent risk factors for cardiovascular disease, and some of these abnormalities, such as hypertension, may also contribute to microvascular complications in diabetes.

There is evidence that NAFLD, separate from its co-occurrence with diabetes and the metabolic syndrome may be an independent risk factor for cardiovascular disease. In a study involving 6.5 years of follow up in over 2,000 adults with T2DM, NAFLD was associated with an approximately 2-fold increased risk of cardiovascular disease, which appeared to be independent of other variables, such as sex, age, smoking, diabetes duration, hemoglobin A1c, and LDL cholesterol (14). In a second study from the same group, NAFLD was independently associated with cardiovascular disease in type 1 DM (T1DM) (15). There also is limited evidence suggesting that NAFLD may be an independent risk factor for diabetic retinopathy and chronic kidney disease (16). Further studies are needed to establish the strength of the associations of NAFLD with these long-term diabetes complications and whether it has an actual causal role.

### **Pathophysiological links between NAFLD and type 2 diabetes (T2DM)**

The pathogenesis of NAFLD is not yet fully understood, but insulin resistance appears to be a critical contributing factor, with obesity as the most common cause of the insulin resistant state. As body fat stores expand with calorie excess and progressive obesity, alterations in lipid metabolism together with inflammation in adipose tissue and ectopic sites of fat deposition lead to insulin resistance predominantly secondary to post-receptor abnormalities in insulin signaling pathways (17).

Elevated circulating free fatty acid levels, in part related to diminished suppression of adipose tissue lipolysis by insulin, result in increased delivery of free fatty acids to the liver. The synthesis of excess triglyceride in the liver is driven by this supply of fatty acids and the accumulation of excess liver fat is further exacerbated by impaired hepatic fatty acid oxidation secondary to insulin resistance. When glucose levels are elevated in the context of pre-diabetes or overt diabetes, this provides further substrate for triglyceride synthesis. Additionally, impaired very low density lipoprotein (VLDL) secretion, which commonly occurs with insulin resistance, further contributes to hepatic fat accumulation. Insulin resistance is not only a factor in obesity and diabetes, but also may be an underlying mechanism for NAFLD even in non-obese individuals without diabetes, as noted in a euglycemic insulin clamp study (18). However, insulin resistance most commonly is associated with NAFLD in the context of obesity, and the development and progression of NAFLD usually occurs in association with both insulin resistance and a state of ongoing excess calorie intake.

There may not only be an increased risk for NAFLD secondary to diabetes, but there also is evidence suggesting that NAFLD conversely may be a risk factor for the development of T2DM. In a study comparing NAFLD patients and control subjects, none of whom had diabetes at baseline, those with NAFLD were more likely to have diabetes and metabolic syndrome when re-evaluated eleven years later (19). When overt diabetes develops in the setting of preceding insulin resistance and obesity, the diabetic state may be an independent additional factor contributing to progression of NAFLD and the ultimate development of cirrhosis. In a study of over 400 adults with NAFLD, those with moderate to severe fibrosis were more likely to have diabetes (20). Thus, in examining

associations between DM and NAFLD, it is important to consider not only the occurrence of NAFLD with diabetes, but also the effects of diabetes on NAFLD progression to NASH.

### **Liver disease in type 1 diabetes (T1DM)**

T1DM is an autoimmune disorder in which obesity is not believed to have a significant causal pathogenic role. However, with the high prevalence of obesity in the general population, patients with T1DM not uncommonly are overweight or obese. These individuals may develop NAFLD, with the prevalence of NAFLD correlating with the degree of obesity as reflected in their body mass index (BMI) (15). Although altered glucose and lipid metabolism in inadequately controlled T1DM could theoretically contribute to the development of NAFLD, it is unclear if the prevalence of NAFLD is higher in T1DM than in non-diabetics with similar degrees of obesity.

Regarding liver abnormalities in T1DM, it is important to recognize the occurrence of glycogen hepatopathy (21) and distinguish this clinically from NAFLD. Excess liver glycogen deposition resulting in hepatomegaly was originally described during the early years after introduction of insulin for management of T1DM as a component of the Mauriac syndrome. This syndrome, which likely represents consequences of sustained, very poor metabolic control in diabetes in childhood, includes hyperlipidemia, growth failure, delayed sexual maturation, and Cushingoid appearance, in addition to hepatic glycogen accumulation. Glycogen hepatopathy occurs more commonly today in the absence of the other features of the Mauriac syndrome. It can develop in adults or children with poorly controlled T1DM and is characterized by overloading of hepatocytes with glycogen, resulting in hepatic enlargement, modestly elevated transaminases, and sometimes abdominal pain, nausea, and vomiting (21). The pathogenic mechanism appears to involve increased glycogen synthesis and decreased glycogenolysis in the liver as a consequence of the simultaneous presence of insulin and sustained high glucose levels (22). Glycogen hepatopathy cannot be distinguished from NAFLD by ultrasound and ultimately requires liver biopsy for a firm diagnosis. However, it differs clinically from NAFLD, in that liver size, transaminase elevations, and associated symptoms typically resolve rapidly on improvement in diabetes control with glycogen hepatopathy but not with NAFLD (23).

## Prevention and treatment of fatty liver disease in diabetes

### *Management of body weight and obesity*

The strategies used to prevent and treat NAFLD in general also apply to this disease in the setting of T2DM. Achieving and maintaining appropriate body weight is the single most important means of preventing NAFLD. Additionally, the best approach to reversing the course of established NAFLD in overweight or obese patients is weight loss. Weight reduction by lifestyle modification is a safe and effective means of preventing and treating NAFLD. The usual goal in obese subjects is to achieve sustained weight loss of 7-10% of body weight with a combination of a balanced, calorie-restricted diet and increased physical activity. Diets that include substantial ingestion of sweet beverages or a high content of meats have been associated with an increased risk of NAFLD (24). High fructose consumption also is postulated to be associated with the development of NAFLD (25). For patients with NAFLD, weight loss can improve serum insulin levels, liver function, and quality of life (26). A rate of weight loss of up to 1 kg/week is considered to be safe in the setting of NAFLD. It was suggested in a study of 41 patients followed for approximately 8 months that rapid weight loss can result in worsening of the liver disease (27). It is also advisable that individuals at risk for NAFLD reduce or altogether avoid alcohol consumption. Among patients with NAFLD, alcohol abuse is linked to progression of liver disease (28).

Three pharmacological agents have been approved by the US Federal Drug Administration in the past two years for weight loss in overweight or obese patients: phentermine/topiramate in combination (29), lorcaserin (30), and naltrexone/bupropion in combination (31). These agents represent a reasonable therapeutic option to consider for weight reduction in patients who have not been able to achieve adequate weight loss by lifestyle changes. However, adequate data are not available to evaluate their effects on NAFLD.

For patients who have been unable to achieve adequate weight reduction by diet and lifestyle modification, bariatric surgery can be considered for the proper candidate with NAFLD. In a meta-analysis involving 15 studies, improvement in steatosis was observed in 91% of patients and decreased fibrosis in 65.5% (32). Total resolution of NASH occurred in close to 70% of patients. A majority of these studies were prospective in design and employed

Roux-en-Y gastric bypass as the type of bariatric surgery. Gastric bypass can significantly improve hepatic function and overall histology, likely mediated by several molecular factors. For example, a study of seven morbidly obese patients with NAFLD showed improvement in hepatic factors regulating fibrogenesis such as transforming growth factor- $\beta$ 1,  $\alpha$ -smooth muscle actin, and inflammatory markers such as interleukin 8 (33). The available evidence thus indicates that bariatric surgery, in particular Roux-en-Y gastric bypass, is generally effective in obese patients with NAFLD in association with its established marked effects in reducing body weight.

### *Effects of T2DM treatment and specific glucose-lowering drugs on NAFLD*

It is well established that good blood glucose control reduces both acute and chronic complications in T2DM. Adequate glucose control thus should be a primary goal in T2DM, irrespective of the presence or absence of NAFLD. A study involving 39 T2DM patients with NAFLD in Japan found that a decrease in hemoglobin A1c and the use of insulin were associated with an improvement in hepatic fibrosis over a median 2.4-year period between liver biopsies independent of changes in BMI (34). The decrease in hepatic fibrosis correlated better with blood glucose control as measured by the change in hemoglobin A1c than use of insulin. Additional studies will be required to firmly establish whether improved blood glucose control in general in T2DM, independent of changes in obesity, can result in prevention or reversal of NAFLD.

Limited data are available on the potential effects on NAFLD of specific non-insulin pharmacological agents used in the management of blood glucose levels in T2DM.

### **Metformin**

Metformin is the most commonly prescribed first line oral agent in T2DM. Its primary actions include decreasing hepatic gluconeogenesis and net hepatic glucose production and increasing glucose uptake in skeletal muscle. Due to the risk of lactic acidosis, there is a relative contraindication to the use of metformin in liver disease. Small studies have shown that metformin is well tolerated in NAFLD and suggest that it can result in improved liver transaminases. For example, a study of 20 subjects with NAFLD treated with metformin for four months showed improvement in liver transaminase levels when compared to non-compliant individuals within the group (35). However, larger analyses of metformin in

NAFLD have shown no improvement in liver histology. In a meta-analysis that combined data from three studies, there was no improvement in hepatic steatosis or fibrosis following metformin treatment (36). Thus, metformin overall has not been shown to be effective in NAFLD.

### **Thiazolidinediones (TZDs)**

TZDs are second line oral agents for glucose control in T2DM that decrease insulin resistance by activating nuclear peroxisome proliferator-activated receptor- $\gamma$ , thus modifying the transcription rates of multiple genes. This results in augmented insulin sensitivity and leads to increased glucose uptake in peripheral tissues and reduced hepatic glucose production. Pioglitazone is the most widely used TZD, with much less current use of rosiglitazone because of a history of concerns about its potential cardiovascular side effects. Data from multiple studies have suggested potential beneficial effects of TZDs on NAFLD, presumably as a consequence of their actions to decrease insulin resistance. In a meta-analysis that included five clinical trials involving subjects both with and without overt diabetes, TZDs were found to improve steatosis but not fibrosis. However, in a subset of subjects without diabetes, the pooled analysis showed significant improvements in fibrosis as well as steatosis (36). Pioglitazone further showed a greater decrease in fibrosis compared to rosiglitazone or placebo in the analysis. Additional studies will be required to resolve whether there are specific patient groups for whom pioglitazone can effectively decrease the development or progression of NAFLD.

### **Glucagon-like peptide-1 (GLP-1) analogs**

GLP-1 analogs are stabilized (long-acting) agonists that bind receptors for the endogenous, intestinally-secreted hormone, GLP-1. Three members of this drug class are approved in the US, including exenatide, liraglutide, and albiglutide. They improve blood glucose control by enhancing glucose-dependent insulin secretion, slowing gastric emptying, suppressing postprandial glucagon production, and decreasing food intake through enhanced satiety. They are administered by subcutaneous injection (from twice daily to once weekly for different preparations), and they most often are used as second-line agents in conjunction with other glucose-lowering drugs or insulin. A recent small study from Japan showed improved steatosis and NASH histology (lower NAS score) following liraglutide treatment in overweight or obese subjects with prediabetes (37). This was associated with improved

glucose tolerance and a small decrease in BMI. While these initial data are intriguing, further studies will be needed to establish whether or not liraglutide or other GLP-1 analogs can be useful in preventing or treating NAFLD.

### **Dipeptidyl peptidase-4 (DPP-4) inhibitors**

DPP-4 inhibitors, currently sitagliptin, saxagliptin, linagliptin, and alogliptin in the US, influence glucose homeostasis by blocking the deactivation of endogenous GLP-1 and a second incretin hormone, glucose-dependent insulinotropic peptide (GIP). Some of the effects of DPP-4 inhibitors may overlap with those of administered GLP-1 analogues (as noted above), but these drugs likely have additional actions by increasing levels of hormones other than GLP-1. DPP-4 inhibitors have the advantage of being taken orally. Several clinical studies with sitagliptin in subjects with T2DM and NASH have shown decreases in alanine aminotransferase levels (38-40) and, in two studies, improved liver histology (38,40). The beneficial effects on NAFLD occurred in concert with improvement in hemoglobin A1c levels and a decrease or downward trend in BMI. Further studies will be needed to confirm these findings and determine whether DPP-4 inhibitors have sustained beneficial effects on NAFL or NASH.

### ***Effects of statins in NAFLD***

In addition to the usefulness of the multiple members of the statin drug class in treating dyslipidemia, in particular for lowering LDL cholesterol by inhibiting HMG CoA reductase, there is some evidence that statins also can reduce hepatic steatosis in NAFLD (41). Atorvastatin along with another agent, ursodeoxycholic acid, was studied in a clinical trial of over 40 adults with NAFLD (30 non-diabetics and 10 diabetics). Normolipidemic subjects received ursodeoxycholic acid, and hyperlipidemic patients received atorvastatin for six months. Liver transaminases decreased in both groups, but a decrease in steatosis was noted only in the statin patients. Statins do have the rare side effect of hepatotoxicity; however, this has not been observed in statin treated patients with NAFLD (42). In a follow-up study, the decrease in steatosis in response to statins appeared to be sustained for more than 10 years (43). There is ample clinical evidence that statins decrease both primary and secondary cardiovascular disease risk, and they are widely used for this indication in diabetes. Statins are not specifically approved for the prevention or treatment of NAFLD, but there is a need for further studies on the magnitude and duration of

their potential effects on NAFLD both in the presence and absence of diabetes.

### Prospects for the future

Routine screening for NAFLD is not currently recommended for patients with diabetes or otherwise increased risk in the absence of elevated liver transaminases or other evidence for liver disease. This reflects a lack of adequate, evidence-based methods for NAFLD screening and also uncertainties about how to effectively treat NAFLD once diagnosed. As more data emerge on the effects of specific anti-diabetes drugs, weight loss drugs, and other agents such as statins on NAFLD, it will be important to continuously re-evaluate the cost-effectiveness of screening. Since the rate of progression from simple steatosis (NAFL) to steatosis with associated inflammation and fibrosis (NASH) appears to be quite low, screening for NAFL is likely to be appropriate only if effective pharmacological agents are identified that have low cost and highly favorable adverse event profiles. Given the much more frequent progression of patients with NASH to serious liver disease, including hepatocellular carcinoma or liver failure, screening targeted to NASH may be cost-effective even for medications that are more costly and have less favorable side effect profiles. For this reason, it will be important to focus future research on improved non-invasive strategies of screening for NASH, as well as new approaches to treating NASH once it has been diagnosed. T2DM patients manifest increased risk of NAFLD both because of the high prevalence of obesity in T2DM and the role of insulin resistance in the development of diabetes. Early data suggest that some of the pharmacological agents commonly used in the management of blood glucose and dyslipidemia in T2DM may also be efficacious in treating NAFLD. T2DM patients thus represent a population that should be a focus for further study as new screening methods and treatment options for NAFLD become available.

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