CONNECTION BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND DIABETES MELLITUS

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the commonest liver condition in the world, accounting for 20–30% of the adult population, and encompasses a spectrum of liver disorders characterized by fat accumulation within the liver, associated or not with varying degrees of hepatic inflammation and liver fibrosis through to cirrhosis. The prevalence of NAFLD increases significantly in the presence of obesity (60–80%) and type 2 diabetes (60%). NAFLD is associated with metabolic disorders (type 2 diabetes, obesity and hyperlipidemia) grouped together as the metabolic syndrome (MetS). It is now regarded as the hepatic manifestation of this syndrome and is closely linked to insulin resistance (IR). The presence of NAFLD predicts the development of type 2 diabetes independent of established risk factors. NAFLD patients should therefore be screened for diabetes, including by the Oral Glucose Tolerance Test (OGTT) if there are any abnormalities of fasting blood glucose (FBG) and given appropriate lifestyle advice. Early diagnosis with the institution of lifestyle measures could help prevent or retard the onset of these metabolic disorders. Type 2 diabetes causes more severe non-alcoholic steatohepatitis (NASH), and patients with diabetes have an increased risk for cirrhosis and the development of hepatocellular carcinoma (HCC).

key words: Nonalcoholic fatty liver disease (NAFLD), Nonalcoholic steatohepatitis (NASH), metabolic syndrome, type 2 diabetes (TD2)

Background and Aims

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western countries, where the prevalence approaches 20–30% of the adult population [1] and 75–90% in obese individuals [2,3]. In fact, the number of NAFLD patients is increasing in parallel with the worldwide increase in the population of obese individuals. NAFLD should be suspected in any overweight person with ultrasound evidence of fatty liver, particularly if metabolic complications such as fasting hyperglycemia, raised serum lipids, and high blood pressure are present. Fatty liver (FL) was believed to be a benign condition involving intrahepatic fat accumulation. In fact, up to one third of those with NAFLD are likely to present with non-
alcoholic steatohepatitis (NASH), which may be associated with fibrosis and may progress to cirrhosis, terminal liver failure and hepatocellular carcinoma (HCC) [4-6]. Patients with simple steatosis have a relatively benign prognosis, whereas those with NASH have an increased risk of cirrhosis and end-stage liver disease, approaching 12% over 8 years [7]. Thus, it is now thought that fatty liver disease (FLD) should be treated with various methods such as diet, exercise and drugs.

NAFLD is characterized by accumulation of fat within hepatocytes in the absence of significant alcohol consumption and is a common cause of elevated liver function tests (LFTs) used to screen for liver disease. FLD, in particular NAFLD, is considered as a hepatic manifestation of obesity [8] and, in fact, could be considered a hepatic manifestation of the metabolic syndrome (MetS). Obesity and subsequent development of insulin resistance are major factors in the development of metabolic syndrome, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia and FLD [9]. A vast amount of literature suggests that NAFLD is tightly associated with obesity-related metabolic disorders, such as MetS, T2DM and cardiovascular diseases (CVD) [10,11]. It has been estimated that approximately 70–80 % of T2DM patients have NAFLD [12], and 20–50 % of subjects with NAFLD have T2DM [13,14].

The liver is an important metabolic organ that helps to maintain normal serum glucose concentrations and regulates insulin clearance. Because of its master function in the regulation of glucose and lipid disposal, the liver should be considered as the hepatic trigger of the MetS, rather than its target. In fact, elevated alanin aminotransferase (ALT) levels are closely related to the pathogenesis and prevalence of MetS [15] and T2DM [16,17]. ALT activity is a useful marker for predicting the risk of T2DM [18] and other metabolic disorders [15,16]. Thus, several prospective epidemiological studies have shown that elevated LFTs indicating elevated serum liver enzyme concentrations predict future development of T2DM [10,17,19-21] independently of confounding factors such as age, body weight, % whole body fat and fasting glucose [10,17,19,20]. For example, in a study where individuals were followed up every 6 months, only three parameters that increase gradually prior to T2DM onset were identified: fasting plasma glucose, serum ALT and triglyceride concentrations. All three components are directly related to liver fat content independent of obesity [22]. These data suggest that fat accumulation is a pathogenic component of T2DM.

### Fatty liver and insulin resistance

Fatty liver is associated with obesity and metabolic syndrome. In fact, NAFLD has been proposed as the hepatic manifestation of MetS, having insulin resistance (IR) as a common pathophysiologic mechanism [22-23]. Insulin resistance, often caused by obesity, especially visceral obesity, plays a major role in inducing hepatic steatosis, which can also be induced by other components of the metabolic syndrome [24,25]. Insulin resistance and chronic low-grade systemic inflammation are pathogenic mechanisms involved in all components of this syndrome [26,27]. Several studies have shown that, rather than obesity or adiposity, fat in the liver is the best correlate of insulin resistance [28,29]. When the liver becomes fatty, the ability of insulin to inhibit glucose productions is impaired. This leads to increased plasma glucose concentration, a potent stimulus for insulin production and a determinant for progression towards T2DM.

The liver is a key site of insulin action: it is the main source of endogenous glucose production (EGP), a major site for the synthesis
and disposal of lipids and the primary site of insulin degradation. Once the liver gets fatty, the ability of insulin to inhibit EGP is impaired. Hepatic insulin resistance is the major factor responsible for the development of fasting hyperglycemia as well as the compensatory hyperinsulinaemia, thus increasing whole-body IR.

Insulin resistance occurs when normal insulin concentrations fail to achieve a normal metabolic response so that higher-than-normal insulin concentrations are needed for a physiological response, such as stimulation of glucose uptake by muscle or suppression of glucose production by the liver. In obesity, pre-diabetes and T2DM, this translates into a dampened insulin-mediated glucose uptake that results in insulin hypersecretion and hyperinsulinemia. In a vicious cycle, the insulin-resistant liver leads to hyperinsulinemia as a result of increased insulin production from the pancreatic beta cells (and perhaps impaired insulin degradation) [30], while higher serum insulin levels further favor liver fat accumulation [31,32].

By its effects on lipogenesis (via sterol regulatory element-binding protein 1), hyperinsulinemia promotes energy accumulation as fat and reduces energy expenditure. These changes favor an increase in fat mass, increased lipolysis, and elevated levels of free fatty acids, further reducing insulin signaling in a dose-dependent manner and increasing both hepatic glucose and lipid production [33]. Additionally, in the liver, insulin resistance leads to unrestrained hepatic glucose production from impaired glycogen synthesis and failure to suppress gluconeogenesis.

**Relationship between NAFLD and MetS and risk of developing T2DM**

Now it is clear that the relationship between NAFLD and IR/MetS is bidirectional: liver fat content is significantly increased in patients with MetS, while in turn the presence of NAFLD is an important predictor of MetS and of future risk of T2DM [23,34].

The metabolic syndrome is associated with a 4–to 11–fold risk of fatty liver and can precede the onset of fatty liver by several years [35]. Furthermore, the presence of the metabolic syndrome is also a marker for disease severity; patients with fatty liver who fulfill criteria for the metabolic syndrome are more than three times more likely to have NASH or advanced hepatic fibrosis as compared with subjects with fatty liver alone [36]. At the same time, an early diagnosis of fatty liver is an opportunity to identify the metabolic disorders that the individual may have as well as for interventions to prevent the development of diseases such as T2DM.

Despite the fact that liver biopsy is the only reliable tool to diagnose NAFLD, in clinical practice are usually used non-invasive markers. The initial diagnosis of NAFLD is usually made by hepatic imaging or by abnormal liver tests. Ultrasonography (US) is the most common way to diagnose steatosis, but it lacks sensitivity when liver fat is less than 30% [37]. Raised aminotransferases levels are indicators of liver injury and NAFLD with elevated ALT levels is closely related to the pathogenesis and prevalence of MetS, including T2DM [15]; however, the great majority of NAFLD patients have normal liver enzyme levels [37]. While LFTs are insensitive markers of NAFLD, since the majority (up to 80%) of subjects with fatty liver (FL) have normal serum liver enzyme concentrations, two predictive indices to help accurately identify subjects with NAFLD using available clinical and laboratory data, have been proposed recently [38]. Fatty Liver Index (FLI) uses an equation with γ-glutamyl transferase (GGT), triglycerides, Body
Mass Index (BMI), and waist circumference, whereas the NAFLD Fatty Liver Score (NAFLD-FLS) includes the presence of T2DM, MetS, levels of ALT, aspartate aminotransferase (AST) and fasting insulin. These two indices were predictive of diabetes in both men and women in a large French cohort followed over a 9–year period [39], suggesting their clinical relevance for screening patients at high risk of progression to diabetes. These observations indicate that patients with fatty liver without known diabetes should be screened for the presence of the metabolic syndrome and for T2DM by current methods: primary fasting blood glucose (FBG) and HbA1c, while the Oral Glucose Tolerance Test (OGTT) can be used as a second-line screening test.

A number of different criteria exist for the diagnosis of MetS but those proposed by the International Diabetes Federation are preferred because they have the highest sensitivity in predicting NAFLD [40]. Suggested testing includes estimation of FBG, fasting serum lipids (total cholesterol, high-and low-density lipoprotein cholesterol and triglycerides), and serum uric acid. Up to one third of patients may have unrecognized type 2 diabetes or impaired glucose tolerance. Therefore, a standard 75g oral glucose tolerance test is recommended for nondiabetic patients with fatty liver. Serum insulin measurement (as part of the OGTT) is optional, but can provide a useful estimate of the degree of insulin resistance. Further, postprandial hyperinsulinemia is striking in patients with NAFLD and correlates with advanced hepatic fibrosis [41].

At later stages of established diabetes, the amount of liver fat influences the severity of insulin resistance. Patients with T2DM and NAFLD have substantially higher hepatic and peripheral IR and worse glycemic control, as demonstrated by increased levels of HbA1c, compared with patient without NAFLD [34].

In conclusion, a significant proportion of T2DM cases could apparently be prevented if individuals did not have FL (estimated using LFTs or FL scores). Thus, interventions aiming at decreasing hepatic fat content are important in the prevention of T2DM.

Liver-related morbidity and mortality in type 2 diabetes

T2DM causes more severe NASH, and patients with diabetes have an increased risk for cirrhosis. The development of hepatocellular carcinoma (HCC) is the most worrisome liver-related complication in these patients.

There are plentiful data linking T2DM with liver-related mortality, most likely as a consequence of advanced non-alcoholic steatohepatitis (NASH). In autopsy studies, diabetes has been associated with a 2.6–fold increase in the prevalence of NASH [42]. In one of the few studies with biopsy-proven NAFLD [43], up to 85 % of diabetics had histological evidence of NASH, and fibrosis was found in 25% of liver biopsies. T2DM is also a common complication of cirrhosis, being diagnosed in 10-20% of patients. Notably, in cirrhosis of various etiologies, the presence of diabetes generally leads to an increased risk of hepatocellular failure but not of diabetes-related complications.

In general, risk factors for advanced liver damage in T2DM are older age, longer duration of T2DM, and higher prevalence of MetS and all of its components. The risk of HCC is increased with long-standing diabetes and among patients treated with insulin, probably because severe hyperinsulinemia might facilitate the development of HCC [44]. HCC may be diagnosed in NASH, even in pre-cirrhotic stages. These considerations indicate the need for close
surveillance in patients with NAFLD and long-lasting T2DM.

A reduction in liver fat would seem an attractive target for antidiabetic drugs as well as therapies aimed at preventing the development of NASH and cirrhosis. Notably, treatment with Metformin reduces HCC risk [45]. Prospective studies are needed to define prognosis and treatment options.

**Conclusion and future perspectives**

NAFLD is a global problem that is present in more than 10% of the world population. In developed countries where obesity and its related disorders (diabetes and MetS) are common, the prevalence of NAFLD peaks in excess of 30%. Obesity is the most significant risk factor for NAFLD, with few cases that can occur in subjects with normal body weight. Although some patients with NAFLD have type 2 diabetes, its presence signals a higher risk of having more histologically severe NAFLD with inflammation and fibrosis.

As insulin resistance is one of the metabolic hallmarks of type 2 diabetes as well as NAFLD, it is not surprising that the two conditions frequently coexist. Plentiful data support the role of NAFLD as a major player in the pathogenesis of T2DM. The fatty and insulin-resistant liver contributes importantly to hyperglycemia (and thus to the evolution towards T2DM) as well as to aggravation of other cardiovascular risk factors.

The epidemiological association between diabetes and advanced NASH carries important clinical implications. The importance of NAFLD in T2DM goes far beyond its potential impact on morbidity and mortality observed in the general population. Due to its complex interrelation with insulin resistance and each component of the metabolic syndrome, NAFLD can favor the onset of T2DM, worsen its progression and its chronic complications on one hand, and increase the risk of liver-related death, particularly by hepatocellular carcinoma, on the other hand.

Strategies addressing obesity and diabetes in the community will lead to a significant reduction in the prevalence of NAFLD and NASH. In the same time, the presence of NAFLD as a strong predictor of MetS and both micro- and macrovascular complications of diabetes should not be ignored by the international guidelines for the management of MetS and diabetes.

**REFERENCES**


