Nonalcoholic Fatty Liver Disease

The New Complication of Type 2 Diabetes Mellitus

Fernando Bril, MD[a], Kenneth Cusi, MD[a,b,*]

KEYWORDS

• Obesity • Nonalcoholic fatty liver disease (NAFLD)
• Nonalcoholic steatohepatitis (NASH) • Thiazolidinediones • Pioglitazone • Diabetes
• Insulin resistance

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) is increasingly common in patients with type 2 diabetes mellitus (T2DM).
- NAFLD should be considered as part of a systemic disease, characterized by the accumulation of lipids in tissues where they are usually not stored, causing cellular dysfunction (known as lipotoxicity).
- Although the presence of NAFLD results in worse atherogenic dyslipidemia and more difficult to control hyperglycemia, the presence of T2DM accelerates the progression of liver disease in patients with NAFLD.
- A high level of suspicion is required by health care providers to diagnose NAFLD in patients with T2DM, especially because plasma aminotransferases are not reliable as markers of liver disease in patients with NAFLD.
- Among the different pharmacologic agents tested, pioglitazone has the highest degree of evidence for patients with T2DM and nonalcoholic steatohepatitis, and should be strongly considered in this population.

Disclosure: K. Cusi has received research support from Janssen and Novartis, and served as a consultant for (in alphabetical order) Janssen, Lilly, Pfizer, and Tobira Therapeutics, Inc; F. Bril has nothing to disclose.

[a] Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Florida College of Medicine, 1600 South West Archer Road - Room H2, Gainesville, FL 32610, USA; [b] Division of Endocrinology, Diabetes, and Metabolism, Malcom Randall Veterans Affairs Medical Center, 1601 South West Archer Road, Gainesville, FL 32608, USA
* Corresponding author. Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Florida College of Medicine, 1600 Southwest Archer Road, Room H-2, Gainesville, FL 32610.
E-mail address: Kenneth.Cusi@medicine.ufl.edu

Endocrinol Metab Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.ecl.2016.06.005 **endo.theclinics.com**

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis (>5% of hepatocytes by histology or >5.6% by nuclear magnetic resonance techniques) in the absence of secondary causes such as alcohol consumption, viral hepatitis, medications (eg, amiodarone, methotrexate, valproate), and autoimmune hepatitis.[1,2] It encompasses a wide range of liver diseases from fairly benign forms such as isolated steatosis (hepatic triglyceride accumulation with minimal or no inflammation) to nonalcoholic steatohepatitis (NASH; steatosis with inflammation and necrosis) and eventually cirrhosis and/or hepatocellular carcinoma (HCC).[1,2] Although NAFLD has been proposed to increase the incidence of new-onset type 2 diabetes mellitus (T2DM),[3] there is also a consensus that the presence of T2DM is a key factor for the progression of NAFLD to its most severe forms, with worse steatohepatitis, relentless fibrosis, and a higher incidence of HCC.[4–6]

However, unlike retinopathy, neuropathy, and nephropathy, NAFLD is currently a largely unrecognized complication of T2DM. Frequently overlooked in clinical practice by both endocrinologists and primary care physicians, NAFLD results in serious metabolic,[7,8] cardiovascular (CV),[9] and hepatic[10,11] consequences to patients with T2DM. Understanding the complicated relationship between NAFLD and T2DM is extremely important, in order to provide better clinical care to these complex patients. Although it may be argued that NAFLD often precedes the development of T2DM,[3] this can also be said about retinopathy,[12] neuropathy,[13,14] and nephropathy,[15] which are also found in insulin-resistant patients with prediabetes but without overt hyperglycemia.

This article focuses on the underlying mechanisms and health risks associated with the development of NASH in patients with T2DM, in the hope that a better understanding of the broad metabolic, hepatic, and CV implications will alert clinicians to be more proactive in the early diagnosis and treatment of these challenging patients.

EPIDEMIOLOGY

As a result of the obesity epidemic, NAFLD has become the most frequent chronic liver disease in the United States, with an estimated prevalence of 34% in the general population (based on screening using liver proton magnetic resonance spectroscopy [^{1}H-MRS]).[16] In the setting of T2DM, the prevalence of NAFLD is at least 2-fold higher, with a range from 57% to 80%, depending on the diagnostic test performed.[17–19]

Most importantly, the presence of T2DM has been associated with a faster progression to NASH and advanced fibrosis,[4,5] supporting the concept that NASH should be considered as a complication of T2DM. In cross-sectional studies involving middle-aged patients with T2DM and NAFLD, Leite and colleagues[20] found that 78% of 92 patients had NASH and ~50% had advanced fibrosis, whereas Fracanzani and colleagues[21] reported that the association of T2DM with NASH and advanced fibrosis was independent of any other risk factors in a larger cohort of 458 patients. In a report in 698 patients with NASH from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)[22] patients with definite NASH were much more likely to have diabetes and insulin resistance than those with milder liver disease. Among 1069 middle-aged patients with NAFLD, diabetes was associated with an adjusted odds ratio (OR) of 1.76 for NASH (95% confidence interval [CI],1.1–2.7; $P<.001$) and of 2.57 for fibrosis (95% CI,1.6–4.1; $P<.0001$).[23] Two recent large population-based studies have confirmed that ~17% of patients with T2DM may have significant fibrosis when assessed by noninvasive imaging tools.[24,25]

Longitudinal studies produced similar conclusions. In a small (n = 103) study with paired biopsies, Adams and colleagues[5] found that, after a mean interval of