Nonalcoholic Fatty Liver Disease in Diabetes: A Call to Action

Preface

NAFLD and Liver Health: Today's New Challenge in Diabetes Care

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The magnitude of the epidemic of nonalcoholic fatty liver disease (NAFLD) affecting people with type 2 diabetes is just now beginning to be fully appreciated, although it has been brewing for decades, propelled by the twin epidemics of obesity and type 2 diabetes. The term "nonalcoholic fatty liver disease" encompasses individuals with liver disease ranging from hepatic steatosis to steatohepatitis and cirrhosis, in the absence of ongoing or recent intake of significant amounts of alcohol or the presence of other secondary causes of steatosis. Steatohepatitis is the more severe form of the disease, in which liver steatosis is associated with inflammation and hepatocyte injury (i.e., hepatocyte ballooning), often promoting advanced liver fibrosis and cirrhosis.

NAFLD is the most common chronic liver disease in people with type 2 diabetes and may be considered a relatively "new" complication, although it was described in people with diabetes more than 4 decades ago (1). Recent studies suggest that, in the United States, >70% of people with type 2 diabetes have hepatic steatosis (2–5), a proportion that climbs to 90% in those with a BMI ≥35 kg/m^2 (3).

Driven by insulin resistance, whether lean or obese, steatohepatitis develops in at least half of all people with type 2 diabetes (4) and is a significant risk factor for future cirrhosis (6), even for individuals without obesity. The risk of developing steatohepatitis is higher the more severe the insulin resistance is, such as in obesity and type 2 diabetes (7). Steatohepatitis is believed to be the link for the significant increase in the rate of hepatocellular carcinoma (HCC) observed in people with diabetes (8).

NAFLD also increases by at least twofold the risk of having type 2 diabetes and cardiovascular disease (CVD) (9,10). Between 12 and 20% of individuals with type 2 diabetes are believed to have clinically significant fibrosis (histological stage ≥F2) (11), but that percentage has been higher in some studies (12). People with type 1 diabetes are also at an increased risk of cirrhosis from nonalcoholic steatohepatitis (NASH), particularly if they have obesity (13), a fact of which most clinicians are unaware. Cirrhosis from NASH is a major cause of liver transplantation in the United States (14).

It seems paradoxical that many clinicians and patients remain unaware of the health risks posed by NAFLD in diabetes and that so many cases remain undiagnosed (15–17). Whether in primary care or diabetes specialty clinics, few patients are stratified for their risk of cirrhosis, and those who are identified are rarely referred for dietary counseling or specialty care.

Some medications available today to treat obesity or type 2 diabetes, such as glucagon-like peptide 1 (GLP-1) receptor agonists and pioglitazone, are recommended in the clinical practice guidelines of the American Diabetes Association (18) and other medical societies (13,14,17,18) for the dual purpose of treating NASH in obesity or type 2 diabetes. However, these guidelines have yet to be broadly adopted by practitioners. Also, contrary to current guidelines, statins are often not prescribed when NAFLD is present or are even discontinued if there are mildly elevated plasma aminotransferase levels, despite the high cardiovascular risk in such patients (13,14,17,18). It is estimated that poor management of comorbidities in people with NAFLD accounts for as much as 66% of all-cause deaths and 83% of cardiovascular deaths in this population (19).

The time for action is now, as NAFLD threatens millions of people with prediabetes or type 2 diabetes. Promoting liver health is today's "new" (but, really, not so new) challenge in diabetes care (20). We have missed looking at the liver in diabetes as an organ susceptible to cirrhosis and HCC from chronic metabolic stress (i.e., broadly considered as "metabolic

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dysfunction" from insulin resistance, hyperglycemia, lipotoxcity, and other causes). We find ourselves where we were decades ago, when the diabetes professional community was beginning to promote screening for eye and kidney complications in people with diabetes. Simple screening strategies implemented since then have proved that identifying disease early could greatly reduce morbidity and mortality from diabetes complications. The good news is that cirrhosis is also preventable with early intervention, but the threat will grow unabated if diabetes care teams remain unfamiliar with best practices for diagnosing and managing these patients.

To bridge this knowledge gap, this *Diabetes Spectrum* From Research to Practice section focuses on key aspects of caring for patients with NAFLD, so all diabetes team members can participate in educating patients about prevention and treatment choices when this disease is present. The five articles that make up this research section combine evidence-based recommendations with valuable practical guidance. Aligned with the latest American Diabetes Association (ADA) standards of care for NAFLD (18), the articles are organized in a logical progression from awareness about the magnitude of the problem of liver disease in diabetes, to its underlying mechanisms, and finally to its diagnosis and treatment.

In our first article (p. 9), Zobair M. Younossi and Linda Henry make it clear that people with type 2 diabetes are at the highest risk of steatohepatitis, cirrhosis, and HCC (21). NAFLD accelerates the progression from prediabetes to type 2 diabetes and increases the risk of CVD. The message is loud and clear that clinical inertia causes millions of people in the United States, and likely worldwide, to die every year from preventable liver disease and the extrahepatic comorbidities of NAFLD (19), a trend that must be reversed with early diagnosis and treatment.

Next (p. 20), Juan Patricio Nogueira and I explain how the interaction between genetics and insulin resistance in type 2 diabetes causes metabolic dysfunction, which, in susceptible individuals, triggers steatohepatitis and disease progression (22). Amelioration of insulin resistance translates into a reversal of steatohepatitis and cardiometabolic disease in people with NAFLD (23,24). This is why current treatment guidelines target insulin resistance by either weight loss (via lifestyle modification, GLP-1 receptor agonist therapy, or bariatric surgery) or the use of pioglitazone therapy.

This article sets the stage for the third article of our collection (p. 29), by three primary care colleagues and I, that describes the evolution of and rationale underpinning the ADA's current NAFLD recommendations (18) and other guidelines (25). The aim of this article is to explain the reasoning behind the recommendations to increase their practical application in clinical settings. The article provides practical advice for handling several clinical challenges, including risk-stratifying and treating patients for NAFLD, determining when to refer patients to a liver specialist, ensuring the provision of appropriate multidisciplinary care, and reducing overall cardiovascular risk.

In our fourth article (p. 39), nutritionists Shira Zelber-Sagi and J. Bernadette Moore elegantly review the different eating plans that can help to prevent cirrhosis and improve cardiometabolic health (26). Their take-home message is that the Mediterranean diet represents the best long-term approach to prevent and treat NAFLD. This eating pattern is high in vegetables, legumes, nuts and seeds, fruits, whole grains, seafood, fiber, polyphenols, and vitamins. The authors also discuss the roles of physical activity and bariatric surgery in NAFLD treatment and include a table with practical recommendations for facilitating lifestyle modification for busy clinicians.

In the last article in this series (p. 48), Idoia Genua and I discuss current and future pharmacological approaches to NAFLD with the understanding that reversal of steatohepatitis will often require long-term pharmacological treatment in addition to lifestyle modification (27). As previously mentioned, medications that reverse steatohepatitis include some approved to treat obesity (primarily GLP-1 receptor agonists) and others for type 2 diabetes (e.g., pioglitazone, sodium–glucose cotransporter 2 inhibitors, and GLP-1 receptor agonists). Of relevance, these drugs not only treat liver disease, but also reduce cardiovascular risk.

In closing, I would like to thank the wonderful editorial team at *Diabetes Spectrum* who recognized the urgency of promoting liver health in diabetes and invited me to serve as guest editor of such an important and timely collection. They worked tirelessly to offer a high-quality, practical collection to their readership. On behalf of the editorial team and myself, I also thank all of the authors who shared their time and expertise to create the first-ever collection on this essential topic for *Diabetes Spectrum*. On a personal level, making liver health a priority has been a long-held dream of mine that is slowly becoming true (28). My hope is that this collection will inspire diabetes care providers to spring into action to curb liver disease among all people with diabetes.

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