EDITORIAL

Nonalcoholic fatty liver disease in type 1 diabetes: where are we?

François R. Jornayvaz[1,2,3]

1 Division of Endocrinology, Diabetes, Nutrition and Therapeutic Patient Education, Department of Medicine, Geneva University Hospital, Geneva, Switzerland
2 Diabetes Center, Faculty of Medicine, Geneva University, Geneva, Switzerland
3 Department of Cell Physiology and Metabolism, Faculty of Medicine, Geneva University, Geneva, Switzerland

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Nonalcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease worldwide, with a global prevalence of approximately 25%.[1] NAFLD prevalence is even higher in patients with type 2 diabetes, reaching about 55%, and up to 90% in obese individuals with a body mass index above 40 kg/m^2. NAFLD is characterized by the accumulation of lipids in the liver, particularly in the absence of high-risk alcohol consumption, and is usually a diagnosis of exclusion. It is often associated with type 2 diabetes, as insulin resistance (IR) and hyperinsulinemia are known to be favoring factors.[2] However, recent studies have reported a growing incidence of NAFLD also in type 1 diabetes (T1DM).[3,4] The increasing prevalence of metabolic syndrome in these patients seems to explain, at least in part, this phenomenon.[5,6] Nevertheless, other mechanisms, such as oxidative stress, poor glucose control, and long-lasting hyperglycemia, but also exogenous insulin administration, may play an important role in T1DM-associated NAFLD.[7]

Liver biopsy is the gold standard for the diagnosis of NAFLD.[8] Histologically, NAFLD is defined as the presence of at least 5% hepatic steatosis. However, liver biopsy is an invasive procedure, and imaging studies are therefore more frequently used to diagnose NAFLD, as hepatic fat content can be evaluated using conventional imaging, such as ultrasonography, computed tomography, and magnetic resonance imaging. Nevertheless, an approach consisting in evaluating indirect IR markers, such as estimated glucose distribution rate, visceral adiposity index, or triglyceride to high-density lipoprotein cholesterol ratio, to assess the risk of developing NAFLD in patients with T1DM[9] could be a valuable tool in primary care medicine.

In this issue of *Polish Archives of Internal Medicine*, Grzelka-Woźniak et al[10] analyzed indirect IR markers in 151 patients with T1DM treated at 2 centers, the Medical University of Lodz and the Poznan University of Medical Sciences in Poland. The aim of the study was to explore the relationship between indirect IR markers and the presence of NAFLD in patients with T1DM. NAFLD was diagnosed using transient elastography and controlled attenuation parameter measurement. In this cohort, the patients with NAFLD were significantly older and had a longer history of diabetes. They also had higher glycated hemoglobin (HbA_{1c}) values and a greater total daily dose of insulin. As expected, the patients with NAFLD had a higher body mass index and waist-to-hip ratio. Interestingly, indirect IR markers were predictive of the presence of NAFLD independently of sex, diabetes duration, and HbA_{1c} levels. Indeed, the T1DM patients with NAFLD were less insulin-sensitive, had a significantly lower estimated glucose distribution rate, a higher visceral adiposity index, and a higher triglyceride to high-density lipoprotein cholesterol ratio. Finally, the prevalence of NAFLD in this cohort was approximately 40%,[10] which is in line with other reports.[11] The main limitation of this study was the use of transient elastography results and not the gold-standard liver biopsy to diagnose NAFLD and its severity.

The pathophysiology of NAFLD in T1DM remains only partially known. Based on the study by Grzelka-Woźniak et al,[10] it can be speculated that decreased insulin sensitivity might be the primary factor involved in NAFLD development, which further triggers IR. Since T1DM management only relies on subcutaneous administration of exogenous insulin, one of the factors influencing the pathophysiology of NAFLD development in these patients might be a defect in insulin delivery and/or of insulin clearance.[12] Notably, carcinoembryonic antigen–related cell adhesion molecule 1 (CEACAM1), which is a cell transmembrane protein that plays a key role in insulin degradation and thus its clearance, could be of significance. CEACAM1 mediates excess

Correspondence to:
François R. Jornayvaz, MD, Division of Endocrinology, Diabetes, Nutrition and Therapeutic Patient Education, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, CH-1211 Genève 14, Switzerland, phone: +41 223 729 302, email: Francois.Jornayvaz@hcuge.ch
Received: March 1, 2023.
Accepted: March 2, 2023.
Published online: May 23, 2023.
Pol Arch Intern Med. 2023; 133 (5): 16504
doi:10.20452/pamw.16504
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insulin removal through its phosphorylation induced by the ligand-activated insulin receptor to maintain normal insulinemia. Two main mechanisms can compromise CEACAM1 phosphorylation and action: hyperinsulinemia and impaired pulsatility of insulin secretion. Therefore, considering the importance of insulin secretion pulsatility for CEACAM1's efficiency to clear insulin, continuous high insulinemia exposure due to exogenous insulin injections not only downregulates insulin receptor density, but also downregulates insulin clearance, thus increasing insulinemia and IR. Other factors involved in NAFLD development in T1DM include intrahepatic lipogenesis (enhanced by insulin notably by increasing sterol regulatory element–binding proteins)[13] or hyperglucagonemia,[14] among others (for review, see Memaj and Jornayvaz[3]).

In conclusion, this elegant study[10] adds to the growing body of evidence on an increased prevalence of NAFLD in patients with T1DM. Indirect IR markers could be easily used in primary care to better assess the risk for NAFLD in these patients, and therefore to avoid delaying NAFLD diagnosis, as this condition can evolve not only to nonalcoholic steatohepatitis, but also to cirrhosis and even hepatocellular carcinoma.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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HOW TO CITE Jornayvaz FR. Nonalcoholic fatty liver disease in type 1 diabetes: where are we? Pol Arch Intern Med. 2023; 133: 16504. doi:10.20452/pamw.16504

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