

Early warning of liver disease in diabetics

Juan Pablo Arab,* Carolina Ramírez,* Marco Arrese*

* Departamento de Gastroenterología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.

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Original Abstract

Background. The negative impact of diabetes mellitus is well recognized, yet little is known about the effect of this disease on the liver, an organ susceptible to nonalcoholic fatty liver disease related to insulin resistance. We evaluated whether adults with newly diagnosed diabetes were at increased risk of serious liver disease. **Methods.** We used administrative health databases for the province of Ontario (1994-2006) to perform a population based matched retrospective cohort study. The exposed group comprised 438 069 adults with newly diagnosed diabetes. The unexposed comparison group- those without known diabetes-consisted of 2 059 708 individuals, matched 5:1 to exposed persons, by birth year, sex and local health region. We excluded individuals with preexisting liver or alcohol-related disease. The primary study outcome was the subsequent development of serious liver disease, namely, liver cirrhosis, liver failure and its sequelae, or receipt of a liver transplant. **Results.** The incidence rate of serious liver disease was 8.19 per 10 000 person-years among those with newly diagnosed diabetes and 4.17 per 10 000 person-years among those without diabetes. The unadjusted hazard ratio was 1.92 (95% confidence interval [CI] 1.83-2.01). After adjustment for age, income, urban residence, health

care utilization and pre-existing hypertension, dyslipidemia, obesity and cardiovascular disease, the hazard ratio was 1.77 (95% CI 1.68-1.86). **Interpretation.** Adults with newly diagnosed diabetes appeared to be at higher risk of advanced liver disease, also known as diabetic hepatopathy. Whether this reflects nonalcoholic fatty liver disease or direct glyceic injury of the liver remains to be determined.

Key words. Nonalcoholic liver disease. Type 2 diabetes mellitus. Hepatic steatosis.

Comment

The coexistence of diabetes mellitus (DM) and chronic liver disease (CLD) is commonly seen in daily clinical practice and indeed these two conditions are associated with each other more frequently than expected by chance.¹ The intricacies of this association are multiple and their relationship is of bidirectional nature. Thus, while cirrhosis itself and some etiologic agents of cirrhosis, such as the hepatitis C virus, can contribute to development of DM through a myriad of mechanisms,² DM may also be considered a metabolic pathway leading to CLD via the development of non-alcoholic fatty liver disease [NAFLD].³

Non-alcoholic fatty liver disease (NAFLD) is a clinico-pathological entity defined by the presence of hepatic histological changes that are similar to those observed in heavy-drinkers but detected in patients that deny significant alcohol consumption and do not have other known causes of chronic liver disease, such as viral hepatitis or drugs.^{4,5} The histological hallmark of NAFLD is the accumulation of fat in the liver (conventionally set as more than 5% by weight) which may or may not be accompanied by the presence of necro-inflammatory changes and/or hepatic fibrosis.⁶ When the latter features are present the term non-alcoholic steatohepatitis [NASH] is used. The subgroup of patients with NASH are deemed to have a more aggressive form of the disease that poses the risk of developing cirrhosis and hepatocellular carcinoma [HCC].⁷

Correspondence and reprint request: Marco Arrese, MD
Departamento de Gastroenterología,
Facultad de Medicina, Pontificia Universidad Católica de Chile.
Marcoleta 367. Postal Code: 833-0024. Santiago, CHILE.
Pone/Fax: 56-2-6397780;
E-mail: marrese@med.puc.cl

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NAFLD is now recognized as one of the most common liver diseases worldwide and is emerging as a relevant cause of liver-related mortality. Epidemiological studies have shown that NAFLD affects a substantial proportion of the general population of several countries.^{8,10} Current estimates from different sources indicate that up to 30% of the general population is affected by NAFLD.^{8,11} This high frequency is mainly due to the close relationship between this type of fatty liver and obesity, a condition that has now reached epidemic proportions in the world.¹² In fact, the prevalence of NAFLD in morbidly obese population can reach up to 75%.^{11,13} Another group with high prevalence of NAFLD is that of patients with type 2 DM. In fact, NAFLD prevalence among these patients ranges from 49% to 62%. Moreover, patients with type 2 DM are more likely to have the histologically more aggressive form of NAFLD (i.e. NASH), with a prevalence of 12.2% among those with diabetes compared to 4.7% among non-diabetics.¹⁴

From the above-mentioned figures one can conclude that NAFLD is a very common disorder in type 2 DM and that those patients with DM are indeed at risk of developing CLD. However, in spite of this data and in contrast with the known risk of retinopathy, chronic kidney disease and atherosclerosis, clinicians are frequently unaware that patients with DM are uniquely prone to develop NAFLD and particularly its more aggressive form NASH.³ An example of this lack of awareness is the fact that potential risk of CLD is not mentioned in the currently used guidelines for DM management.¹⁵ Obviously, data is needed to precisely define at which extent liver cirrhosis may be an under-recognized complication in patients with DM. The recent paper by¹⁶ *et al.* makes a significant contribution in this regard. In their study, the authors used administrative health databases for the province of Ontario from 1994 to 2006 to identify 438,069 adults with newly diagnosed diabetes and matched them in a 5:1 ratio by birth year, sex, and local health region with a group of 2,059,708 individuals without known diabetes. The main study endpoint was incident serious liver disease, defined as cirrhosis, liver failure and its complications, or receipt of a liver transplant, over a median of 6.4 years of follow-up. Results showed that adults with newly diagnosed diabetes had a significantly greater risk of liver disease (unadjusted hazard ratio was 1.92 (95% confidence interval [CI] 1.83-2.01) compared with controls. The association remained significant (hazard ratio was 1.77 (95% CI 1.68-1.86) after adjustment) after adjusting for

other demographical variables that may influence the risk for liver disease such as age, gender, urban versus rural residence, and income level. Moreover, diabetes, with or without pre-existing hypertension, dyslipidemia or obesity, conferred a higher risk of serious liver disease than any of the three other conditions in isolation.¹⁶

The study by Porepa *et al.* has some important limitations that the authors delineate in their report.¹⁶ Among them, misclassification of persons with diabetes, inability to distinguish between newly diagnosed type 1 and type 2 DM and lack of ethnicity data deserve to be mentioned. However, the most important point is that causality cannot be demonstrated in an association study. The possibility exists that some patients with DM already had subclinical cirrhosis at the moment of study entry and that DM may be a consequence of CLD rather than its cause.² This however, is unlikely for most of patients since hepatogenous diabetes is often seen in advanced (and clinically apparent) cirrhosis. Although definitive proof is lacking, currently available basic and clinical data^{7,17} on NAFLD and its risk of progression to CLD is highly suggestive of a causal relationship of NAFLD and the risk of serious liver disease in DM.

The fact that diagnosis of DM is a risk factor for serious liver disease, likely via NAFLD, has important clinical implications. The silent nature of the NAFLD and NASH poses a diagnostic problem. Although detection of steatosis is relatively simple through the use of simple techniques such as abdominal ultrasound (with 93% sensitivity and 89% specificity), discrimination of patients with NASH or advanced fibrosis is difficult.¹⁸ Of note, declining mortality rates in people with DM make plausible that an unknown proportion of older diabetics may already have unrecognized cirrhosis being at risk of cirrhotic complications and HCC. To rely on normal levels of aminotransferases to exclude liver disease in patients with DM may not be an adequate strategy since severe fibrosis may be present in this setting.¹⁹ To date liver biopsy is considered the gold standard for the definitive diagnosis of NAFLD²⁰ but this procedure, in virtue of its invasive nature, is not easily accepted by patients and doctors. In light of lack of guidelines, the pros and cons of liver biopsy in the individual patients should be adequately balanced ideally with the involvement of a hepatologist. Non invasive strategies for assessment of ongoing liver injury or hepatic fibrogenesis in NAFLD are being developed and assessed in clinical studies. Among them, plasma biomarkers of apopto-

sis such as cytokeratin-18 fragments²¹ or new imaging studies such as transient elastography²² or magnetic resonance elastography²³ hold promise and their entrance to clinical practice is eagerly awaited. In the meantime, the first task is to increase the awareness on the risk or the presence of serious liver disease in patients with DM among physicians caring these patients. The hepatological community should develop active educational strategies in this regard.

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