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Review

Risk of type 2 diabetes in patients with non-alcoholic fatty liver disease: Causal association or epiphenomenon?

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver diseases worldwide, causing considerable liver-related mortality and morbidity. Over the last 10 years, it has also become increasingly evident that NAFLD is a multisystem disease, affecting many extra-hepatic organ systems and interacting with the regulation of multiple metabolic pathways. NAFLD is potentially involved in the aetiology and pathogenesis of type 2 diabetes via its direct contribution to hepatic/peripheral insulin resistance and the systemic release of multiple hepatokines that may adversely affect glucose metabolism and insulin action. In this updated review, we discuss the rapidly expanding body of clinical and epidemiological evidence that supports a strong link between NAFLD and the risk of developing type 2 diabetes. We also briefly examine the conventional and the more innovative pharmacological approaches for the treatment of NAFLD that may influence the risk of developing type 2 diabetes.

Keywords: Diabetes risk; Epidemiology; NAFLD; Non-alcoholic fatty liver disease; Type 2 diabetes

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver pathology including simple steatosis, non-alcoholic steatohepatitis (NASH) with varying amounts of fibrosis and cirrhosis [1]. NAFLD has emerged as a public health problem of epidemic proportions in many parts of the world (affecting up to 30% of the adult population in the United States and Europe) [1,2]. The prevalence of NAFLD is much higher in patients with type 2 diabetes (ranging from approximately 50 to 75%). Notably, patients with type 2 diabetes and NAFLD are also more likely to develop the more severe forms of NAFLD, such as NASH, advanced fibrosis, cirrhosis, and in some cases hepatocellular carcinoma [1,2].

Over the past decade, it has become increasingly clear that NAFLD is not only associated with an increased risk of liver-related morbidity or mortality, but also it is a multisystem disease that affects a variety of extra-hepatic organ systems, and interacts with the regulation of multiple metabolic pathways [3]. Strong evidence indicates that cardiovascular disease is the leading cause of mortality in patients with NAFLD [3,4]. As detailed below, there is now also convincing evidence suggesting that NAFLD may often precede the development of type 2 diabetes. This supports the assertion that the conventional paradigm of NAFLD representing the simple "hepatic manifestation" of the metabolic syndrome is outdated, and that NAFLD might be regarded as an early predictor and determinant for the development of diabetes and other clinical traits of the metabolic syndrome [5]. This finding may have potentially

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relevant clinical implications for the diagnosis, prevention and treatment of type 2 diabetes.

Specifically, in this narrative review we discuss the rapidly expanding body of clinical evidence that supports a strong association between NAFLD and the risk of new-onset type 2 diabetes, and the putative biological mechanisms underlying this association. We also briefly discuss some of the treatment options for NAFLD that may influence the risk of diabetes.

To this end, although this is not a formal systematic review, we extensively searched PubMed database to identify relevant articles published up to January 2016, using the keywords "non-alcoholic fatty liver disease" or "fatty liver" combined with "incident type 2 diabetes" or "diabetes risk".

2. Epidemiological evidence linking NAFLD to the risk of new-onset type 2 diabetes

In this review, we have not discussed the large number of prospective, population-based studies that used serum levels of liver enzymes (or other surrogate markers of NAFLD such as the fatty liver index) to diagnose NAFLD. These studies have consistently shown that mildly elevated serum liver enzymes (mainly serum gamma-glutamyltransferase) are independent, long-term predictors of new-onset type 2 diabetes in various ethnic populations (Asian, American and European people) [6–8].

Data from observational cohort (prospective or retrospective) or case-control studies that used non-invasive imaging techniques (predominantly ultrasonography that has high sensitivity and specificity for detecting moderate and severe steatosis) to diagnose NAFLD are summarized in Table 1. There are now about 20 observational studies that have assessed the association between NAFLD and the risk of new-onset type 2 diabetes [9–25].

The main characteristics of the study populations, the length of follow-up period, the diagnostic criteria for diabetes, the relative risks of developing diabetes and the covariates included in multivariate regression models have been specified in the table.

Amongst these published studies, nearly all (except for the study by Okamoto et al. [9]) have shown that NAFLD was associated with a substantially increased risk of new-onset type 2 diabetes. The risk of diabetes among these published studies varied markedly from a 33% increase [14] to a 5.5 fold increase in risk [11]. This wide interstudy variation in risk might reflect differences in NAFLD severity, since the study by Park et al. [15] showed that the 5-year incidence rate of type 2 diabetes increased progressively according to the ultrasonographic severity of NAFLD at baseline (normal: 7.0%, mild: 9.8%, moderate-to-severe: 17.8%) in a cohort of 25,232 South Korean non-diabetic middle-aged men. Even after adjusting for multiple confounding variables, the hazard ratios (HRs) for diabetes development were higher in the mild-NAFLD group (adjusted-HR 1.09; 95% confidence interval [CI] 0.81–1.48) and in the moderate-to-severe-NAFLD group (adjusted-HR 1.73; 95% CI 1.00–3.01) compared with the no-NAFLD group, respectively. In addition, this wide interstudy variability in NAFLD-associated risk of type 2 diabetes might also reflect differences in the demographic characteristics of the study populations, in the length of follow-up (ranging from a mean period of 3 to 12.8 years) and in the varying degree of confounder adjustment in individual studies (Table 1).

Using data from an occupational cohort study of over 12,000 South Korean individuals with measurements of insulin resistance (by homeostasis model assessment [HOMA-IR]), overweight/obesity and NAFLD (as detected by ultrasonography) at baseline, Sung et al. [16] have compared the effect of these three risk factors (singly or in combination) on the risk of new-onset diabetes at 5-year follow-up. These data showed that each of these three risk factors was associated with an approximate doubling of the diabetes risk even after adjustment for other established risk factors (for example, with an adjusted odds ratio [OR] of 2.42, 95% CI 1.74–3.36, for NAFLD). When all three risk factors occurred together in the same individual (and this occurred in approximately 50% of patients with incident diabetes at follow-up), there was an approximately 14-fold increase in diabetes risk after adjusting for potential confounding variables [16].

Notably, and most interestingly, in the same observational cohort of Korean individuals, the authors have further assessed the risk of new-onset type 2 diabetes at 5 years of follow-up in the following three subgroups:

- in subjects in whom there was resolution of fatty liver over 5 years, i.e., fatty liver that had been present at baseline was not present at follow-up examination;
- in subjects in whom there was a development of new fatty liver between baseline and the follow-up examinations;
- in subjects in whom there was an increase in severity of fatty liver status, from mild fatty liver noted at baseline to moderate-severe fatty liver, identified at follow-up examination [20].

Interestingly, these data showed that changing fatty liver status over a 5-year period was associated with markedly different risks of incident type 2 diabetes. In particular, as also shown in Fig. 1, there was a significant diabetes risk reduction in those subjects in whom fatty liver on ultrasonography resolved over time. In particular, in those subjects, risk of incident diabetes decreased to the background risk of someone who had never had fatty liver. Conversely, the subjects in whom the severity of fatty liver worsened over 5 years (from mild to moderate-severe) showed a marked increase in risk of incident diabetes compared with the risk in people with resolution of fatty liver, supporting the notion that more severe forms of NAFLD are associated with higher risk of incident diabetes [20]. Similarly, Yamazaki et al. [21] recently assessed the relationship between improvement of NAFLD and risk of incident type 2 diabetes in a retrospective cohort of 4604 non-diabetic Japanese individuals followed-up for a period of 10 years. They found that NAFLD at baseline was associated with an approximately 2.5-fold increased risk of incident diabetes, and that NAFLD improvement was significantly associated with a 70% risk reduction of developing diabetes over time, even after adjusting for age, sex, family history of diabetes, BMI, impaired fasting glycaemia, dyslipidemia, hypertension, and physical exercise [21]. However, these two latter studies are not intervention trials that focused on treating NAFLD; so caution is needed in interpreting these results.