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HETEROGENEITY IN DIABETES AND BETA CELLS

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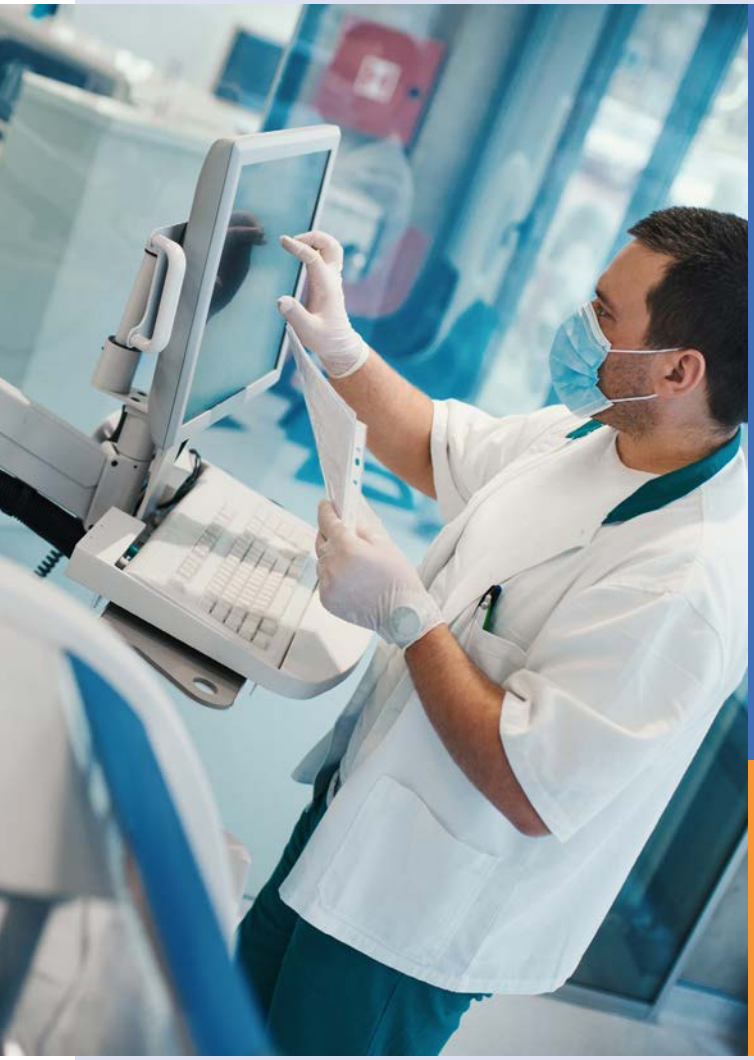

Nonalcoholic fatty liver disease in type 2 diabetes

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Abstract

Type 2 diabetes (T2D) increases the risk of developing nonalcoholic fatty liver disease (NAFLD), along with the risk of T2D disease progression and mortality. NAFLD is a heterogeneous disease, in terms of both histologic presentation and rate of progression. This variable histology correlates with prognosis; compared with patients with no or mild fibrosis, those with bridging fibrosis or cirrhosis have a lower survival rate and greater risk of hepatic decompensation. The reasons for the heterogeneity in disease progression have not been fully elucidated. Older age, higher body mass index, insulin resistance, and components of metabolic syndrome, in particular T2D, are associated with disease progression and mortality; genetics also play a role. Moderate drinking (within the limits of a NAFLD diagnosis) may also be associated with the severity of liver damage, particularly in patients with T2D. Although a diagnosis of nonalcoholic steatohepatitis (the severe form of NAFLD) is associated with an increased risk of mortality and liver-related outcomes, this increased risk is not significant after adjusting for confounders, such as stage of fibrosis, age, sex, and T2D. Thus, it is clear that our knowledge regarding the drivers of NAFLD progression is still insufficient.

Key words: Disease progression, heterogeneity, nonalcoholic fatty liver disease, type 2 diabetes

Introduction

Over 50% of patients with type 2 diabetes (T2D) will develop nonalcoholic fatty liver disease (NAFLD), which leads to an increased risk of liver-related morbidity, as well as liver-related and all-cause mortality.[1,2] In spite of a homogenous presentation (i.e., bright liver upon ultrasound and mild anomalies in liver enzymes), NALFD is an extremely heterogeneous disease, with the diagnosis ranging from patients with simple steatosis or nonalcoholic fatty liver (NAFL) through to those with the aggressive nonalcoholic steatohepatitis (NASH).[2,3] Furthermore, there is marked variability in the progression towards advanced fibrosis, with some patients progressing rapidly and others never progressing beyond NAFL. In addition to increasing the risk of NAFLD development, T2D also increases the risk of disease progression and mortality.[3] In this paper, I briefly discuss NAFLD nosography, epidemiology, prognosis, outcomes, and the predictors of outcomes as a basis for this heterogeneity. It should be noted that there has been a proposal to redefine NAFLD as metabolic dysfunction-associated fatty liver disease (MAFLD).[4,5] While I believe this proposition is sound, in this paper I use the term NAFLD, as this was the term used in the studies discussed.

Nosography

The term 'fatty liver' was first described in the English medical vocabulary almost 200 years ago.[4,5] In the mid-20th century, reports emerged of fatty liver disease associated with diabetes and obesity. However, it was not until 1980 that the terms NAFLD and NASH were coined by a histopathologist in Rochester to describe patients (mostly obese) who denied the misuse of alcohol, but had liver lesions akin to those induced by alcohol: steatosis, inflammation, ballooning of the hepatocyte, and centrilobular fibrosis.[5] The variability in the presentation of these histologic features highlights the disease's heterogeneity; the term NAFLD encompasses patients with steatosis alone (NAFL), those with steatosis associated with lobular inflammation or ballooning, and those with all three features (which combined define NASH).[6] Additionally, patients may have various degrees of fibrosis ranging from an almost normal liver through to extensive fibrosis and cirrhosis.[5]

Epidemiology

Determining the prevalence of subtypes of NAFLD in the general population and, more specifically, in those with T2D is hindered by the fact that a liver biopsy is required to make a definitive diagnosis. This has made epidemiologic studies very difficult, and data from the literature are generally either lacking or unreliable. In my opinion, the best available data (as of late 2021) for patients with NAFLD and T2D come from the interim results of our ongoing Quantitative Imaging in Diabetes-NASH (QUID-NASH) study. The primary aims of this study were: to validate the diagnostic accuracy of a panel of non-invasive tests (the 'Nash FibroTest' panel, which includes FibroTest [or FibroSure], NashTest-2, and SteatoTest-2, compared with histopathologic evaluation; and to develop a "virtual liver biopsy" based on blood markers and quantitative imaging data.[3] Patients included in this prospective, multicenter study were outpatients with T2D who were scheduled to have a liver biopsy for suspected NAFLD (based on ultrasonography and mild increases in transaminases), and had no other etiology for liver disease. Published evaluable data are available for 272 patients (median age 59 years, 62% female), which is a relatively large number compared with historic epidemiologic trials in this field. The characteristics of these patients are typical for T2D, with a high body mass index (BMI, median 32 kg/m^2), a median glycated hemoglobin of 7.5%, approximately two-thirds of patients with diagnosed hypertension, and a certain degree of vascular complications. What is striking in this population are the very mild anomalies of the liver function tests; median platelet count and bilirubin were normal.[3] Additionally, the median gamma-glutamyl transferase (GGT) level was just above normal (56 IU/L), while aspartate transaminase (AST) and alanine transaminase (ALT) levels were at the upper limit of normal (35 and 49 IU/L, respectively).[3] In spite of these mild anomalies, upon biopsy, all patients met the criteria for NAFLD, and there was heterogeneity in the dichotomous variable of NASH versus non-NASH. Compared with previous publications, a high proportion of patients were diagnosed with NASH (59.6%). There was also marked heterogeneity in the degree of fibrosis, ranging from no fibrosis (stage F0, 19.9% of patients) to extensive fibrosis (F3, 27.2% or F4, 10.7% of patients). Thus, in spite of a relatively homogeneous presentation, there was a great variety of lesions in the liver.

Prognosis

Survival

The next question is, does this variability in nosography (which corresponds to heterogeneity in epidemiologic data) also correspond to a real variability in prognosis? And the answer is yes. Long-term data (mean follow-up of 13.7 years) in patients with biopsy-confirmed NAFLD at baseline show that, compared with matched reference populations, those with steatosis only at baseline had no significant

difference in survival, whereas those with NASH at baseline had significantly lower overall survival (70% vs. 80%, P = 0.01).[7] In a more recent, very large study (N = 1773, 42% with diabetes) in patients with biopsy-confirmed NAFLD at baseline (median follow-up of 4 years), death from any cause was lower in those with no, mild, or moderate fibrosis at baseline (F0–F2, 0.32 deaths/100 person-years) than in those with F3 fibrosis (0.89 deaths/100 person-years) or cirrhosis (F4, 1.76 deaths/100 person-years).[8] This means histopathologic classification is very relevant from a clinical point of view.

Nonfatal outcomes

Longitudinal studies show that people with simple steatosis (NAFL) have a low risk of developing cirrhosis.[6] In one such study in patients with NAFLD (48% with diabetes), after a mean follow-up of 8.3 years, cirrhosis developed in 4% of patients with NAFL alone, compared with 26% of those with NASH.[9] Long-term nonfatal outcomes are also related to the degree of fibrosis. In the above-mentioned study (N = 1773), patients with minimal or no fibrosis at baseline (F0–F2) were very unlikely to develop hepatic decompensation (0.05 events per 100 person-years), defined as new onset of any one of the following: ascites, variceal bleeding, or encephalopathy.[8] In contrast, those with bridging fibrosis (F3) and, to a greater degree, those with cirrhosis (F4) at baseline had a higher risk of decompensation (0.99 and 2.69/100 person-years, respectively). Of interest, while the rate of hepatocellular carcinoma was very low in patients with F0–F2 fibrosis (0.04/100 patient-years), it was numerically higher in those with F3 than F4 fibrosis (0.34 vs. 0.14/100 patient-years). While this finding may be the result of unaccounted-for bias, it serves as a reminder that hepatocellular carcinoma is not a complication of cirrhosis, but rather a complication of chronic liver disease. Indeed, in our clinic, we commonly see diabetic NAFLD patients who develop hepatocellular carcinoma in the absence of cirrhosis.

Predictors of outcomes

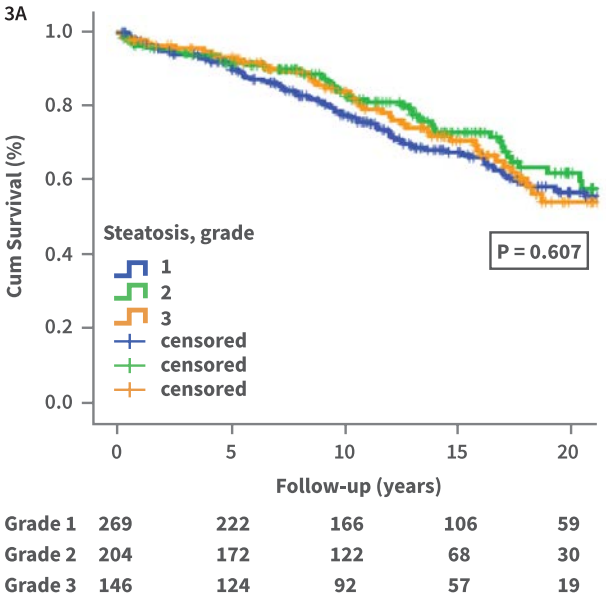
We have seen above that the degree of fibrosis corresponds to mortality and risk of disease progression. However, not all patients with NALFD show progression of fibrosis,[2] which leads us to the question: why do some patients progress while others do not? From studies of NAFLD in general, not specifically in diabetes, we know that older age, higher BMI, insulin resistance, and components of metabolic syndrome, in particular T2D, are associated with disease progression and mortality.[10] There are limited data available for the predictors of NAFLD progression specifically in patients with diabetes. The final results of the QUID-NASH study may provide an insight into predictive factors in patients with NAFLD and T2D.

The risk of NAFLD development and progression, as well variable prevalence between different ethnic groups is, to some extent, determined by genetics.[11] For example, numerous studies have shown the importance of the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene; the *PNPLA3*^{I148M} variant is associated with an increased risk of hepatic steatosis, fibrosis, and cirrhosis. Of interest, there are also gene variants that provide protection against NAFLD development or progression, such as hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) rs72613567. Although this variant has no effect on the development of steatosis, it protects against hepatic fibrosis and inflammation, hepatocyte ballooning, and advanced NAFLD and NASH. There are very few data specifically related to the influence of genetics on NAFLD development in patients with T2D. However, results of a study presented at the 2021 American Association for the Study of Liver Diseases meeting confirmed the association of *PNPLA3* polymorphisms with NAFLD in patients with T2D.[12]

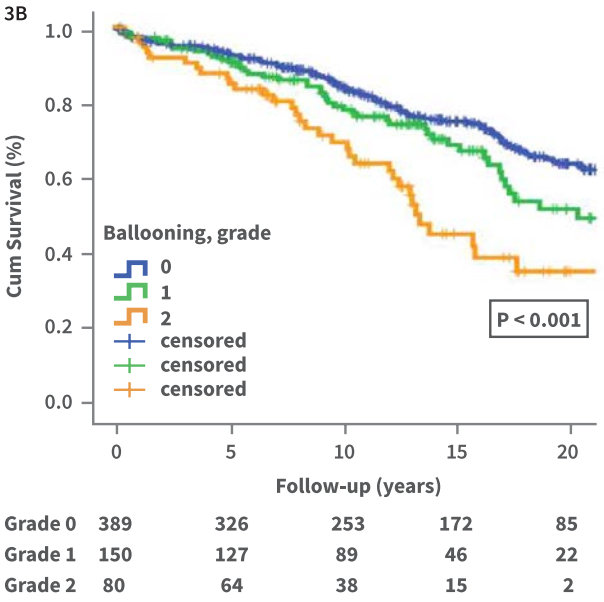
Although the diagnosis of NAFLD (by definition) excludes heavy alcohol drinkers, even moderate or binge drinking may influence the severity of liver damage.[13] In a Finnish study of 6732 individuals with no liver disease at baseline, alcohol use, even within the limits of the NAFLD definition, was associated with an increased risk of severe liver disease, and this risk was exacerbated in people with diabetes.[14]

As NASH is a severe form of NAFLD, it would be logical to assume that its presence is related to disease progression (as outlined above); however, that is not necessarily the case. Long-term studies in patients with NAFLD show that, while the presence of NASH increases the risk of all-cause mortality and liver-related outcomes, this increased risk is not significant after adjusting for confounders, such as stage of fibrosis, age, sex, and T2D.[15,16] Because there is a clear association between NASH and higher stages of fibrosis, the true impact of NASH may be lost when fibrosis is adjusted for. Another possible explanation is that, at the histopathologic level, the exact drivers of disease progression remain unknown. We know that it is not steatosis or lobular inflammation; there is no significant association between the grade of these features and survival (**Figure 1**).[15] In contrast, the degree of ballooning and portal inflammation are associated with survival, as well as with the degree of fibrosis (**Figure 1**). Portal inflammation is accounted for in the diagnosis of other liver diseases, but it is not a component of the NAFLD activity score. Thus, it is clear that our knowledge regarding the drivers of NAFLD progression is still insufficient.

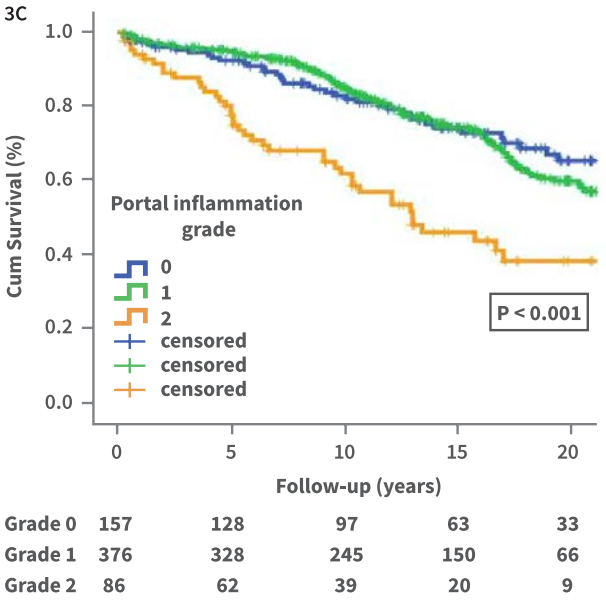
Figure 1: *Survival free of liver transplantation based on liver histology features in patients with NAFLD (N=619) who were followed up for a median of 12.6 years. A) steatosis grade, B) ballooning grade, C) portal inflammation grade, D) lobular inflammation grade. Reprinted from Gastroenterology, Vol 149(2), Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease, 389-397.e310, Copyright 2015, with permission from Elsevier.*



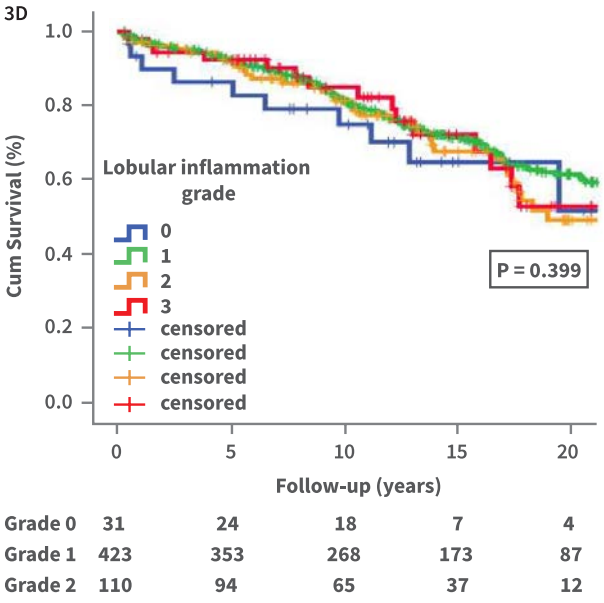
Grade 1	269	222	166	106	59
Grade 2	204	172	122	68	30
Grade 3	146	124	92	57	19



Grade 0	389	326	253	172	85
Grade 1	150	127	89	46	22
Grade 2	80	64	38	15	2



Grade 0	157	128	97	63	33
Grade 1	376	328	245	150	66
Grade 2	86	62	39	20	9



Grade 0	31	24	18	7	4
Grade 1	423	353	268	173	87
Grade 2	110	94	65	37	12
Grade 3	55	48	31	16	6

Conclusions

The marked heterogeneity of NAFLD is apparent in the variability in progression towards advanced fibrosis, with some patients progressing rapidly and others never progressing beyond NAFL. The pathogenesis of NAFLD progression is still poorly understood, which hampers our understanding of the disease heterogeneity. There is a clear association between fibrosis stage and disease outcome, but this finding does not address the question of why some patients develop fibrosis while others do not. The risk of NAFLD development and progression is, to some extent, determined by genetics. It is also possible that progression is associated with, or even driven by, metabolic syndrome and insulin resistance, as well as by moderate alcohol intake.

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