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Fibrosis Progression Rate in Biopsy-proven Nonalcoholic Fatty Liver Disease among People with Diabetes versus People without Diabetes: A Multicenter Study

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Abstract

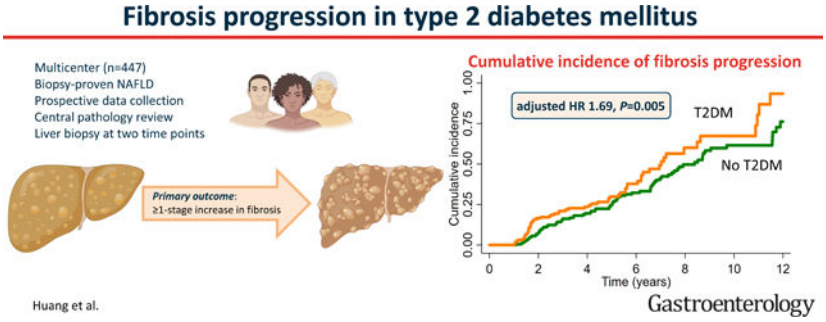
Background and aims: There are limited data regarding fibrosis progression in biopsy-proven nonalcoholic fatty liver disease (NAFLD), between people with type 2 diabetes mellitus (T2DM) versus people without T2DM. We assessed the time to fibrosis progression in people with T2DM versus people without T2DM in a large, multicenter, study of people with NAFLD who had paired liver biopsies.

Methods: This study included 447 adult participants (64% female) with NAFLD who had paired liver biopsies >1 year apart. Liver histology was systematically assessed by a central pathology committee blinded to clinical data. The *primary outcome* was the cumulative incidence of a ≥1-stage increase in fibrosis, compared between participants with T2DM versus participants without T2DM.

Results: The mean (±SD) age and BMI were 50.9 (±11.5) years and 34.7 (±6.3) kg/m^2, respectively. The median (IQR) time between biopsies was 3.3 (1.8–6.1) years. Participants with T2DM had a significantly higher cumulative incidence of fibrosis progression at 4-years (24% versus 20%), 8-years (60% versus 50%), and 12-years (93% versus 76%), P=0.005. Using a multivariable Cox proportional hazards model adjusted for multiple confounders, T2DM remained an independent predictor of fibrosis progression (adjusted hazard ratio 1.69, 95%CI 1.17 – 2.43, P=0.005). The cumulative incidence of fibrosis regression by ≥1 stage was similar between participants with T2DM versus participants without T2DM, (P=0.24).

Conclusion: In this large, multicenter cohort study of well-characterized participants with NAFLD and paired liver biopsies, we demonstrate that fibrosis progresses faster in participants with T2DM compared to participants without T2DM. These data have important implications for clinical practice and trial design.

Graphical Abstract



Keywords

Nonalcoholic steatohepatitis; NAFLD; cirrhosis; type 2 diabetes mellitus

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) affects a third of the global adult population and is one of the fastest-growing causes of liver-related morbidity and mortality [1–5]. NAFLD encompasses nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), the inflammatory form of NAFLD that may progress to advanced fibrosis and hepatocellular carcinoma [6–10]. The risk of all-cause and liver-related mortality in NAFLD increases substantially with each increment in the fibrosis stage, and individuals with advanced fibrosis are at the highest risk of hepatic decompensation and death [11–14]. Concurrent with the obesity epidemic, up to 10% of the global population has type 2 diabetes mellitus (T2DM), more than a third of individuals with T2DM have NASH, and around one in six harbors advanced fibrosis [15, 16]. In general, liver fibrosis progresses by one stage over seven years for individuals with NASH, but the time to fibrosis progression in people with T2DM versus people without T2DM is unknown [17].

While several studies have described an association between T2DM and fibrosis progression [18–22], the time to fibrosis progression in biopsy-proven NAFLD, compared between people with T2DM versus people without T2DM has not been systematically assessed. Therefore, we conducted a large, multicenter cohort study within the NASH Clinical Research Network (CRN) consortium to examine the time to fibrosis progression, and time to fibrosis regression, between people with and without T2DM who had available paired liver biopsies.

METHODS

Study design

This study included adult participants with NAFLD who had paired liver biopsies that were at least one year apart, recruited at eight sites across the United States as part of the ongoing National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored NASH CRN consortium. This multi-center study included participants from the non-interventional registries of the NASH CRN consortium (NAFLD Database Study Phases 1, 2, and 3) and participants from the placebo arms of the PIVENs (NCT00063622) and FLINT (NCT01265498) trials [23, 24]. A total of 447 well-characterized participants

who underwent serial liver biopsy assessments at two distinct time points were included. All participants provided written informed consent, and the study was approved by the institutional review board at each participating site and the data coordinating center.

Inclusion and exclusion criteria

Participants ≥18 years of age with biopsy-proven NAFLD and written informed consent were included. Participants were included if they underwent a liver biopsy, had laboratory and physical measurements within six months of the liver biopsy, and underwent a subsequent liver biopsy more than one year after the first liver biopsy. Participants were excluded if they were enrolled in the treatment arm of a clinical trial, had type 1 diabetes mellitus, had liver disease other than NAFLD, had an Alcohol Use Disorders Identification Test questionnaire suggestive of unhealthy alcohol use[25], had received a liver transplant, or had hepatocellular carcinoma.

Clinical and laboratory data

Clinical and laboratory data were obtained at baseline (enrollment) and prospectively at 48-week intervals in a protocol-mandated manner. Clinical and laboratory data were also recorded at the time of any liver biopsies. The presence of T2DM at baseline was based on the clinical practice recommendations from the American Diabetes Association and included any of the following criteria: HbA1c ≥ 6.5%; fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L); plasma glucose ≥ 200 mg/dL (11.1 mmol/L); medical diagnosis of T2DM or use of medications to treat T2DM [26], while the metabolic syndrome was defined based on ATP III criteria (having at least 3 of the following 5 factors: impaired fasting glucose ≥110 mg/dL; waist circumference ≥88 cm in women, ≥102 cm in men, triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <50 mg/dL in women, 40 mg/dL in men, systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg [27].

Histological assessment

All participants underwent a liver biopsy at baseline, followed by subsequent liver biopsies at time points determined by the standard of care; in participants with more than two biopsies, the latest biopsy was compared to the first biopsy. Liver histology assessment for grade and stage was conducted per NASH-CRN protocol as a consensus review of glass slides for each feature of the NAS score and stage. The biopsy specimens were examined by the NASH CRN central pathology committee, which comprised of at least three pathologists during each assessment. Pathologists were unaware of clinical data or the sequence of the biopsy at the time of review. H&E and trichrome stained slides were reviewed for NAS components (steatosis, lobular activity, and ballooning degeneration) and fibrosis stage per NASH-CRN criteria and practice [28]. Separately, a diagnosis of NASH, borderline NASH, NAFLD not NASH, or not NAFLD was made based on recognition of the distinctive features of steatohepatitis independent of the NAS. [29].

Outcome measures

The *primary outcome* was the cumulative incidence of a ≥1-stage increase in fibrosis, compared between participants with T2DM versus participants without T2DM. The

secondary outcome was the cumulative incidence of a ≥1-stage decrease in fibrosis, compared between participants with T2DM versus participants without T2DM.

Statistical analyses

Descriptive statistics of participant demographic, laboratory, histological, and imaging characteristics at baseline were presented and dichotomized by the presence of T2DM at baseline. Baseline categorical variables were compared with chi-square, and continuous variables were compared using a t-test or Wilcoxon two-sample test where appropriate. Survival analysis was conducted to evaluate time-to-fibrosis progression. The Cox proportional hazards model was used to evaluate the hazards ratio (HR) for fibrosis progression, and fibrosis regression, between participants with T2DM at baseline versus participants without T2DM at baseline, adjusted for age, gender, BMI, Hispanic ethnicity, and baseline fibrosis stage. Participants with fibrosis stage 4 at baseline were excluded from the analysis for fibrosis progression since there can be no further progression measured with the NASH CRN scoring system, and participants with fibrosis stage 0 at baseline were excluded from the analysis for fibrosis regression since there can be no further regression. The fibrosis progression rate was defined by the increase in fibrosis stage over time between biopsies (years) and compared between participants with T2DM at baseline versus participants without T2DM at baseline using linear regression, adjusted for age, gender, ethnicity/race, body mass index, and baseline fibrosis stage [30]. In the analysis for fibrosis progression rate, participants with fibrosis regression on the latest biopsy were censored. The proportion of participants who progressed from fibrosis stage 0–2 at baseline to advanced fibrosis (stage 3–4) on the latest liver biopsy was compared between participants with T2DM at baseline versus those without T2DM at baseline using the chi-squared test. The Cox proportional hazards model was used to evaluate the HR for fibrosis progression, and fibrosis regression, between the top quartile of HbA1c values versus the others (decided a priori). Multiple sensitivity/subgroup analyses were performed, these included comparing the participants in the current study with participants in the wider NASH-CRN who did not receive a second biopsy; determining the association between progression in non-invasive tests and the presence of T2DM; including only participants with a biopsy specimen length ≥ 15 mm; excluding participants who developed incident T2DM after enrollment into the study; and adjusting for center effects, participation in a clinical trial, and the impact of medication classes on fibrosis progression. Statistical significance was defined as a two-tailed P value of ≤0.05. Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), Stata software, version 15.1 (StataCorp), and GraphPad Prism.

RESULTS

Characteristics of the study population

A total of 3,446 participants were enrolled between October 2004 through March 2022 (Figure 1), including 83 participants who were enrolled in the placebo arm of the PIVENs trial[23] and 142 who were enrolled in the placebo arm of the FLINT trial, before applying inclusion and exclusion criteria [24]. After applying inclusion and exclusion criteria (Figure 1), a total of 447 adult participants with NAFLD (64% female) and available paired liver

biopsies were included in this study. The final study cohort included 65 and 82 participants from the placebo arms of the PIVENS and FLINT trials, respectively. The mean (±SD) age and BMI were 50.9 (±11.5) years and 34.7 (±6.3) kg/m^2, respectively. Most participants (85%) were White, and 10% were Hispanic. The number of participants with baseline fibrosis stage 0, 1, 2, 3, and 4 was 93, 116, 103, 115, and 20, respectively. The median (IQR) time between biopsies was 3.3 (1.8–6.1) years.

Participants with T2DM at baseline were older (53.0 years versus 49.1 years, $P<0.001$), had a greater proportion of females (70% versus 58%, P=0.006), had higher BMI (35.6 kg/m^2 versus 33.9 kg/m^2, P=0.005), were more likely to have the metabolic syndrome (74% versus 61%, $P=0.006$), had higher NAS (5.0 versus 4.5, $P=0.003$), had a higher proportion of definite or borderline NASH (79% versus 57%, $P<0.001$), had a greater proportion with advanced fibrosis (stage 3–4) (39% versus 22%, $P<0.001$) on initial biopsy, and had a shorter median [IQR] time between biopsies (2.8 [1.7–5.5] years versus 3.9 [2.0–6.9] years, $P=0.001$) compared to participants without T2DM.

Progression and regression of fibrosis

The transitions of the fibrosis stages are summarized in Supplemental Table 1. Overall, 151 participants (35%) experienced fibrosis progression, 194 participants (43%) had no change in the fibrosis stage, and 102 participants (23%) had fibrosis regression. A greater proportion of participants with T2DM progressed from stage 0–2 fibrosis at baseline to advanced fibrosis (stage 3–4) versus participants without T2DM (26.0% versus 14.1%, $P=0.008$) despite a shorter median (IQR) time between biopsies (2.8 [1.7–5.5] years versus 3.9 [1.7–5.5] years, $P=0.001$). There was no difference in the proportion with regression from advanced fibrosis (stage 3–4) to stage 0–2 fibrosis between participants with T2DM versus participants without T2DM (27% versus 22%, $P=0.52$).

Fibrosis progression in participants with T2DM versus participants without T2DM

Among participants with baseline fibrosis stage 0 or 1, the mean (SD) fibrosis progression rate was higher in participants with T2DM versus participants without T2DM (+0.23 [0.39] stages per year versus +0.16 [0.26] stages per year, $P=0.048$), after adjustment for age, gender, ethnicity/race, body mass index, and baseline fibrosis stage.

Participants with T2DM at baseline had a significantly higher cumulative incidence of fibrosis progression by ≥1 stage at 4-years (24% [95% CI 18–31] versus 20% [95% CI 14–26]), 8-years (60% [95% CI 47–73] versus 50% [95% CI 41–59]) and 12-years (93% [95% CI 76–99] versus 76% [CI 64–87]), $P=0.005$ after adjustment for age, gender, ethnicity/race, body mass index, and baseline fibrosis stage, compared with participants without T2DM at baseline (Figure 2).

Association of T2DM with fibrosis progression

In unadjusted analysis, T2DM at baseline was associated with fibrosis progression (HR 1.45, 95% CI 1.04 – 2.03, $P=0.03$) (Table 2). After multivariable adjustment for age, gender, BMI, race/ethnicity, and baseline fibrosis stage, the presence of T2DM at baseline remained statistically significant and an independent predictor of fibrosis progression (adjusted HR

1.69, 95% CI 1.17 – 2.43, *P*=0.005). HbA1c ≥ 7.0% was not associated with fibrosis progression in both unadjusted and multivariable-adjusted analyses (Supplemental Table 2).

Fibrosis regression in participants with T2DM versus participants without T2DM

The cumulative incidence of fibrosis regression by ≥1 stage was similar between participants with T2DM versus participants without T2DM at 4-, 8-, and 12-years (*P*=0.24) (Supplemental Figure 1). The presence of T2DM was not a predictor of fibrosis regression, both in unadjusted and multivariable-adjusted analyses (Table 2).

Subgroup and sensitivity analyses

Sensitivity analyses were conducted after excluding 69 participants without T2DM at baseline who developed incident T2DM after study enrollment. T2DM remained an independent predictor for fibrosis progression, after adjustment for age, gender, BMI, Hispanic ethnicity, and baseline fibrosis stage (adjusted HR 1.73, 95% CI 1.13 – 2.65, *P*=0.01), but was not a predictor of fibrosis regression (Supplemental Table 3). The cumulative incidence of fibrosis progression by ≥1 stage remained higher in participants with T2DM versus participants without T2DM (Supplemental Figure 2). The cumulative incidence of fibrosis regression by ≥1 stage remained similar between groups (Supplemental Figure 3). There was a lower proportion of participants with T2DM that were enrolled in clinical trials, compared to those without T2DM (26% versus 39%, *P*=0.002). However, the association between T2DM and fibrosis progression remained consistent even after adjustment for center and clinical trial participation (Supplemental Table 4). Participants in the wider NASH-CRN cohort without a follow-up biopsy had similar demographics to the participants that were included in the current study (with a follow-up biopsy), but were more likely to have cirrhosis (stage 4 fibrosis) and were less likely to have a definite diagnosis of NASH on the baseline biopsy (Supplemental Table 5). Analysis of the wider NASH-CRN cohort (inclusive of participants with and without a follow-up liver biopsy) revealed a higher rate of progression in non-invasive tests between participants with T2DM versus those without T2DM (Supplemental Table 6). Fibrosis progression was associated with an increase in FIB-4 and a decrease in platelets, but not aspartate aminotransferase, alanine aminotransferase, or HbA1c (Supplemental Table 7).

We performed a sensitivity analysis among participants with biopsy specimen length ≥ 15 mm, and determined similar findings to the main analysis (Supplemental Table 8). All participants receive lifestyle and dietary advice, and we provided data on the proportion that received Vitamin E, thiazolidinediones, and glucagon-like peptide-1 receptor agonists between the two groups in Supplemental Table 9. The association of T2DM with fibrosis progression remained consistent after adjusting for medication classes (Supplemental Table 10). Among participants with fibrosis progression, there was a reduction in the NAS and steatosis scores, but not in lobular inflammation or ballooning scores (Supplemental Table 11).

DISCUSSION

Main findings

In this large, multicenter center study of well-characterized participants with paired liver biopsies within the NASH CRN consortium, we determined that fibrosis progresses faster in participants with T2DM versus participants without T2DM. The 4-year (24% versus 20%), 8-year (60% versus 50%), and 12-year (93% versus 76%) cumulative incidences of fibrosis progression were significantly higher in participants with T2DM versus participants without T2DM. Among participants with baseline fibrosis stage 0 or 1, the fibrosis progression rate was significantly higher in participants with T2DM versus participants without T2DM. T2DM remained a significant predictor of fibrosis progression, even after adjustment for age, gender, BMI, race/ethnicity, and baseline fibrosis stage. These findings remained consistent in sensitivity analyses excluding participants who developed incident T2DM after study enrollment. By contrast, the cumulative incidence of fibrosis progression was similar between participants with T2DM versus participants without T2DM, which may be related to the fact that the majority of participants with T2DM had adequate T2DM control. In addition, the NASH-CRN protocol was designed with a focus on determining fibrosis progression, and may not be optimal for identifying regression [28].

These data have important implications. The faster time to fibrosis progression in people with T2DM should be taken into consideration when designing NASH therapeutic trials and underscores the importance of ensuring comparable proportions of participants with T2DM in treatment and control arms [31]. While the incidence of fibrosis progression in participants with T2DM was significantly higher than in those without T2DM, the absolute difference was modest, which may be related to the fact that most of the study participants with T2DM had adequate glycemic control. Care providers should emphasize the importance of lifestyle measures and good glycemic control to people with T2DM.

In context with current literature

Liver fibrosis has been established as the major determinant of outcomes in people with NAFLD [11, 12, 32, 33]. A landmark prospective study of 1,773 people with NAFLD demonstrated an increased risk of liver-related complications and death among those with advanced fibrosis (stage 3–4), highlighting the need to detect and prevent fibrosis progression [13]. A study of 1,770 people with T2DM who underwent vibration-controlled transient elastography [VCTE] by the M probe determined that 17% had a liver stiffness measurement suggestive of advanced fibrosis (defined as ≥9.6 kPa in this study) [34]. A study of 501 people aged ≥50 years with T2DM characterized by elastography (magnetic resonance elastography in 83% and VCTE in the others) determined that the prevalence of advanced fibrosis was 14% [35]. Another study of people with T2DM performed a follow-up VCTE after 3 years and determined that 4% with baseline liver stiffness measurement <10 kPA had a liver stiffness measurement ≥10 kPa on follow-up [36]. Although these studies demonstrated an association between T2DM and fibrosis progression, the time to fibrosis progression between people with T2DM versus people without T2DM was previously unknown. [18, 21, 37]. In addition, previous paired biopsy studies had modest numbers[18, 21], or depended on non-invasive tests or ICD-codes as surrogate measures for fibrosis[37]. The

current study fills this knowledge gap and demonstrates that T2DM is associated with a significantly higher cumulative incidence of fibrosis progression, possibly related to the stimulating effect of hyperinsulinemia and high glucose levels on hepatic stellate cells [38].

Strengths and limitations

This is the first study reporting the time to fibrosis progression in people with T2DM versus people without T2DM. Its strengths include prospective data collection, multicenter study design, large sample size, and well-characterized participants with serial, centrally read liver biopsies. However, it is not without limitations. The sampling variability of liver biopsy may affect the classification of fibrosis stage. Histologic staging may underestimate the changes that are present and more sensitive quantification of histology by image analysis may show additional changes between people with and without T2DM. The reporting of fibrosis stages may have been susceptible to misclassification due to the sampling variability of liver biopsy, although previous studies reporting sampling variability were exacerbated by observational variability [39]. We did not calculate the collagen proportionate area, which may have added further granularity to the results. The median time between biopsies was relatively short (3.3 years) given the slow rate of disease progression in NAFLD, therefore, studies with longer follow-ups may be required. The cumulative incidence of fibrosis progression and regression might differ by fibrosis stage, but the sample size was insufficient to meaningfully analyze the time to fibrosis progression stratified by each fibrosis stage. However, we adjusted for the baseline fibrosis stage in our analyses. The analysis for fibrosis progression rate was based on previous studies of fibrosis progression in the literature [30], however, we limited the reporting of fibrosis progression rate to participants with stage 0 or 1 fibrosis. The majority of participants with T2DM had an HbA1c consistent with adequate glycemic control, and we speculate that a larger cohort of participants may be necessary to determine the role of different levels of glycemic control on fibrosis progression and regression. We excluded participants who had been randomized to the active treatment arm of the completed PIVENS or FLINT trials. However, we did not exclude participants in active treatment arms of clinical trials conducted outside of the NASH CRN, which may have introduced some degree of bias. We acknowledge that fibrosis progression and regression may not always be a linear process, with paired biopsy studies revealing that histological improvement may be followed by worsening, and vice-versa [40]. The current analysis was based on irregular biopsy intervals and may represent an oversimplification [40]. While we determined that the demographic characteristics of included participants in this study were similar to those within the NASH CRN without a follow-up biopsy, there may have been some degree of selection bias, as care providers may have been less likely to request a liver biopsy in people who were assessed to have an improvement. Future studies that perform protocolled interval biopsies may be helpful.

Conclusion

In this large, multicenter cohort study of well-characterized participants with NAFLD and paired liver biopsies, we demonstrate that fibrosis progresses faster in people with T2DM compared to people without T2DM. T2DM remained a strong and independent predictor for fibrosis progression, even after adjustment for multiple confounders. The faster fibrosis progression in people with T2DM should be taken into consideration when designing

therapeutic trials and underscores the unmet need for efficacious therapies in this high-risk group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data transparency statement:

Data will not be made publicly available.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviations:

NASH	nonalcoholic steatohepatitis
NAFLD	nonalcoholic fatty liver disease
T2DM	type 2 diabetes mellitus

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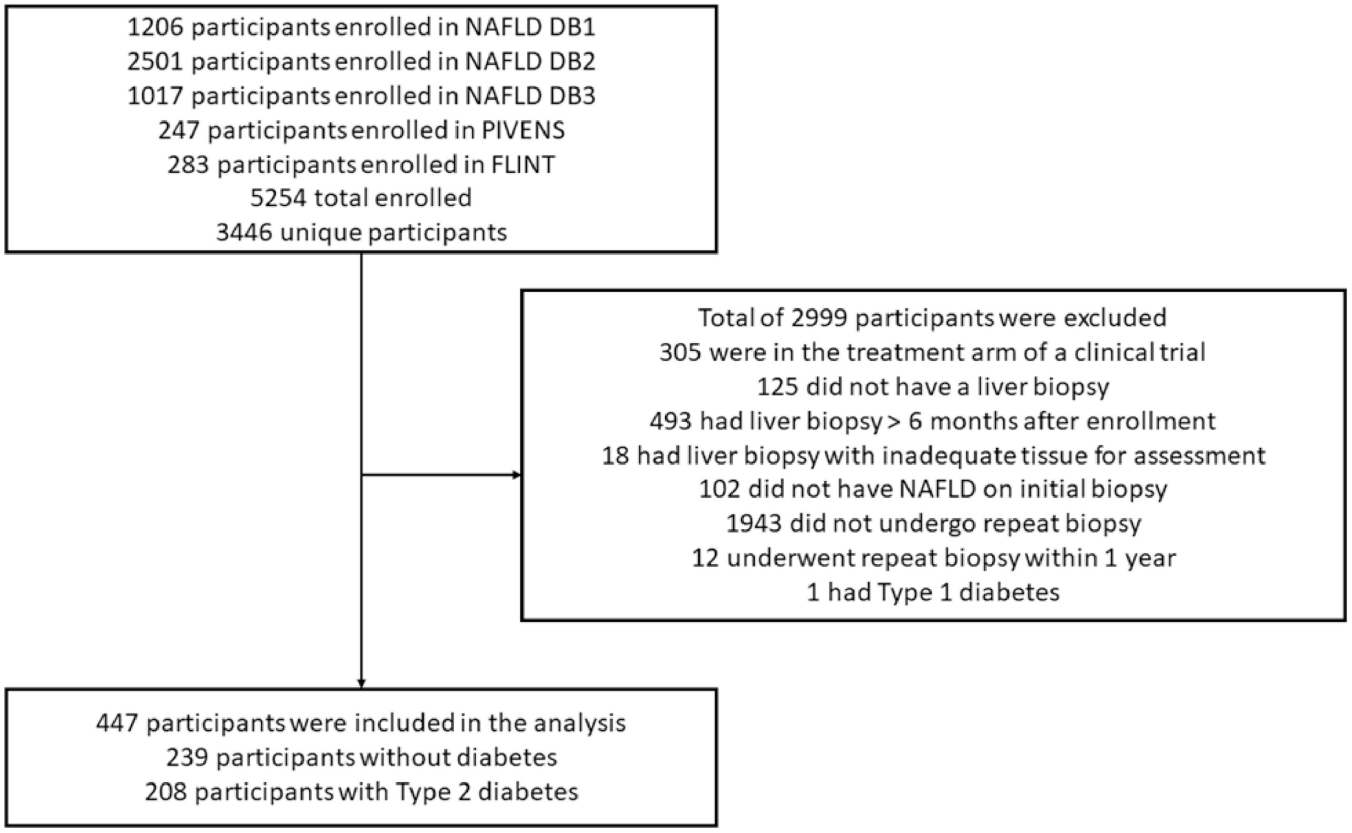

Figure 1.
Study flow diagram

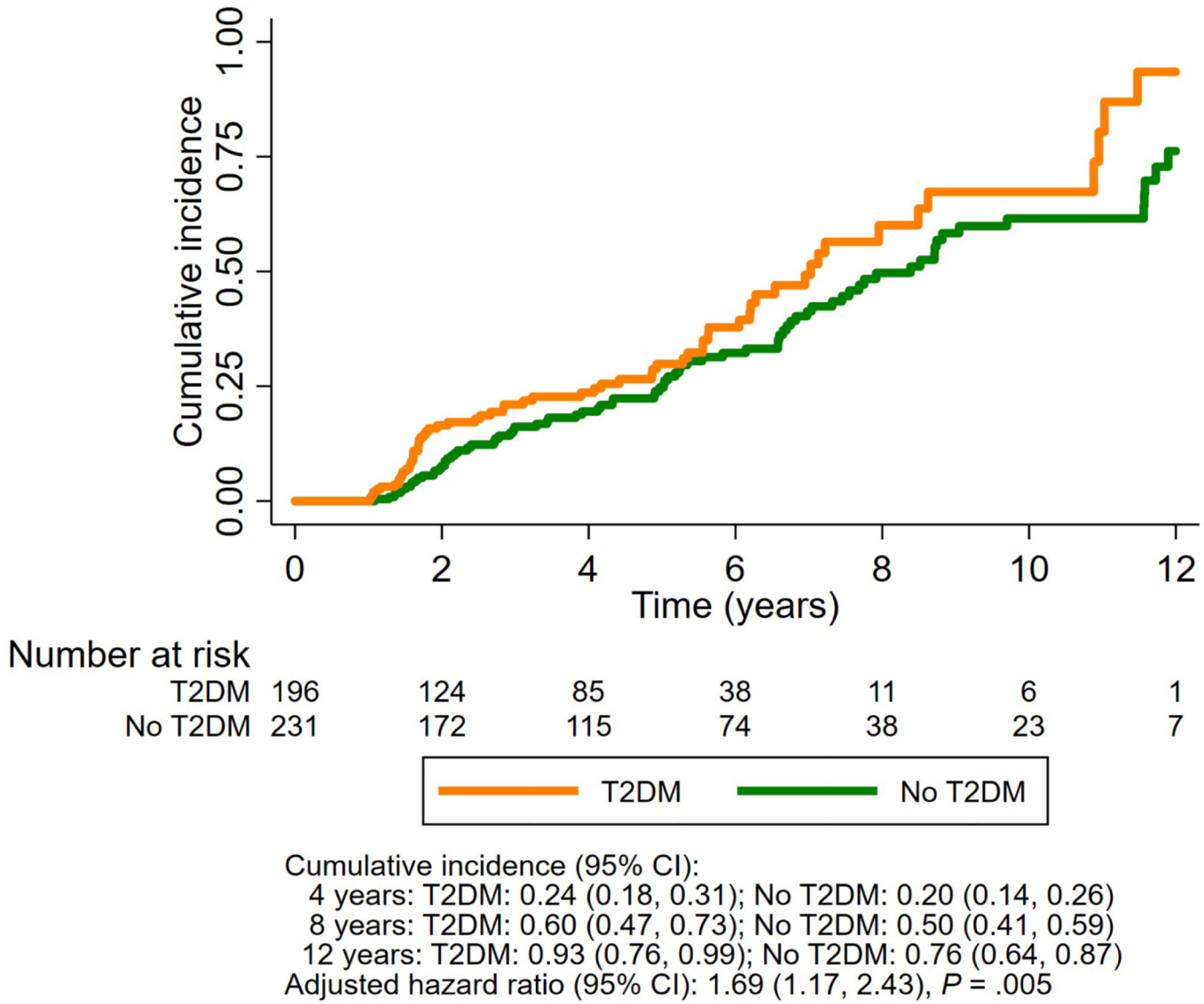

Figure 2.

Cumulative incidence of fibrosis progression in nonalcoholic fatty liver disease, among participants with T2DM versus participants without T2DM

Abbreviation: T2DM, type 2 diabetes mellitus

Table 1.

Baseline characteristics of participants with paired biopsies, stratified by the presence of T2DM at baseline

Variable	Overall (N=447)	No T2DM (N=239)	T2DM (N=208)	*P*-value
Demographics				
Age — yr	50.9 (11.5)	49.1 (12.1)	53.0 (10.4)	<0.001
Sex — no. (%)				0.006
Male	163 (36%)	101 (42%)	62 (30%)	
Female	284 (64%)	138 (58%)	146 (70%)	
Race — no. (%)				0.09
White	381 (85%)	210 (88%)	171 (82%)	
Other or not reported	66 (15%)	29 (12%)	37 (18%)	
Hispanic ethnic group				0.15
Yes	46 (10%)	20 (8%)	26 (13%)	
No	401 (90%)	219 (92%)	182 (88%)	
Body-mass index				
Mean (SD)	34.7 (6.3)	33.9 (6.1)	35.6 (6.4)	0.005
Distribution — no. (%)				0.005
<25	13 (3%)	10 (4%)	3 (1%)	
25 to <30	91 (20%)	61 (26%)	30 (14%)	
30 to <35	168 (38%)	80 (33%)	88 (42%)	
≥35	175 (39%)	88 (37%)	87 (42%)	
Median time between biopsies (IQR) — yr	3.3 (1.8, 6.1)	3.9 (2.0, 6.9)	2.8 (1.7, 5.5)	0.001
Comorbidities— no. (%)				
Hypertension	256 (57%)	108 (45%)	148 (71%)	<0.001
Coronary artery disease	19 (4%)	7 (3%)	12 (6%)	0.16
Metabolic syndrome	298 (67%)	145 (61%)	153 (74%)	0.006
Baseline histologic features				
NAFLD activity score	4.8 (1.6)	4.5 (1.6)	5.0 (1.6)	0.003
Steatosis score				0.12

Gastroenterology. Author manuscript; available in PMC 2024 August 01.

Variable	Overall (N=447)	No T2DM (N=239)	T2DM (N=208)	P-value
0	11 ** (2%)	3 (1%)	8 (4%)	
1	149 (33%)	86 (36%)	63 (30%)	
2	161 (36%)	79 (33%)	82 (39%)	
3	126 (28%)	71 (30%)	55 (26%)	
Lobular inflammation score				0.17
0	2 (<1%)	2 (1%)	0 (0%)	
1	205 (46%)	117 (49%)	88 (42%)	
2	179 (40%)	93 (39%)	86 (41%)	
3	61 (14%)	27 (11%)	34 (16%)	
Ballooning score				<0.001
0	111 (25%)	78 (33%)	33 (16%)	
1	142 (32%)	76 (32%)	66 (32%)	
2	194 (43%)	85 (36%)	109 (52%)	
Fibrosis stage – mean (SD)	1.7 (1.2)	1.4 (1.2)	2.0 (1.1)	<0.001
Stage 0	93 (21%)	70 (29%)	23 (11%)	<0.001
Stage 1	116 (26%)	64 (27%)	52 (25%)	
Stage 2	103 (23%)	51 (21%)	52 (25%)	
Stage 3	115 (26%)	46 (19%)	69 (33%)	
Stage 4	20 (4%)	8 (3%)	12 (6%)	
NASH diagnosis				<0.001
Definite/borderline NASH	301 (67%)	137 (57%)	164 (79%)	
NAFLD, not NASH	146 (33%)	102 (43%)	44 (21%)	
Biopsy specimen length — mm	20.0 (9.5)	18.7 (8.8)	21.5 (9.9)	0.002
Laboratory results – Median (IQR)				
ALT — U/L	63 (44, 94)	66.0 (47, 96)	60.5 (40, 92)	0.08
AST — U/L	44 (32, 67)	43 (32, 69)	45 (31, 64)	0.50
ALP — U/L	79 (65, 96)	79 (67, 94)	78 (65, 99)	0.98
Total bilirubin — mg/dl	0.6 (0.4, 0.8)	0.7 (0.5, 0.9)	0.5 (0.4, 0.8)	<0.001
INR – mean (SD)	1.02 (0.15)	1.01 (0.09)	1.02 (0.19)	0.45

Variable	Overall (N=447)	No T2DM (N=239)	T2DM (N=208)	*P*-value
Serum creatinine — mg/dl, mean (SD)	0.83 (0.18)	0.87 (0.19)	0.78 (0.17)	<0.001
eGFR — ml/min/1.73 m^2	93.5 (79.6, 104.7)	91.7 (78.7, 104.1)	95.6 (81.2, 105.3)	0.19
Serum albumin — g/dl	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)	0.75
Platelets per μL	242 (203, 287)	245 (204, 287)	238 (201, 287)	0.56
FIB-4	1.2 (0.8, 1.7)	1.1 (0.8, 1.7)	1.3 (0.9, 1.8)	0.03
HbA1c — %	6.0 (5.5, 6.7)	5.6 (5.3, 5.9)	6.8 (6.2, 7.4)	<0.001
Fasting glucose – mg/dL	100.0 (89.0, 118.0)	93.0 (86.0, 101.0)	118.0 (98.0, 143.0)	<0.001
Fasting insulin – ng/mL	19.0 (13.6, 29.0)	18.3 (13.0, 25.4)	20.0 (14.2, 32.9)	0.03
HOMA-IR	4.7 (3.3, 7.8)	4.2 (3.0, 5.9)	5.9 (3.8, 10.8)	<0.001
Total cholesterol - mg/dL	188.0 (163.0, 220.0)	194.0 (173.0, 222.0)	179.0 (158.0, 215.0)	0.002
HDL cholesterol – mg/dL	41.0 (35.0, 50.0)	41.0 (34.0, 51.0)	41.0 (35.0, 49.0)	0.65
LDL cholesterol – mg/dL	115.0 (90.0, 141.0)	121.0 (97.0, 147.0)	106.0 (83.0, 135.0)	<0.001
Triglycerides – mg/dL	152.0 (109.0, 211.0)	148.0 (105.0, 208.0)	160.5 (111.5, 218.5)	0.08

[*] Values are medians (IQR) unless otherwise noted. Percentages may not total 100 because of rounding. Data were missing for the following variables: metabolic syndrome (N=4), biopsy length (N=1), insulin (N=3), HOMA-IR (N=3), HDL cholesterol (N=1), LDL cholesterol (N=9).

Abbreviations: T2DM, type 2 diabetes mellitus; INR, international normalized ratio; IQR interquartile range; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

[†] Race and ethnic group were reported by the participant.

[‡] Body-mass index is the weight in kilograms divided by the square of the height in meters. A body-mass index of less than 25 indicates normal weight, of 25 to less than 30 overweight, 30 to less than 35 obese, and 35 or above morbid obesity.

[§] The NAFLD activity score was assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2).

[¶] The fibrosis stage was assessed on a scale of 0 to 4, with higher scores indicating more severe fibrosis and stage 4 defining cirrhosis.

[‖] The eGFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

[**] Among these 11 participants, 8 had advanced fibrosis (stage 3 or 4) and a diagnosis of borderline or definite NASH; 1 participant had F1 fibrosis and a diagnosis of definite NASH; and 2 participants had F2 fibrosis and a diagnosis of borderline NASH.

Table 2.

Predictors of (A) fibrosis progression and (B) fibrosis regression

(A) Predictors of fibrosis progression	**Hazard Ratio (95% CI)**	***P*-value**
T2DM, unadjusted	1.45 (1.04 – 2.03)	0.03
T2DM, adjusted for age and sex	1.42 (1.00 – 2.00)	0.05
T2DM, adjusted for age, sex, BMI, and Hispanic race/ethnicity	1.52 (1.07 – 2.17)	0.02
T2DM, adjusted for age, sex, BMI, Hispanic race/ethnicity, and baseline fibrosis stage	1.69 (1.17 – 2.43)	0.005
(B) Predictors of fibrosis regression	**Hazard Ratio (95% CI)**	***P*-value**
T2DM, unadjusted	1.15 (0.77 – 1.71)	0.49
T2DM, adjusted for age and sex	1.36 (0.90 – 2.07)	0.15
T2DM, adjusted for age, sex, BMI, and Hispanic race/ethnicity	1.38 (0.90 – 2.11)	0.14
T2DM, adjusted for age, sex, BMI, Hispanic race/ethnicity, and baseline fibrosis stage	1.29 (0.84 – 1.99)	0.24

Abbreviation: T2DM, type 2 diabetes mellitus; BMI, body mass index