Type 2 diabetes increases the risk of progression to metabolic dysfunction-associated steatohepatitis-related cirrhosis in a real world setting

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Introduction

There is an ongoing debate about whether type 2 diabetes (T2D) is independently related to a higher risk of progression to cirrhosis in metabolic dysfunction-associated steatohepatitis (MASH). Prospective, real-world data better reflects the clinical presentation. However, prospective data on the role of T2D as an independent cardiometabolic risk factor of fibrosis progression in MASH are currently lacking.

Research Question and Aim

Is T2D an independent risk factor for MASH progression to cirrhosis?
Here, we examined the relationship between T2D and the development of cirrhosis in a longitudinal observational study of people with metabolic dysfunction associated steatotic liver disease (MASLD).

Methods

Cohort

- Data were derived from the U.S. TARGET-NASH study [1]
  - ✓ Longitudinal observational cohort study including people with MASLD managed in Hepatology and Endocrinology Practices in the USA.
  - ✓ Diagnosis of T2D was derived from medical history, medication use or HbA1c ≥6.5 %
  - ✓ Index: earliest evidence of MASH during a 3-year retrospective period
- *Inclusion criteria:*
  - ✓ Age >18 years
  - ✓ Non-cirrhotic or compensated cirrhotic MASH (from clinics or biopsy)
- *Exclusion criteria:*
  - ✓ AUDIT >7
  - ✓ Diagnosis of cirrhotic/non-cirrhotic MASH >3 years before enrollment

Methods

- Risk for advanced fibrosis (≥F3) at index by non-invasive indices (NITs): Fibrosis-4 (FIB-4) and NAFLD fibrosis score (NFS)

Statistical Analysis

- Hazard ratios were derived from univariable and multivariable modeling

Table 1. FIB-4 and NFS fibrosis risk categories

Fibrosis-4 (FIB-4)	
Low fibrosis risk	FIB-4 <1.3 for participants aged <65 years or FIB-4 <2.0 for participants aged ≥65 years
High fibrosis risk	FIB-4 >2.67
NAFLD fibrosis score (NFS)	
Low fibrosis risk	NFS <-1.455
High fibrosis risk	>0.675 for participants aged <65 y or NFS >0.12 for participants aged ≥65 years

Results

Table 2. People with T2D are at an elevated risk of advanced fibrosis at index as determined by NITs

	T2D ´(n=1211)	No-T2D (n=1204)	p-value
Age at index date (years)	57.2 (11.7)	53.2 (13.6)	<0.001
Female sex	63.8%	53.6%	<0.001
BMI (kg/m^2) at index	35.4 (7.8)	32.0 (7.1)	<0.001
HbA1c (%)	7.3 (1.5)	5.6 (0.4)	<0.001
Disease severity at index (%)			<0.001
Compensated MASH cirrhosis	35.3%	19.9%	
Non-cirrhotic MASH	64.7%	80.1%	
FIB-4 (au)	2.4 (2.7)	1.9 (2.2)	<0.001
FIB-4 category			
High fibrosis risk	26.9%	17.0%	<0.001
Intermediate risk	27.2%	23.6%	
Low fibrosis risk	45.9%	59.4%	
NFS (au)	0.3 (1.8)	-1.6 (1.7)	<0.001
NFS category			
High fibrosis risk	44.4%	10.2%	<0.001
Intermediate risk	39.6%	33.2%	
Low fibrosis risk	16.0%	56.6%	
Liver stiffness (VCTE-LSM) (kPa)	14.6 (9.8)	11.1 (8.0)	<0.001
CAP (dB/m)	314.5 (59.0)	305.5 (52.5)	0.10

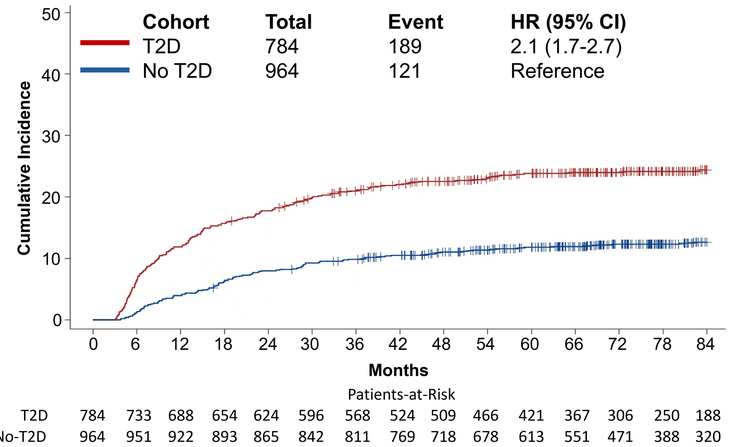
Data are shown as mean (standard deviation (SD)) and as percentages for categorical variables.

Table 3. T2D is associated with a higher prevalence of advanced fibrosis at index as determined by liver biopsy

	T2D (n=1211)	No-T2D (n=1204)	p-value
Fibrosis stage[1]			
n	178	218	<0.001
0	10.7%	17.9%	
1	18.5%	31.2%	
2	13.5%	16.5%	
3	29.2%	17.0%	
4	28.1%	17.4%	
Not Available (n)	2	4	

[1]Most recent fibrosis stage from Brunt or NAS up to or at index.

Figure 1. People with T2D and non-cirrhotic MASH have higher progression rates to cirrhosis than those without T2D



- People with non-cirrhotic MASH and T2D have a higher hazard ratio (HR) for progression to compensated cirrhotic MASH compared to those without T2D (No-T2D) after adjustment for age and sex (2.1 (1.6-2.6)) and also in the subgroups of different fibrosis risk at index (high FIB-4: 1.9 (1.1-3.1); low FIB-4: HR 2.1 (1.4-3.1)).
- Risk of progression from compensated to decompensated cirrhosis was independent of the presence of T2D at index in all individuals (1.2 (CI 0.9-1.5)) and across fibrosis risk groups (high fibrosis risk: 1.2 (0. 8-1.7); low fibrosis risk: 0.9 (0.2-4.7)).

Conclusion

Among people with MASH, the presence of T2D is associated with a higher risk of progression from MASH to cirrhosis. This underlines the importance of early case-finding of MASH in people with T2D to reduce the growing individual and societal burden of MASLD-related severe liver disease.

References

[1] Barritt et al. (2017). Design and rationale for a real-world observational cohort of patients with nonalcoholic fatty liver disease: The TARGET-NASH study. *Contemp Clin Trials,* 61, 33-38

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