

## Impact of non-alcoholic steatohepatitis on carotid atherosclerosis progression in type 2 diabetes

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**Background/Aims:** There is increasing concern about cardiovascular risk in individuals with non-alcoholic fatty liver disease. We aimed to evaluate whether hepatic steatosis with or without significant fibrosis is associated with the progression of carotid atherosclerosis in patients with type 2 diabetes mellitus (T2DM). **Methods:** From a longitudinal observational cohort, total 1,120 T2DM patients who underwent repeated carotid artery ultrasonography every 1-2 years were enrolled in this study. The ultrasonographic findings at baseline and those after 6-8 years were compared to detect the progression of carotid atherosclerosis. The presence and degree of hepatic steatosis were determined using abdominal ultrasonography, and patients with hepatic steatosis were further evaluated for the presence of hepatic fibrosis by calculating fibrosis-4 (FIB-4) index. The association between liver status and progression of carotid atherosclerosis was investigated. **Results:** Of 1,120 patients, 636 (56.8%) patients were classified as hepatic steatosis group at baseline. After 6-8 years, total 431 (38.5%) patients showed carotid atherosclerosis progression. Hepatic steatosis was significantly associated with 6-8-year progression of carotid atherosclerosis (adjusted OR[AOR]: 1.360, 95% CI: 1.004-1.844;  $p=0.047$ ). Among patients with hepatic steatosis, only individuals with hepatic fibrosis showed significant association with carotid atherosclerosis progression (AOR: 1.636, 95% CI: 1.024-2.612;  $p=0.039$ ). Furthermore, subjects who had hepatic steatosis combined with significant fibrosis and 4 or more components of metabolic syndrome criteria showed markedly increased risk of atherosclerosis progression (AOR: 2.776, 95% CI: 1.276-6.039;  $p=0.010$ ). The association between hepatic fibrosis and atherosclerosis progression was more prominent in patients with younger age, lower BMI, higher insulin sensitivity or those without metabolic syndrome (all  $p<0.05$ ). **Conclusions:** Hepatic steatosis with significant fibrosis is independently associated with the progression of carotid atherosclerosis in patients with T2DM.

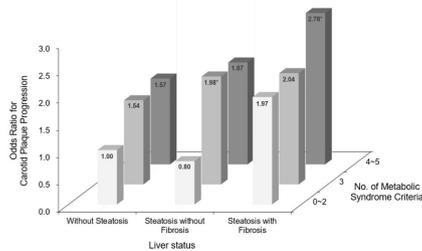


Figure. Risk of Carotid Plaque Progression by Subgroups Divided by Liver Status and No. of Metabolic Syndrome Criteria

\* p value < 0.05 versus subgroup with 0-2 metabolic syndrome criteria without hepatic steatosis

	Steatosis without Fibrosis		Steatosis with Fibrosis	
	OR (95% CI)	p value	OR (95% CI)	p value
Model 1	1.170 (0.891-1.538)	0.259	1.815 (1.314-2.507)	< 0.001
Model 2	1.352 (1.018-1.796)	0.037	1.494 (1.071-2.084)	0.018
Model 3	1.235 (0.890-1.715)	0.207	1.657 (1.148-2.391)	0.007
Model 4	1.171 (0.813-1.687)	0.397	1.710 (1.129-2.590)	0.011
Model 5	1.141 (0.777-1.675)	0.500	1.740 (1.111-2.723)	0.015
Model 6	1.107 (0.747-1.642)	0.612	1.636 (1.024-2.612)	0.039

Table. Multiple Logistic Regression Analysis of the Association Between Liver Status and the Progression of Carotid Plaque

OR, odds ratio; CI, confidence interval.

Model 1 = Crude OR without any adjustment

Model 2 = Model 1 + gender, age

Model 3 = Model 2 + DM Duration, HbA1c, LDL-C, HDL-C, statin use

Model 4 = Model 3 + alcohol history, smoking history, exercise status

Model 5 = Model 4 + SBP, DBP, KITT, Presence of CKD stage III-V

Model 6 = Model 5 + BMI