Impact of liver fibrosis on the progression of carotid atherosclerosis in patients with type 2 diabetes

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OBJECTIVE

- The aim of this study was to investigate the relationship between NAFLD with or without significant fibrosis and the risk of carotid atherosclerosis progression assessed by clinical, laboratory, and repeated imaging findings in T2DM patients.

METHODS

- A retrospective cohort study investigating 1,120 patients from Seoul Metabolic Syndrome Cohort since November 1997 to September 2016.
- Presence of hepatic steatosis was assessed by abdominal ultrasonography or Comprehensive NAFLD score. Hepatic fibrosis was defined as FIB-4 index ≥ 1.45 .
- Repeated carotid ultrasonography was performed at 6-8 year intervals. The progression of carotid atherosclerosis was defined as an appearance of newly developed lesion of carotid plaque on repeated ultrasonography.

RESULTS

Table 1. Baseline Characteristics of the Study Participants

Study Population N = 1,120	No Steatosis N = 484	Steatosis Only N = 414	Steatosis with Fibrosis N = 222	p-value
Age, years	55.4 $\pm$ 9.4	52.4 $\pm$ 9.7*	59.8 $\pm$ 7.8 [†]	< 0.001
Male, n (%)	216 (44.6%)	211 (51.0%)	104 (46.8%)	0.163
BMI, kg/m ²	23.2 $\pm$ 2.8	25.6 $\pm$ 3.0*	26.1 $\pm$ 3.2*	< 0.001
Waist Circumference, cm	79.2 $\pm$ 7.5	85.8 $\pm$ 8.0*	87.2 $\pm$ 7.8*	< 0.001
Metabolic Syndrome, n/total n (%)	174/466 (37.3%)	282/404 (69.8%)	150/221 (67.9%)	< 0.001
Regular alcohol consumption, n/total n (%)	182/437 (41.6%)	183/392 (46.7%)	70/204 (34.3%)	0.014
Smoking, ever, n/total n (%)	166/420 (39.5%)	174/384 (45.3%)	70/194 (36.1%)	0.072
Regular exercise, n/total n (%)	135/383 (35.2%)	172/360 (47.8%)	78/187 (41.7%)	0.002
Hypertension, n (%)	130 (26.9%)	135 (32.6%)	97 (43.7%)	< 0.001
SBP, mmHg	131.1 $\pm$ 16.7	135.0 $\pm$ 16.9*	138.3 $\pm$ 16.4*	< 0.001
DBP, mmHg	84.3 $\pm$ 10.6	88.3 $\pm$ 11.2*	87.4 $\pm$ 10.6*	< 0.001
DM Duration, years	7.2 $\pm$ 6.9	5.5 $\pm$ 5.3*	6.1 $\pm$ 5.5	< 0.001
HbA1c, %	8.3 $\pm$ 2.1	8.7 $\pm$ 1.9*	8.0 $\pm$ 1.6 [†]	< 0.001
KITT, %/min	2.4 $\pm$ 1.0	1.9 $\pm$ 0.8*	1.8 $\pm$ 0.7*	< 0.001
T.Cholesterol, mg/dL	188.6 $\pm$ 38.5	201.8 $\pm$ 45.1*	197.7 $\pm$ 39.3*	< 0.001
Triglyceride, mg/dL	115.7 $\pm$ 63.3	172.3 $\pm$ 140.0*	157.7 $\pm$ 89.2*	< 0.001
HDL-C, mg/dL	54.2 $\pm$ 14.8	48.4 $\pm$ 12.2*	50.6 $\pm$ 12.8*	< 0.001
LDL-C, mg/dL	110.1 $\pm$ 32.3	118.9 $\pm$ 35.7*	113.6 $\pm$ 35.3	0.002
eGFR (MDRD), mL/min/1.73m ²	94.5 $\pm$ 30.9	93.0 $\pm$ 28.0	88.0 $\pm$ 27.4*	0.022
Platelet, /uL	210.7 $\pm$ 59.2	240.0 $\pm$ 53.4*	183.3 $\pm$ 38.6 [†]	< 0.001
Statin use, n (%)	63 (13.0%)	53 (12.8%)	25 (11.3%)	0.797
Aspirin use, n (%)	62 (12.8%)	58 (14.0%)	35 (15.8%)	0.568
Carotid IMT, mm	0.75 $\pm$ 0.15	0.76 $\pm$ 0.15	0.81 $\pm$ 0.14 [†]	< 0.001
Presence of plaque, n (%)	153 (31.6%)	127 (30.7%)	80 (36.0%)	0.365

KITT, rate constant for plasma glucose disappearance
* p values < 0.05 versus no steatosis [†] p values < 0.05 versus steatosis only

Figure 1. Progression of Carotid Atherosclerosis by Presence of Hepatic Steatosis

Adjusted for age, gender, SBP, DBP, DM Duration, HbA1c, KITT, Presence of CKD stage III-V, total cholesterol, statin use, alcohol history, and obesity. Obesity is defined as BMI ≥ 25 kg/m².
* p value < 0.05, crude [†] p value < 0.05, adjusted

Table 2. Stepwise Logistic Regression Analysis of the Association Between Hepatic Status and Carotid Atherosclerosis Progression

	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

Model 1 = Crude OR without any adjustment
Model 2 = Model 1 + age, gender
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

Figure 2. Carotid Atherosclerosis Progression by Subgroups (Hepatic Status and Metabolic Syndrome Criteria)

Adjusted for age, gender, DM Duration, HbA1c, LDL-C, HDL-C, statin use, alcohol history, smoking history, exercise status, SBP, DBP, KITT, Presence of CKD stage III-V, and BMI.
* p value < 0.05 versus subgroup with 0-2 metabolic syndrome criteria with no hepatic steatosis

Figure 3. Hepatic Status and Carotid Atherosclerosis Progression by Metabolic Confounders

CONCLUSIONS

- Hepatic steatosis with significant fibrosis is independently associated with progression of carotid atherosclerosis in patients with T2DM
- The association was more prominent relative to criteria for metabolic syndrome
- The findings were still significant in subgroups of patients who were metabolically-healthy.
- Identification of hepatic steatosis with significant fibrosis may be helpful to predict and prevent risk of atherosclerosis progression in individuals with T2DM