Angiology
2015, Vol. 66(5) 472-480

DOI: 10.1177/0003319714537872
ang.sagepub.com
SAGE

Association Between Nonalcoholic Fatty Liver Disease and Carotid Artery Inflammation Evaluated by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography

Seung Hwan Moon, MD[1], Tae Soo Noh[1], Young Seok Cho, MD[1], Seon Pyo Hong, MD[1], Seung Hyup Hyun, MD[1], Joon Young Choi, MD, PhD[1], Byung-Tae Kim, MD, PhD[1], and Kyung-Han Lee, MD, PhD[1]

Abstract

We assessed the association between nonalcoholic fatty liver disease (NAFLD) and carotid artery inflammation measured by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography. Participants were 755 consecutive otherwise healthy adult males who underwent a general health screening program. Carotid FDG uptake, represented as maximum target-to-background ratio, was increased with mild (n = 237; 1.61 ± 0.14; $P = .033$) and moderate NAFLD (n = 145; 1.63 ± 0.16; $P = .005$) compared with controls (n = 373; 1.58 ± 0.15). In patients aged >50 years, moderate NAFLD was the only independent risk factor for high carotid FDG uptake (odds ratio, 2.12; 95% confidence interval, 1.10-4.07; $P = .001$). Apparently healthy adult males with NAFLD have elevated carotid FDG uptake as well as increased carotid intima–media thickness, suggesting that they may be at an increased risk of having inflammatory atherosclerotic plaques in the carotid arteries.

Keywords

nonalcoholic fatty liver disease, atherosclerosis, carotid artery, FDG, PET/CT

Introduction

Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome (MetS), and patients with NAFLD have an increased risk of cardiovascular (CV) disease.[1-4] This observation has raised interest in the potential link between NAFLD and the development and progression of carotid atherosclerosis; accumulating data suggest a positive association.[5-8] Hence, NAFLD has been shown to correlate with greater carotid intima–media thickness (cIMT)[9] as well as increased prevalence of carotid atherosclerotic plaques.[10]

Inflammation plays a fundamental role in the initiation, progression, and rupture of atherosclerotic plaques.[11,12] Furthermore, it is the inflammatory component of atherosclerotic lesions that triggers plaque rupture and thrombosis, causing key complications.[12] Although conventional imaging modalities can detect luminal stenosis, they cannot assess the inflammatory status of plaques. Therefore, imaging the inflammatory component of atherosclerosis may provide prognostic information useful for selecting patients at increased risk that could benefit from appropriate preventive management.

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) depicts atherosclerotic plaques with active inflammation.[13] Studies have shown that FDG uptake is directly related to macrophage accumulation in atherosclerotic lesions, reflecting inflammation severity.[14] Furthermore, FDG uptake in major arteries has been shown to be an indicator of CV risk.[15,16] As such, carotid FDG

[1]Department of Nuclear Medicine and Molecular imaging, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Corresponding Author:
Kyung-Han Lee, Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Republic of Korea.
Email: khnm.lee@samsung.com

uptake may provide information of increased CV risk beyond traditional risk factors.

Considerable evidence associating carotid FDG uptake to clinical risk factors indicate a close link between carotid inflammation and MetS and CV disease. However, the precise relation between NAFLD and carotid FDG activity has not been properly investigated. Therefore, we evaluated asymptomatic adults to investigate the association between NAFLD and carotid FDG uptake.

Methods

Study Patients

Study candidates were 1126 consecutive males who participated in a general health screening program that included abdominal ultrasonography and FDG PET/computed tomography (CT) at our institute between January 2009 and November 2009. From this population, 1054 patients who had also undergone carotid ultrasonography for cIMT measurement and had all clinical data necessary for Framingham risk score (FRS) calculation were selected.[17] Among these patients, 21 patients were excluded for PET/CT data loss (n = 14) or obscured carotid uptake by high activity adjacent tissue (n = 7). Additionally, patients with diabetes mellitus (n = 108) and those who were positive for hepatitis C virus (HCV) or anti-HCV antibody (n = 11) were excluded because of potential influence on serum glucose level or hepatic glucose metabolism. Sonography demonstrated fatty liver in 517 patients and no evidence of fatty liver in 469 patients.

Based on drinking habit questionnaires, patients with fatty liver whose alcohol intake exceeded 280 g/wk were considered having alcoholic fatty liver disease (n = 135) and were excluded from further analysis. This resulted in a total of 382 study patients with NAFLD. Among patients without fatty liver, 373 with alcohol intake <280 g/wk were included as the control group. Thus, a total of 755 patients were finally included for analysis. None of the patients had cancer or CV symptoms. The study was conducted under the review and approval of the institutional review board.

All study patients underwent anthropometric measurements for height, weight, blood pressure (BP), and waist circumference (WC). Body mass index (BMI) was calculated from as weight (kg)/height^2 (m^2). Information on age and medical history were obtained from electronic medical records. Current smoking was defined as having smoked in the last 30 days. Diabetes was defined as a fasting glucose >126 mg/dL or use of hypoglycemic medications. Hypertension was defined as a systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of medication prescribed for hypertension. Use of medications was based on prescriptions entered by clinical staff. Laboratory tests included serum triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), and serum high-sensitivity C-reactive protein (hsCRP) concentration.

Ultrasonography for Fatty Liver Assessment and cIMT Measurement

Abdominal ultrasonography was performed using a SEQUOIA-512 (Siemens, Mountain View, California), LOGIQ 700 Expert (GE Healthcare, Milwaukee, Wisconsin), or LOGIQ E9 (GE Healthcare) device. The presence of FLD and severity of fatty liver infiltration were determined as follows. Mild NAFLD was defined as mildly increased liver echogenicity and clear depiction of hepatic and portal vein walls. Moderate NAFLD was increased echogenicity obscuring the hepatic and portal vein walls. Severe NAFLD was defined as markedly increased echogenicity with poor penetration of the deep parenchyma and diaphragm. Carotid intima–media thickness was measured with a standard protocol using an automated IMT package and a high-resolution B-mode ultrasound (General Electric, Horten, Norway).

Positron Emission Tomography/CT Imaging

All patients were instructed to fast for at least 6 hours before the PET/CT study and blood glucose levels were <200 mg/dL at the time of FDG injection. Imaging was performed on a GE STE scanner (GE Healthcare; 751 patients) or a GE Discovery LS scanner (4 patients). Measurement of carotid FDG uptake was not significantly affected by interscanner difference. The CT images were acquired first at 45 minutes after FDG (370 MBq) injection using an 8-slice (140 keV, 40-120 mAs adjusted to body weight; section width of 5 mm) or 16-slice helical CT (140 keV, 30-170 mAs with an Auto A mode; section with of 3.75 mm). No intravenous or oral contrast materials were used. Emission PET images were then acquired from thigh to head for 4 minutes/frame in 2-dimensional mode. Attenuation-corrected PET images (voxel size, 4.3 × 4.3 × 3.9 mm^3) were reconstructed using CT data by an ordered-subsets expectation maximization algorithm (28 subsets, 2 iterations).

Positron Emission Tomography/CT Image Analysis

Transaxial FDG PET and PET/CT tomographic slices of 3.3 mm (Discovery LS) or 4.3 mm (STE scanner) thickness were analyzed on a Xeleris workstation. Circular or ellipsoidal regions of interest (ROIs) were manually placed over the carotid arteries on every other tomographic slice beginning from the merging point with the brachiocephalic trunk or aortic arch up to 4 to 6 slices above the bifurcation site as previously described.[18] Care was taken to include all arterial outer walls while excluding nonvascular tissue of significant activity. From each arterial ROI, mean and maximum standard uptake values (SUVs) were obtained. Blood-pool activity was measured by placing circular ROIs in the mid-lumen of the inferior vena cava on 5 different tomographic slices and averaging the values to obtain the background SUV. The mean and maximum SUVs of each arterial segment was averaged for both carotid arteries and then divided by the background SUV to yield the

Table 1. Clinical Characteristic of Study Patients.[a]

	Control (n = 373)	Mild NAFLD (n = 237)	Moderate NAFLD (n = 145)	*P*
Age, years	51.70 ± 5.80	51.88 ± 6.63	51.67 ± 6.05	.921
Systolic BP, mm Hg	117.08 ± 15.40	118.20 ± 14.55	119.46 ± 15.79	.261
Diastolic BP, mm Hg	76.21 ± 10.52	77.16 ± 9.22	77.90 ± 10.20	.194
High BP (≥130/85 mm Hg), n (%)	149 (39.9)	110 (46.4)	71 (48.9)	.107
BMI, kg/m^2	23.47 ± 2.05	25.06 ± 2.16[b]	26.32 ± 2.44[b,c]	<.001
Obesity (BMI ≥ 25), n (%)	85 (22.8)	121 (51.1)[b]	104 (71.7)[b,c]	<.001
WC, cm	83.03 ± 5.95	87.76 ± 6.04[b]	90.86 ± 6.25[b,c]	<.001
Central obesity (WC ≥90), n (%)	53 (14.2)	85 (35.9)[b]	84 (57.9)[b,c]	<.001
FBG, mg/dL	93.23 ± 11.89	97.30 ± 16.88[d]	103.60 ± 23.57[b,e]	<.001
Insulin, uIU/mL	7.08 ± 3.14	9.35 ± 4.12[b]	11.51 ± 6.51[b,c]	<.001
Total-C, mg/dL	193.47 ± 30.90	199.25 ± 33.15	198.10 ± 36.43	.077
HDL-C, mg/dL	53.01 ± 12.10	46.83 ± 9.86[b]	44.01 ± 10.20[b]	<.001
LDL-C, mg/dL	119.67 ± 27.09	126.23 ± 28.25[d]	126.21 ± 30.99	.006
TG, mg/dL	116.54 ± 56.60	155.22 ± 74.48[b]	173.35 ± 81.56[b,e]	<.001
hsCRP, mg/dL	0.12 ± 0.28	0.10 ± 0.13	0.13 ± 0.28	.539
ALT, U/L	20.95 ± 8.76	27.78 ± 13.96[b]	39.01 ± 24.21[b,c]	<.001
AST, U/L	22.60 ± 8.33	25.23 ± 12.51[d]	31.88 ± 17.95[b,c]	<.001
GGT, U/L	33.20 ± 29.81	43.19 ± 40.80[f]	52.72 ± 51.15[b]	<.001
Statin medication, n (%)	14 (3.75)	15 (6.33)	10 (6.90)	.293
Metabolic syndrome, n (%)	70 (18.76)	54 (22.78)	29 (20.00)	.483

Abbreviations: NAFLD, nonalcoholic fatty liver disease; BP, blood pressure; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; hsCRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; SD, standard deviation.

[a]Data are mean ± SD.

[b]$P < .001$, compared to control group.

[c]$P < .001$, compared with mild NAFLD.

[d]$P < .05$, compared to control group.

[e]$P < .01$, compared with mild NAFLD.

[f]$P < .01$, compared to control group.

mean and maximum target-to-background ratios (TBRs) for each patient.

Definition of Variables

Patients over the average +1 standard deviation (SD) of maximum TBR (≥1.75) were regarded as having elevated carotid FDG uptake and over the average + 1SD of cIMT (≥0.8 mm) were classified as having elevated cIMT.[6,18] Framingham risk score of patients was obtained using a calculator of the openly accessible Web site, http://reference.medscape.com/calculator/framingham-cardiovascular-disease-risk. Under this scoring system, the risk of general CV disease at 10 years is ≤20% for those with relatively low risk and >20% for relatively highest risk.

Following abnormal clinical variables, laboratory findings were defined based on the criteria of MetS modified for Asians[6,19,20]: central obesity WC ≥90 cm, high TG (fasting serum TG >150 mg/dL), low HDL-C (fasting serum HDL-C <40 mg/dL), high FBG (≥100 mg/dL), and high BP (≥130/85 mm Hg).

Overweight was defined as BMI ≥25 according to the recommendation.[21,22] The remaining abnormal laboratory findings were defined based on the reference ranges at our institution. High LDL-C was defined as >130 mg/dL, high total cholesterol was defined as >240 mg/dL, high ALT was defined as >40 U/L, high AST was defined as >40 U/L, high GGT was defined as >50 U/L, and high hsCRP was defined if hsCRP was >0.3 mg/dL. Median of age 51 years was used as cutoff value to categorize study patients into 2 groups for an age-dependent analysis.

Statistical Analysis

Continuous variables were expressed as mean ± SD in tables and mean ± standard error (SE) for figures. For continuous variables, analysis of variance with post hoc Scheffe test was used to compare difference between 3 groups, and chi-square test was used for dichotomous variables. Association between variables was assessed by logistic regression analysis. The SPSS for windows (version 16.0; SPSS Inc, Chicago, Illinois) was used to perform all statistical analysis and Prism for windows (version 6.04; Graphpad software Inc). Two-sided *P* values <.05 were considered significant.

Results

Clinical Characteristics of Study Patients

The clinical characteristics of the study patients categorized according to NAFLD status are summarized in Table 1. Study

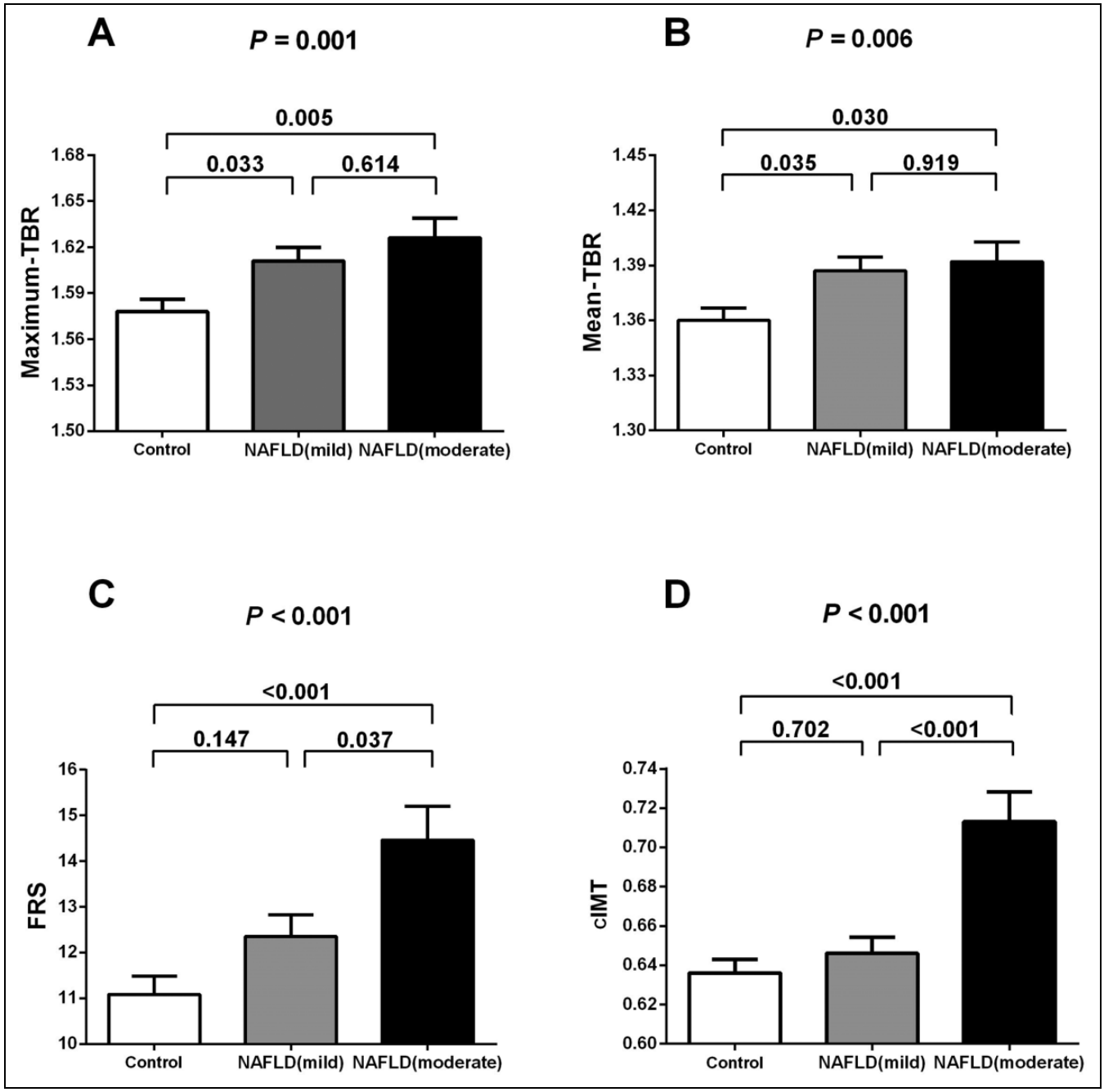

Figure 1. Relation of NAFLD to TBR of carotid FDG uptake, FRS, and cIMT. Maximum-TBR (A), mean-TBR (B), FRS (C), and cIMT (D) according to grading of NAFLD as control (n = 373), mild (n = 237), and moderate (n = 145). Bars are mean ± standard error. TBR indicates target-to-background ratio; FDG, ^{18}F-Fluorodeoxyglucose; FRS, Framingham risk score; cIMT, carotid intima–media thickness; NAFLD, non-alcoholic fatty liver disease.

patients had a mean age (±SD) of 51.7 ± 6.1 years (range: 33-97). Of a total of 755 patients, sonographic evidence of fatty liver disease was present in 382 patients (mild in 31.4%, n = 237; moderate in 19.2%, n = 145) and absent in 373 patients (49.4%). Comparison of clinical characteristics revealed no significant difference in age or BP between the 3 groups. However, mild and moderate NAFLD groups had significantly greater BMI and WC compared with controls. Laboratory findings showed significantly higher FBG, insulin, total cholesterol, LDL-C, TG, ALT, AST, and GGT and lower HDL-C levels of mild and moderate NAFLD groups compared with controls (Table 1). When divided by a maximum TBR threshold of 1.75, there were 111 (14.7%) patients with elevated FDG uptake and 644 (85.3%) patients with low FDG uptake. When divided by a cIMT threshold of 0.8 mm, there were 116 (15.4%) patients with elevated cIMT and 639 (84.6%) patients with low cIMT.

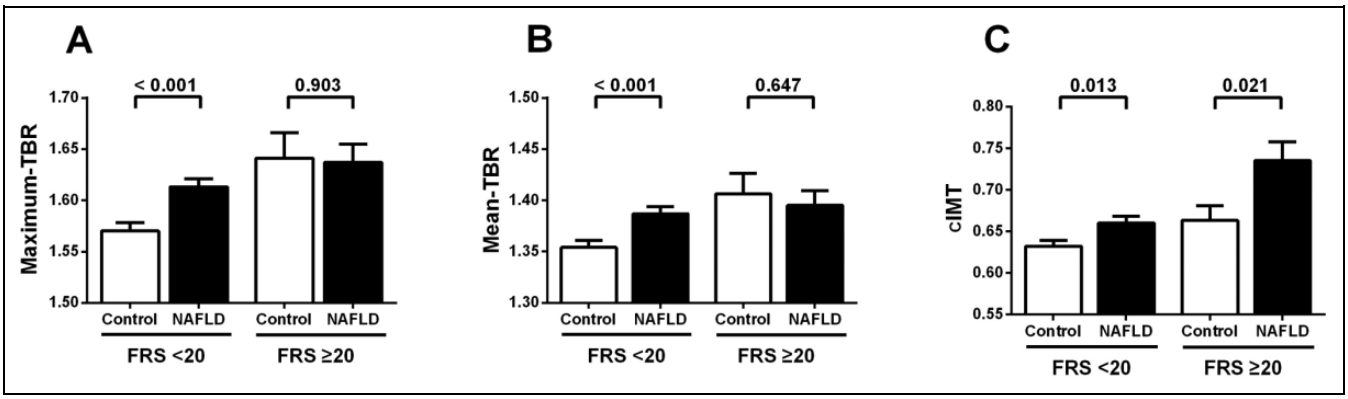

Figure 2. Relation of NAFLD to TBR of carotid FDG uptake and cIMT according to FRS. Maximum-TBR (A), mean-TBR (B), and cIMT (C) in patients categorized by FRS, according to the presence of NAFLD (n = 382) or its absence (control; n = 373). Bars are mean ± standard error. TBR indicates target-to-background ratio; FDG, ^{18}F-Fluorodeoxyglucose; FRS, Framingham risk score; cIMT, carotid intima–media thickness; NAFLD, nonalcoholic fatty liver disease.

Carotid FDG Uptake According to NAFLD

Carotid FDG uptake, FRS, and cIMT were significantly higher in patients with NAFLD than controls (Figure 1). Average values of maximum TBR and cIMT (±SE) of all study patients were 1.60 ± 0.15 and 0.65 ± 0.15 mm, respectively. Maximum TBR in patients with mild (1.61 ± 0.14) and moderate NAFLD (1.63 ± 0.16) were significantly greater than those in controls (1.58 ± 0.15; $P = .033$ and .005, respectively). Mean TBR in mild (1.39 ± 0.11) and moderate NAFLD (1.39 ± 0.13) were also higher than controls (1.36 ± 0.13; $P = .035$ and .030, respectively). However, neither maximum nor mean TBR was different between mild and moderate NAFLD groups (Figure 1A and B). The FRS of patients with moderate NAFLD (14.5 ± 8.9) was significantly higher than those of controls and mild NAFLD (11.1 ± 7.6, 12.3 ± 7.3; $P < .001$, $P = .037$, respectively). Mean value of cIMT of all patients was 0.65 ± 0.15 mm. Carotid intima–media thickness of patients with moderate NAFLD (0.71 ± 0.18 mm) was significantly greater than those of controls and mild NAFLD (0.64 ± 0.13, 0.65 ± 0.13 mm, respectively; both $P < .001$; Figure 1C and D).

Carotid FDG Uptake and cIMT According to NAFLD in Patients Stratified by FRS

When patients were categorized by estimated risk based on FRS (<20% vs ≥20%), difference in carotid FDG uptake between patients with NAFLD and controls varied according to the categorized risk (Figure 2A and B). Among patients at low CV risk (FRS < 20%), maximum and mean TBR of patients with NAFLD (1.61 ± 0.15 and 1.39 ± 0.12) was significantly higher than that of controls (1.57 ± 0.15 and 1.35 ± 0.13; $P < .001$ and <.001, respectively). However, among patients at high risk (FRS ≥ 20%), maximum and mean TBRs of patients with NAFLD (1.64 ± 0.14 and 1.40 ± 0.11) were not different from that of controls (1.64 ± 0.17 and 1.41 ± 0.14). This infers that the effect of NAFLD on carotid FDG uptake is prominent in the low-risk group but not in the high-risk group. In contrast with FDG uptake, significant differences in cIMT between patients with NAFLD and controls were observed in both the low-risk group (0.63 ± 0.13 vs 0.66 ± 0.15 mm; $P < .013$) and high-risk group (0.66 ± 0.12 vs 0.735 ± 0.18 mm; $P < .021$; Figure 2C).

Independent Determinants of Carotid FDG Uptake

The results of logistic regression analysis to determine the association between maximum TBR and clinical variables are summarized in Tables 2 and 3. In univariate analysis conducted with patients of all age, central obesity, high AST, age > 50 years, elevated cIMT, high ALT, obesity, and moderate NAFLD were significant factors related to high carotid FDG uptake.

Multivariate analysis using clinical variables with significant univariate association revealed that central obesity and elevated cIMT were independent determinants of high carotid FDG uptake. Importantly, NAFLD showed significant interaction with age. Nonalcoholic fatty liver disease in patients >50 years of age (NAFLD × age) was the most powerful determinant for high carotid FDG uptake (Table 2). As a result, in the age-stratified subgroup analysis, moderate NAFLD was the only independent determinant for high carotid FDG uptake for patients aged >50 years (Table 3).

The results of univariate and multivariate logistic regression analyses for clinical determinants of high cIMT are summarized in Table 4. Moderate NAFLD and age >50 years were independent determinants for elevated cIMT, and high total cholesterol was marginally significant. No significant interaction among other clinical variables for cIMT was observed.

Discussion

We investigated the association between NAFLD and carotid FDG uptake in a cohort of asymptomatic middle-aged and elderly males. Carotid FDG uptake and cIMT were

Table 2. Association Between Elevated Carotid ^{18}F-Fluorodeoxyglucose Uptake and Clinical Variables.

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Central obesity (WC $\geq$ 90)	2.05	1.36–3.11	.001	1.97	1.13–3.43	.016
High AST (>40 U/L)	3.06	1.56–5.99	.001	2.23	0.95–5.26	.065
Age (>50)	1.83	1.20–2.77	.004	0.80	0.42–1.54	.519
Elevated cIMT (>0.8 mm)	1.88	1.15–3.08	.012	1.82	1.07–3.08	.026
High ALT (>40 U/L)	1.92	1.11–3.32	.019	1.49	0.72–3.06	.277
Obesity (BMI $\geq$ 25)	1.49	1.00–2.24	.050	0.99	0.57–1.70	.979
NAFLD						
Mild	1.56	0.98–2.48	.057	0.67	0.31–1.45	.314
Moderate	1.63	0.96–2.77	.069	0.24	0.07–0.75	.015
High BP ($\geq$130/85 mm Hg)	1.21	0.80–1.81	.353	–	–	–
High hsCRP (>0.3 mg/dL)	1.40	0.66–2.99	.376	–	–	–
High FRS (>20%)	1.23	0.71–2.15	.447	–	–	–
High TG (>150 mg/dL)	1.14	0.75–1.74	.513	–	–	–
High LDL–C (>130 mg/dL)	1.14	0.75–1.71	.529	–	–	–
Low HDL-C (<40 mg/dL)	0.87	0.54–1.41	.585	–	–	–
High GGT (>50 U/L)	1.09	0.66–1.80	.719	–	–	–
High FBG (>100 mg/dL)	0.98	0.61–1.57	.982	–	–	–
High total-C (>240 mg/dL)	1.00	0.49–2.02	.990	–	–	–
Age (>50) $\times$ NAFLD						
Mild	–	–	–	3.01	1.11–8.03	.027
Moderate	–	–	–	6.90	1.95–24.40	.003

Abbreviations: OR, odds ratio; CI, confidence interval; WC, waist circumference; AST, aspartate aminotransferase; cIMT, carotid intima–media thickness; ALT, alanine aminotransferase; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; BP, blood pressure; hsCRP, high-sensitivity C-reactive protein; FRS, Framingham risk score; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; GGT, γ-glutamyl transferase; FBG, fasting blood glucose.

Table 3. Association Between Elevated Carotid ^{18}F-Fluorodeoxyglucose Uptake and Clinical Variables According to Age-Group.

	Age > 50 Years (n = 388)						Age $\leq$ 50 Years (n = 367)					
	Univariate			Multivariate[a]			Univariate			Multivariate[a]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Central obesity (WC $\geq$ 90)	2.35	1.38–4.00	.02	1.63	0.82–3.24	.164	1.70	0.86–3.35	.123	–	–	–
NAFLD												
Mild	2.34	1.27–4.34	.007	2.05	0.95–4.40	.067	1.69	0.62–4.64	.309	–	–	–
Moderate	2.81	1.43–5.52	.003	2.12	1.10–4.07	.024	1.46	0.49–4.36	.493	–	–	–
High AST (>40 U/L)	3.55	1.51–8.36	.004	2.14	0.69–6.59	.186	2.31	0.73–7.34	.155	–	–	–
Obesity (BMI $\geq$25)	1.69	1.01–2.83	.047	1.05	0.53–2.07	.884	1.29	0.67–2.49	.453	–	–	–
High ALT (>40 U/L)	2.05	0.96–4.38	.063	1.14	0.42–3.08	.799	2.08	0.92–4.69	.077	–	–	–
Elevated cIMT (>0.8 mm)	1.71	0.95–3.09	.073	1.30	0.67–2.51	.438	1.68	0.66–4.33	.278	–	–	–
High FBG (>100 mg/dL)	0.76	0.41–1.39	.370	–	–	–	1.34	0.62–2.89	.450	–	–	–
High LDL-C (>130 mg/dL)	1.25	0.75–2.11	.392	–	–	–	1.03	0.53–1.99	.942	–	–	–
High hsCRP (>0.3 mg/dL)	1.45	0.56–3.77	.448	–	–	–	1.31	0.37–4.65	.672	–	–	–
High GGT (>50 U/L)	0.77	0.38–1.55	.464	–	–	–	1.80	0.87–3.73	.116	–	–	–
Low HDL-C (<40 mg/dL)	0.82	0.45–1.47	.504	–	–	–	1.12	0.48–2.66	.789	–	–	–
High TG (>150 mg/dL)	1.13	0.66–1.94	.660	–	–	–	1.27	0.65–2.48	.475	–	–	–
High total-C (>240 mg/dL)	1.18	0.46–3.01	.729	–	–	–	0.93	0.31–2.76	.892	–	–	–
High FRS (>20%)	1.06	0.57–1.98	.841	–	–	–	0.85	0.19–3.81	.835	–	–	–
High BP ($\geq$130/85 mm Hg)	1.02	0.61–1.73	.925	–	–	–	1.70	0.87–3.30	.118	–	–	–

Abbreviations: OR, odds ratio; CI, confidence interval; WC, waist circumference; NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; BMI, body mass index; ALT, alanine aminotransferase; cIMT, carotid intima–media thickness; FBG, fasting blood glucose; LDL, low-density lipoprotein; C, cholesterol; hsCRP, high-sensitivity C-reactive protein; GGT, γ-glutamyl transferase; HDL, high-density lipoprotein; TG, triglyceride; FRS, Framingham risk score; BP, blood pressure.

[a]Age adjusted.

Table 4. Association Between Elevated cIMT and Clinical Variables.

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (>50 years)	2.28	1.49–3.47	<.001	2.17	1.39–3.37	.001
NAFLD						
Mild	1.07	0.65–1.74	.786	0.96	0.58–1.59	.898
Moderate	2.61	1.61–4.22	<.001	2.16	1.30–3.58	.003
High FRS (>20%)	2.04	1.24–3.36	.005	1.46	0.86–2.48	.154
High FBG (>100 mg/dL)	1.80	1.17–2.77	.007	1.37	0.86–2.16	.177
High total-C (>240 mg/dL)	2.16	1.21–3.86	.009	1.93	0.98–3.78	.055
High LDL-C (>130 mg/dL)	1.45	0.97–2.16	.066	1.18	0.75–1.86	.463
Central obesity (WC $\geq$ 90 cm)	1.38	0.91–2.10	.128	–	–	–
Low HDL-C (<40 mg/dL)	0.74	0.47–1.17	.210	–	–	–
Obesity (BMI $\geq$ 25)	1.25	0.84–1.86	.271	–	–	–
High BP ($\geq$130/85 mm Hg)	0.89	0.59–1.33	.583	–	–	–
High TG (>150 mg/dL)	1.10	0.73–1.66	.629	–	–	–
High GGT (>50 U/L)	1.09	0.67–1.78	.719	–	–	–
High hsCRP (>0.3 mg/dL)	1.14	0.51–2.50	.745	–	–	–
High AST (>40 U/L)	0.88	0.36–2.15	.792	–	–	–
High ALT (>40 U/L)	1.08	0.58–1.98	.803	–	–	–

Abbreviations: OR, odds ratio; CI, confidence interval; WC, waist circumference; AST, aspartate aminotransferase; cIMT, carotid intima–media thickness; ALT, alanine aminotransferase; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; BP, blood pressure; hsCRP, high-sensitivity C-reactive protein; FRS, Framingham risk score; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; GGT, γ-glutamyl transferase; FBG, fasting blood glucose.

significantly higher in patients with NAFLD compared with those without fatty liver. This suggests that otherwise healthy individuals with NAFLD are at an increased risk of having inflammatory carotid atherosclerosis.

There is accumulating data pointing to an association of NAFLD with clinical risk factors for carotid atherosclerosis and other CV diseases.[4,10] It remains controversial, however, whether this simply reflects a sharing of risk factors between the 2 diseases or whether NAFLD may actually exacerbate atherosclerotic disease independently of other risk factors.[3,23,24] Tahara and coworkers investigated the relation between clinical risk factors and increased carotid artery FDG uptake and observed an association of inflammatory carotid atherosclerosis with the MetS.[25] Our study also confirms that carotid FDG uptake is increased proportional to the number of MetS components.[25] In addition, our study further demonstrates that NAFLD is a significant factor for high carotid FDG uptake, independent of other MetS components. In fact, with the exception of obesity, high carotid FDG uptake did not show statistically significant levels of association with other components of the MetS when NAFLD was included for analysis in our study.

Another question regarding NAFLD and carotid atherosclerosis is whether an association also applies to otherwise healthy, low-risk populations.[26] This is exemplified by a recent study that failed to observe an independent association between liver fat and carotid atherosclerosis in healthy individuals.[26] However, our results in a large cohort of otherwise healthy men reveal a clear association of NAFLD with elevated carotid FDG uptake as well as increased cIMT. Interestingly, the association between NAFLD and high carotid FDG uptake was more prominent in patients with low FRS-based CV risk. This suggests that NAFLD may be an important factor for the development of inflammatory carotid atherosclerosis in patients who are relatively free from other CV risk factors.

In NAFLD, raised circulating ALT, AST, and GGT activities are often observed. In fact, fatty liver disease appears to be the most common cause of elevated ALT and AST.[27] These enzymes indicate hepatocellular damage and are often raised in CV disease-related conditions including insulin resistance and MetS.[28] Moreover, elevated serum activities of these hepatic enzymes have been linked to an increased risk of carotid atherosclerosis.[29,30] In our study, increased AST activity was associated with high carotid FDG uptake, supporting its possible role as a surrogate marker of inflammatory atherosclerosis in patients with NAFLD.

Advanced age is an established risk factor for CV disease[17] and is also known to increase FDG uptake in carotid and large arteries.[25,31,32] We therefore tested the influence of age on other CV risk factors and reanalyzed the relation between NAFLD and carotid FDG uptake adjusting for age by stratification. As a result, the effect of NAFLD on carotid FDG uptake differed according to patient age. Such an effect was not observed for cIMT. In patients aged >50 years, moderate NAFLD was a crucial determinant that conferred a 210% odds ratio of having high carotid FDG uptake independent of conventional CV risk factors.

Accumulating data show significant links between carotid atherosclerosis, NAFLD, and coronary artery disease.[33-35] Thus, cIMT can be useful for predicting other CV disease such as coronary atherosclerosis.[35] However, cIMT may not be

useful in the relatively healthy population.[36] Carotid FDG uptake can complement cIMT and may be a useful additional indicator that can predict CV events. It has important clinical implications because current risk prediction algorithms including traditional risk factors are insufficient to predict CV events. A fifth of all CV events occur in individuals who have no identifiable traditional risk factors.[37]

This study has limitations. First, grading NAFLD was determined by sonography rather than by CT, which generally provides accurate assessment of hepatic fat. We did not use CT data because the CT acquisition parameters of our PET/CT examinations were adjusted for low radiation dose and were therefore considerably different from routine diagnostic CT. Such parameters are known to significantly influence optimal CT attenuation numbers for grading fat infiltration.[38] Second, generalizability of the study results is restricted due to the limited population consisting of middle-aged and elderly Korean men and the retrospective nature of this cross-sectional study. The lack of actual CV outcome data is also a limitation. Finally, other factors, such as alcohol consumption, were not included in the analysis. Modest alcohol consumption had an independent inverse association with carotid plaques or carotid artery stenosis in males with NAFLD.[39]

In conclusion, this study demonstrates that the presence of NAFLD in otherwise healthy adult males is closely associated with elevated carotid FDG uptake. This indicates that NAFLD may increase the risk of inflammatory carotid atherosclerosis in asymptomatic patients in a manner independent of conventional CV risk factors.

Authors' Note

Both Seung Hwan Moon and Tae Soo Noh contributed equally to the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported by the Samsung Biomedical Research Institute grant # SMX1131891.

References

1. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010; 363(14):1341-1350.
2. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. *Cleve Clin J Med*. 2008; 75(10):721-728.
3. Targher G, Marra F, Marchesini G. Increased risk of cardiovascular disease in non-alcoholic fatty liver disease: causal effect or epiphenomenon? *Diabetologia*. 2008;51(11):1947-1953.
4. Kim NH, Park J, Kim SH, et al. Non-alcoholic fatty liver disease, metabolic syndrome and subclinical cardiovascular changes in the general population. *Heart*. 2014;100(12):938-943.
5. Brea A, Mosquera D, Martin E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler Thromb Vasc Biol*. 2005;25(5):1045-1050.
6. Huang Y, Bi Y, Xu M, et al. Nonalcoholic fatty liver disease is associated with atherosclerosis in middle-aged and elderly Chinese. *Arterioscler Thromb Vasc Biol*. 2012;32(9):2321-2326.
7. Carallo C, Mancuso G, Mauro G, et al. Hepatic steatosis, carotid atherosclerosis and metabolic syndrome: the STEATO Study. *J Gastroenterol*. 2009;44(11):1156-1161.
8. Kim SK, Choi YJ, Huh BW, et al. Non-alcoholic fatty liver disease is associated with increased carotid intima–media thickness only in type 2 diabetic subjects with insulin resistance. *J Clin Endocrinol Metab*. 2014;99(5):1879-1884.
9. Thakur ML, Sharma S, Kumar A, et al. Nonalcoholic fatty liver disease is associated with subclinical atherosclerosis independent of obesity and metabolic syndrome in Asian Indians. *Atherosclerosis*. 2012;223(2):507-511.
10. Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. *J Hepatol*. 2008;49(4):600-607.
11. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340(2):115-126.
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105(9):1135-1143.
13. Choi YS, Youn HJ, Chung WB, et al. Uptake of F-18 FDG and ultrasound analysis of carotid plaque. *J Nucl Cardiol*. 2011; 18(2):267-272.
14. Jezovnik MK, Zidar N, Lezaic L, Gersak B, Poredos P. Identification of inflamed atherosclerotic lesions in vivo using PET-CT. *Inflammation*. 2014;37(2):426-434.
15. Joshi F, Rosenbaum D, Bordes S, Rudd JH. Vascular imaging with positron emission tomography. *J Intern Med*. 2011;270(2): 99-109.
16. Paulmier B, Duet M, Khayat R, et al. Arterial wall uptake of fluorodeoxyglucose on PET imaging in stable cancer disease patients indicates higher risk for cardiovascular events. *J Nucl Cardiol*. 2008;15(2):209-217.
17. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-753.
18. Noh TS, Moon SH, Cho YS, et al. Relation of carotid artery 18F-FDG uptake to C-reactive protein and Framingham risk score in a large cohort of asymptomatic adults. *J Nucl Med*. 2013;54(12): 2070-2076.
19. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. *Diabet Med*. 2006;23(5):469-480.
20. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis

Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.
21. James WP, Chunming C, Inoue S. Appropriate Asian body mass indices? *Obes Rev*. 2002;3(3):139.
22. Weisell RC. Body mass index as an indicator of obesity. *Asia Pac J Clin Nutr*. 2002;11 suppl 8:S681-S684.
23. Khashab MA, Liangpunsakul S, Chalasani N. Nonalcoholic fatty liver disease as a component of the metabolic syndrome. *Curr Gastroenterol Rep*. 2008;10(1):73-80.
24. Moore JB. Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. *Proc Nutr Soc*. 2010;69(2):211-220.
25. Tahara N, Kai H, Yamagishi S, et al. Vascular inflammation evaluated by [18F]-fluorodeoxyglucose positron emission tomography is associated with the metabolic syndrome. *J Am Coll Cardiol*. 2007;49(14):1533-1539.
26. Dick TJ, Lesser IA, Leipsic JA, Mancini GB, Lear SA. The effect of obesity on the association between liver fat and carotid atherosclerosis in a multi-ethnic cohort. *Atherosclerosis*. 2013;226(1):208-213.
27. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001; 50(8):1844-1850.
28. Marchesini G, Avagnina S, Barantani EG, et al. Aminotransferase and gamma-glutamyltranspeptidase levels in obesity are associated with insulin resistance and the metabolic syndrome. *J Endocrinol Invest*. 2005;28(4):333-339.
29. Eroglu S, Sade LE, Polat E, Bozbas H, Ulus T, Muderrisoglu H. Association between serum gamma-glutamyltransferase activity and carotid intima–media thickness. *Angiology*. 2011;62(2):107-110.
30. Wang CC, Lin SK, Tseng YF, et al. Elevation of serum aminotransferase activity increases risk of carotid atherosclerosis in patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2009;24(8):1411-1416.
31. Yun M, Jang S, Cucchiara A, Newberg AB, Alavi A. 18F FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. *Semin Nucl Med*. 2002;32(1):70-76.
32. Bucerius J, Duivenvoorden R, Mani V, et al. Prevalence and risk factors of carotid vessel wall inflammation in coronary artery disease patients: FDG-PET and CT imaging study. *JACC Cardiovasc Imaging*. 2011;4(11):1195-1205.
33. Timoteo AT, Carmo MM, Ferreira RC. Carotid intima–media thickness and carotid plaques improves prediction of obstructive angiographic coronary artery disease in women. *Angiology*. 2013;64(1):57-63.
34. Agac MT, Korkmaz L, Cavusoglu G, et al. Association between nonalcoholic fatty liver disease and coronary artery disease complexity in patients with acute coronary syndrome: a pilot study. *Angiology*. 2013;64(8):604-608.
35. Jeevarethinam A, Venuraju S, Weymouth M, Atwal S, Lahiri A. Carotid intimal thickness and plaque predict prevalence and severity of coronary atherosclerosis: a pilot study. *Angiology*. 2015;66(1):65-69.
36. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J*. 2010;31(16):2041-2048.
37. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003; 290(7):898-904.
38. Ma X, Holalkere NS, Kambadakone RA, Mino-Kenudson M, Hahn PF, Sahani DV. Imaging-based quantification of hepatic fat: methods and clinical applications. *Radiographics*. 2009;29(5): 1253-1277.
39. Sinn DH, Gwak GY, Cho J, et al. Modest alcohol consumption and carotid plaques or carotid artery stenosis in men with non-alcoholic fatty liver disease. *Atherosclerosis*. 2014;234(2):270-275.