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Higher Non-fasting Serum Triglyceride Preceding the Carotid Stenosis Progression

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Abstract

The present study was conducted to investigate whether non-fasting serum triglyceride (TG) levels can be used to assess a risk for the progression of carotid artery stenosis. This was a single-center retrospective study. Consecutive 96 patients with ≥50% stenosis of at least unilateral cervical internal carotid artery and normal fasting serum low-density lipoprotein cholesterol (LDL-C) levels of ≤140 mg/dL were followed up for at least 1 year (mean, 3.1 years), and clinical variables were compared between patients with and without carotid stenosis progression (≥10% increases in the degree on ultrasonography). Carotid stenosis progression was shown in 21 patients, associated with less frequent treatment with calcium channel blockers (CCBs), higher non-fasting TG and glucose levels. In carotid artery-based analyses including <50% stenosis side, stenosis progression was shown in 23 of 121 arteries except for those with complete occlusion and less than 1-year follow-up period because of carotid artery stenting (CAS) or carotid endarterectomy (CEA). Stenosis progression was more frequently observed in symptomatic and/or radiation-induced lesions, and was also accompanied with less frequent treatment with CCBs, higher non-fasting TG and glucose levels in carotid artery-based analyses. The receiver operating characteristic (ROC) curve analyses revealed that a cutoff value of non-fasting TG to discriminate carotid stenosis progression was 169.5 mg/dL for carotid arteries with the baseline stenosis of <50%, and 154.5mg/dL for those of ≥50%. Non-fasting TG level was an independent risk factor of carotid stenosis progression, and more strict control of non-fasting TG may be necessary for higher degree of carotid artery stenosis.

Keywords: carotid artery stenosis, low-density lipoprotein cholesterol, non-fasting, risk factor, triglyceride

Introduction

The relationships between serum triglyceride (TG) levels and the progression of carotid artery stenosis are not well established. Recently, a few studies reported the possibility of higher fasting TG levels as one of the risk factors for the progression of carotid artery stenosis.[1,2] Vouillarmet et al.[1] reported that carotid atherosclerosis progression in patients with diabetes mellitus tended to be associated with higher fasting TG levels. Kitagami et al.[2] demonstrated that higher fasting TG levels are an independent risk factor for carotid stenosis progression in patients with moderate to severe carotid stenosis under normal low-density lipoprotein cholesterol (LDL-C).

In clinical practice, serum TG values are routinely measured after an 8- to 12-hour fast to avoid the effects of diet. Except for a few hours in the early morning, however, most individuals are under a non-fasting state, and therefore fasting levels of TG may not reflect the average daily serum TG levels that may more influence atherosclerosis. In addition, no requirements to fast beforehand are not only comfortable for patients but also simplify blood sampling, resulting in greater advantage of non-fasting lipid measurements rather than fasting ones. Since 2009, in fact, non-fasting lipid testing has become the clinical standard in Denmark according to recommendations from the Danish Society for Clinical Biochemistry that recommended drawing lipid samples in a non-fasting state while it is required for clinicians to re-measure TG concentrations in a

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fasting state if non-fasting TG values are higher than 350 mg/dL.[3] Since 2014, the National Institute for Health and Care Excellence clinical guideline in United Kingdom has also supported non-fasting lipid testing in the primary prevention setting.[4]

Although serum TG levels vary more on a daily basis compared with levels of total cholesterol and LDL-C, atherosclerosis may be a postprandial phenomenon in which remnant lipoproteins play a dominant role.[5,6] Elevated non-fasting TG levels reflect increased levels of remnant lipoproteins, and may be a risk of ischemic heart disease[7,8] and ischemic stroke.[9] On the other hand, to our knowledge, no study has investigated the relationships between non-fasting TG levels and the progression of carotid artery stenosis.

The measurement of non-fasting levels of lipids, particularly TGs, is not standard due to concerns about effects of a meal on the measurement values and limited evidences of the clinical significance. However, it is very useful in clinical practice if non-fasting serum TG values can be used to assess a vascular risk of carotid stenosis progression. The non-fasting measurement would allow clinicians to easily manage TG levels with a minimum of patients' discomfort. Thus, the authors conducted this study to investigate whether non-fasting TG levels are an independent risk factor for the progression of carotid artery stenosis in patients with LDL-C within normal ranges.

Materials and Methods

Study design

This was a single-center, retrospective study. The study included consecutive 98 patients from January 1, 2013 to December 31, 2017 who met the following inclusion criteria: aged 20 years or older at diagnosis, unilateral or bilateral atherosclerotic cervical internal carotid artery stenosis greater than or equal to 50% on the initial digital subtraction angiography (DSA) according to the method used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), at least 1-year follow-up from the first DSA in our hospital, B-mode and color Doppler ultrasonography or magnetic resonance (MR) angiography of the carotid artery one or more times per year, and normal ranges of fasting serum LDL-C levels (less than 140 mg/dL). Excluded from the study were patients who underwent surgical treatment for carotid artery stenosis before January 1, 2013, as well as individuals with carotid artery stenosis caused by dissection and/or less than 1-year follow-up after the first DSA. The study was approved by the ethical committee of our institute and was performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (World Medical Association Declaration of Helsinki 2000). For retrospective analyses, the committee waived the need for formal consent.

Clinical data collection

Experienced vascular neurosurgeons documented all clinical data. The following data were collected from medical records of 98 patients who were first diagnosed with extracranial (cervical) internal carotid artery stenosis on DSA: age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, radiation induction, smoking, alcohol consumption, clinical symptoms (symptomatic or asymptomatic), degree of carotid artery stenosis (the NASCET method) on both sides on ultrasonography at the first DSA to the last follow-up (before surgical treatment or intervention), the signal intensity ratio (SIR) of a carotid plaque on three-dimensional T1-weighted gradient echo MR images,[10] atherosclerotic stenosis other than extracranial carotid artery (intracranial artery, subclavian artery, coronal artery, and artery of lower extremities), drug profile (aspirin, clopidogrel, cilostazol, prasugrel, warfarin, direct oral anticoagulant [DOAC], angiotensin receptor blocker [ARB], calcium channel blocker [CCB], β-blocker, statin, fibrate, eicosapentaenoic acid [EPA]), non-fasting laboratory data (total cholesterol, high-density lipoprotein cholesterol [HDL-C], LDL-C, TG, glucose, hemoglobin A1C [HbA1C]), post-DSA treatment (carotid artery stenting [CAS], carotid endarterectomy [CEA], medication only), and follow-up period. Non-fasting laboratory data were measured within 10 hours postprandially. Hypertriglyceridemia was defined as non-fasting serum TG levels higher than or equal to 175 mg/dL according to the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine joint consensus initiative,[11] and other clinical variables were defined as previously reported.[2]

Indication of CAS and CEA

Patients diagnosed with ≥50% symptomatic carotid atherosclerotic stenosis or those with ≥80% asymptomatic carotid stenosis on DSA met our criteria to perform CAS or CEA and underwent either if patients gave written informed consent. Carotid stenosis was defined as symptomatic if patients had a history of ipsilateral ischemic events attributed to the affected carotid artery within 180 days before DSA, CAS, or CEA. Outside of the period, carotid stenosis was considered asymptomatic.

Progression of carotid artery stenosis and clinical variables

Among enrolled 98 patients, we analyzed the data of 96 patients, because 2 patients underwent CAS or CEA for bilateral carotid stenosis and their follow-up periods for bilateral lesions were less than 1 year before CAS or CEA. In the analysis, patients were divided into two groups, progression and non-progression groups, which were judged only using ultrasonography. The progression group was defined as greater than or equal to 10% increases (the NASCET method) in the degree of carotid stenosis on either side on ultrasonography during the follow-up period compared with that on ultrasonography at the first DSA: carotid stenosis progression was confirmed on DSA when follow-up DSA was performed.[2] Clinical variables were compared between the two groups.

In addition, we performed carotid artery-based analyses in 121 of 192 carotid arteries in 96 patients: 2 carotid arteries in 2 patients were excluded because of complete occlusion, and 69 worse-side carotid arteries in 69 patients were excluded because they underwent CAS or CEA shortly following the first DSA according to the above indication. Clinical variables were compared between the progression (≥10% stenosis increases of the carotid artery on ultrasonography) and non-progression groups as well.

Statistical analysis

All data were analyzed using SPSS software version 25.0 (IBM, Armonk, NY, USA). Categorical variables were reported as a proportion and were analyzed using chi-square or Fisher's exact tests, as appropriate. Continuous variables were reported as a mean ± standard deviation (SD) and were compared using Wilcoxon rank-sum tests between the two groups. The impact of each variable on carotid stenosis progression was determined by multivariate logistic regression analyses using the dichotomous status (progression or non-progression) as the dependent variable. Variables were selected if univariate association was $P < 0.05$ on univariate analyses, although only the variable with the smallest probability value was used as a candidate variable among similar clinical variables that were intercorrelated (Pearson's or Spearman's correlation coefficient ≥0.4). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and the independence of variables was tested using the likelihood ratio test on reduced models. The Kaplan–Meier method was used for cumulative event-free rates with the log-rank test for assessing the statistical differences between the two groups according to cutoff values of non-fasting TG. The receiver operating characteristic (ROC) curves for non-fasting TG or glucose levels were calculated in the reference population by carotid stenosis progression. P values less than 0.05 were considered significant.

Results

The analyzed 96 patients had the mean age of 71.2 years (range: 45–89), and included 90 men (93.8%), 29 symptomatic cases (30.2%), and 92 patients receiving some kind of antiplatelet drugs (95.8%). The mean follow-up period was 1135 days (range: 375–2980). During the follow-up period, progression of carotid artery stenosis was shown in 21 of 96 patients, and CAS (11 carotid arteries) or CEA (2 carotid arteries) was performed on either side in nine patients and on bilateral sides in two patients according to the above indication of CAS and CEA. In the progression group, the mean degree of carotid artery stenosis progressed from 31.4% (range: 0–82) to 70.7% (range: 40–100) during the mean follow-up period of 1144 days (range: 55–2704) on ultrasonography (Supplementary Fig. 1a. All Supplementary Figures and Table are available Online). As a representative case, the ultrasonographic findings in a 50-year-old man with a medical history of dyslipidemia, cigarette use, and non-fasting TG value of 192 mg/dL (the patient number 8 in Supplementary Fig. 1a.) were presented: 24% asymptomatic left carotid stenosis (Supplementary Fig. 1b) was deteriorated to 58% stenosis (Supplementary Fig. 1c) in 566 days. A 72-year-old man with a medical history of hypertension, dyslipidemia, mild chronic renal failure and radiation therapy for laryngeal cancer, and non-fasting TG value of 231 mg/dL (the patient number 19 in Supplementary Fig. 1a) had unexpectedly rapid progression of 43% asymptomatic left carotid stenosis to 80% stenosis on ultrasonography in 55 days, which was treated with CAS; on the other hand, the contralateral moderate carotid stenosis was unchanged during 375 days of the follow-up period.

Comparisons of patient baseline characteristics between the progression and non-progression groups

Clinical characteristics of 96 patients are shown in Table 1. Baseline degree of carotid stenosis, the incidence of symptomatic cases, findings on carotid plaque images (SIR of the worse side), and past medical history were not significantly different between the progression and the non-progression groups. Although treatment with antiplatelet drugs, anticoagulant drugs, ARBs, and lipid-lowering drugs including statins was not different between the two groups, CCB was less frequently used in the progression group. Mean values of non-fasting serum total

Table 1 Comparisons of baseline clinical characteristics of patients between the progression and non-progression groups

	Progression (n = 21)	Non-progression (n = 75)	P value	Odds ratio
Age (y)	67.9 ± 10.0	72.1 ± 6.7	0.158[a]	
Male	20	70	1.000[c]	1.429
Body mass index (kg/m^2)	23.2 ± 3.3	23.1 ± 3.5	0.781[a]	
Past medical history				
Hypertension	18	60	0.755[c]	1.500
Diabetes mellitus	15	40	0.138[b]	2.188
Dyslipidemia	11	46	0.113[b]	0.694
Chronic kidney disease	4	9	0.472[c]	1.726
Smoking	18	60	0.755[c]	1.500
Alcohol consumption	10	39	0.723[b]	0.839
Carotid stenosis				
Symptomatic	7	22	0.724[b]	1.205
Degree of stenosis (%)				
Worse side	75.3 ± 17.7	77.6 ± 13.0	0.505[a]	
Contralateral side	20.1 ± 23.1	15.7 ± 26.4	0.494[a]	
SIR of worse side	1.67 ± 0.37	1.67 ± 0.58	0.541[a]	
Radiation-induced	3	3	0.117[c]	4.000
Other atherosclerotic stenosis				
Intracranial artery	3	5	0.367[c]	0.429
Subclavian artery	1	3	1.000[c]	0.833
Coronal artery	6	36	0.113[b]	0.433
Artery of lower extremities	2	9	1.000[c]	0.772
Drug profile				
Aspirin	9	42	0.286[b]	0.589
Clopidogrel	16	40	0.080[c]	2.800
Cilostazol	10	40	0.643[b]	0.795
Prasugrel	0	5	0.282[c]	0
Warfarin	1	3	1.000[c]	1.200
DOAC	2	2	0.207[c]	3.842
ARB	7	24	0.908[b]	1.063
CCB	5	38	0.046[c]	0.304
β-blocker	4	11	0.734[c]	1.370
Statin	15	49	0.601[b]	1.327
Fibrate	0	1	1.000[c]	0
EPA	0	8	0.194[c]	0
Non-fasting laboratory data				
Total cholesterol (mg/dL)	188.1 ± 47.3	172.1 ± 32.6	0.343[a]	
HDL-C (mg/dL)	45.9 ± 11.5	54.3 ± 15.8	0.063[a]	
LDL-C (mg/dL)	113.8 ± 42.2	99.8 ± 26.3	0.063[a]	
TG (mg/dL)	220.1 ± 119.8	137.2 ± 65.1	0.001[a]	
Hypertriglyceridemia (≥175 mg/dL)	13	18	0.002[b]	4.694

Table 1 Continued

	Progression (n=21)	Non-progression (n=75)	P value	Odds ratio
Glucose	158.5 ± 71.4	122.7 ± 43.1	0.004[a]	
HbA1C	6.9 ± 1.2	6.6 ± 1.0	0.528[a]	
Follow-up period (days)	1,487.6 ± 848.8	1,036.7 ± 624.8	0.042[a]	

Values are a mean ± standard deviation or the number of cases. Continuous and categorical variables were compared using Wilcoxon rank-sum[a], chi-square[b], or Fisher's exact[c] tests, as appropriate. ARB: angiotensin receptor blocker, CCB: calcium channel blocker, DOAC: direct oral anticoagulant, EPA: eicosapentaenoic acid, HbA1C: hemoglobin A1C, HDL-C: high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol, SIR, signal intensity ratio, TG, triglyceride.

cholesterol, HDL-C, LDL-C, and HbA1C were not significantly different between the two groups. In contrast, the values of non-fasting TGs and glucoses were significantly higher in the progression group. Follow-up period was significantly longer in the progression group because the patients resultantly continued to be followed up for closer observation in our hospital, not local clinics.

Both non-fasting serum values of TGs as a continuous variable and the proportion of hypertriglyceridemia (≥175 mg/dL) as a categorical variable were significant factors, and the continuous variable with a smaller P value was used for the following analysis. From analysis of the ROC curve for non-fasting TG levels in the reference population by carotid stenosis progression, the area under the curve was 0.730, and the cutoff value of TG was 158.5 mg/dL, with a sensitivity of 0.714 and a specificity of 0.750 (Supplementary Fig. 2). Similarly, from analysis of the ROC curve for non-fasting glucose levels, the area under the curve was 0.716, and the cutoff value was 118.5 mg/dL, with a sensitivity of 0.800 and a specificity of 0.616 (Supplementary Fig. 3); and from analysis of the ROC curve for follow-up period, the area under the curve was 0.645, and the cutoff value was 1,729 days, with a sensitivity of 0.476 and a specificity of 0.840 (Supplementary Fig. 4). Thus, treatment with CCB, higher non-fasting TG values (≥158.5 mg/dL), higher non-fasting glucose values (≥118.5 mg/dL), and longer follow-up period (≥1,729 days) were candidate variables for multivariate logistic regression analyses. Logistic regression analyses indicated that higher non-fasting values of TG and glucose were significantly associated with carotid stenosis progression (OR = 11.735, 95% CI = 3.040–45.297, P <0.001; OR = 8.102, 95% CI = 1.915–34.286, P = 0.004, respectively) (Supplementary Table 1).

Kaplan–Meier plots demonstrated that the progression-free survival rate was significantly higher in patients without hypertriglyceridemia compared with those with hypertriglyceridemia (≥175 mg/dL) (Fig. 1). Contrary to expectations, however, when 160 mg/dL was used as a cutoff value of non-fasting serum TG levels, Kaplan–Meier plots showed no differences in the progression-free survival rate between patients with and without hypertriglyceridemia (Supplementary Fig. 5).

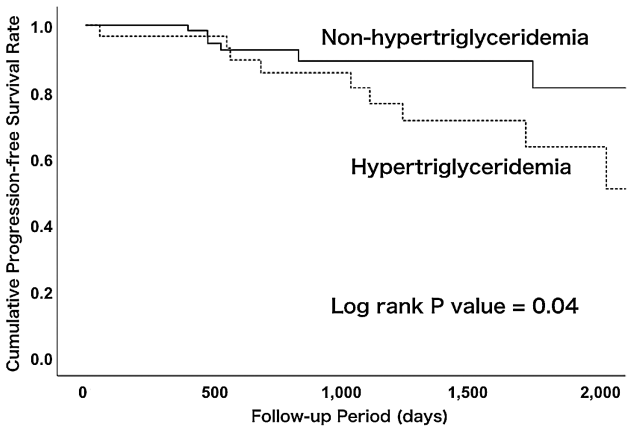

Fig. 1 Kaplan–Meier survival estimates demonstrating significantly worse progression-free survival rate in patients with hypertriglyceridemia (non-fasting TG ≥175 mg/dL). TG: triglyceride.

Comparisons of carotid artery characteristics between the progression and non-progression groups

During the follow-up period, carotid stenosis progression was shown in 23 of 121 carotid arteries. Clinical baseline characteristics of 121 carotid arteries are shown in Table 2. The frequency of symptomatic lesions, radiation-induced lesions, the use of CCB, non-fasting serum TG levels, and non-fasting glucose levels were significantly different between the progression and non-progression groups. On the other hand, baseline degree of carotid artery stenosis, findings on carotid plaque images (SIR), treatment with antiplatelet drugs, anticoagulant drugs, ARBs, and lipid-lowering drugs including statins, or mean non-fasting serum values of total cholesterol, HDL-C,

Table 2 Comparisons of baseline clinical characteristics between the progression and non-progression groups in carotid artery-based analyses

	Progression (n = 23)	Non-progression (n = 98)	P value	Odds ratio
Age (y)	67.4 ± 10.4	72.2 ± 6.9	0.766[a]	
Male	22	93	1.000[c]	1.183
Body mass index (kg/m^2)	23.5 ± 3.5	23.0 ± 3.5	0.553[a]	
Past medical history				
Hypertension	19	80	1.000[c]	1.069
Diabetes mellitus	17	56	0.139[b]	2.125
Dyslipidemia	12	57	0.602[b]	0.785
Chronic kidney disease	4	11	0.482[c]	1.665
Smoking	19	79	1.000[c]	1.142
Alcohol consumption	12	48	0.783[b]	1.136
Carotid stenosis				
Symptomatic	9	7	<0.001[b]	8.357
Degree of stenosis (%)	32.5 ± 29.5	21.5 ± 31.2	0.103[a]	
0–49% stenosis	14	71	0.274[b]	0.592
50–99% stenosis	9	27		
SIR	1.57 ± 0.39	1.68 ± 0.71	0.951[a]	
Radiation-induced	4	4	0.042[c]	4.947
Other atherosclerotic stenosis				
Intracranial artery	4	8	0.239[c]	2.368
Subclavian artery	1	2	0.472[c]	2.182
Coronal artery	8	43	0.427[b]	0.682
Artery of lower extremities	2	11	1.000[c]	0.753
Drug profile				
Aspirin	9	52	0.229[b]	0.569
Clopidogrel	17	52	0.691[b]	2.506
Cilostazol	12	49	0.851[b]	1.091
Prasugrel	0	5	0.582[c]	0
Warfarin	1	4	1.000[c]	1.068
DOAC	2	4	0.320[c]	2.238
ARB	8	31	0.771[b]	1.153
CCB	5	45	0.037[c]	0.327
β-blocker	5	15	0.533[c]	1.537
Statin	17	65	0.484[b]	1.439
Fibrate	0	1	1.000[c]	0
EPA	0	9	0.205[c]	0
Non-fasting laboratory data				
Total cholesterol (mg/dL)	185.7 ± 46.0	174.4 ± 37.6	0.476[a]	
HDL-C (mg/dL)	46.7 ± 11.0	53.0 ± 14.9	0.174[a]	
LDL-C (mg/dL)	110.1 ± 41.9	102.7 ± 31.0	0.746[a]	
TG (mg/dL)	227.0 ± 117.5	149.2 ± 82.4	<0.001[a]	
Hypertriglyceridemia (≥175mg/dL)	15	23	<0.001[b]	6.196

Table 2 Continued

	Progression (n = 23)	Non-progression (n = 98)	P value	Odds ratio
Glucose	155.0 ± 68.3	130.0 ± 52.0	0.015[a]	
HbA1C	6.9 ± 1.2	6.7 ± 1.0	0.493[a]	
Follow-up period (days)	1148.7 ± 681.8	1205.3 ± 901.5	0.687[a]	

Values are a mean ± standard deviation or the number of cases. Continuous and categorical variables were compared using Wilcoxon rank-sum[a], chi-square[b], or Fisher's exact[c] tests, as appropriate. ARB: angiotensin receptor blocker, CCB: calcium channel blocker, DOAC: direct oral anticoagulant, EPA: eicosapentaenoic acid, HbA1C: hemoglobin A1C, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SIR: signal intensity ratio, TG: triglyceride.

Table 3 Multivariate logistic regression analyses using significant variables related to carotid stenosis progression on univariate analyses in carotid artery-based analyses

	Odds ratio	P value	95% Confidence interval
Symptomatic lesion	6.108	0.010	1.540–24.230
Radiation-induced lesion	3.629	0.268	0.376–35.042
CCB	0.513	0.286	0.151–1.742
Hypertriglyceridemia	4.703	0.008	1.511–14.638
Non-fasting glucose ≥118.5 mg/dL	4.435	0.025	1.201–16.377

CCB: calcium channel blocker.

LDL-C, and HbA1C were not significantly different between the two groups.

Both non-fasting serum values of TG as a continuous variable and the frequency of hypertriglyceridemia (≥175 mg/dL) as a categorical variable were significant factors, and the categorical variable with a lower P value was used for the following analysis. From analysis of the ROC curve for non-fasting glucose levels in the reference population by carotid stenosis progression, the area under the curve was 0.667, and the cutoff value was 118.5 mg/dL, with a sensitivity of 0.818 and a specificity of 0.537 (Supplementary Fig. 6). Thus, symptomatic lesion, radiation-induced lesion, treatment with CCB, hypertriglyceridemia, and higher non-fasting glucose values (≥118.5 mg/dL) were candidate variables for logistic regression analyses. Logistic regression analyses indicated that symptomatic lesion, hypertriglyceridemia, and higher non-fasting glucose values (≥118.5 mg/dL) were significantly associated with carotid stenosis progression (OR = 6.108, 95% CI = 1.540–24.230, P = 0.010; OR = 4.703, 95% CI = 1.511–14.638, P = 0.008; OR = 4.435, 95% CI = 1.201–16.377, P = 0.025, respectively) (Table 3). Kaplan–Meier plots demonstrated that the progression-free survival rate was significantly higher in carotid arteries without hypertriglyceridemia compared with those with hypertriglyceridemia (≥175 mg/dL) (Supplementary Fig. 7). From analysis of the ROC curve, the area under the curve was 0.756, and the cutoff value of non-fasting TG was 158.5 mg/dL, with a sensitivity of 0.703 and a specificity of 0.762 (Fig. 2a). When 160 mg/dL was used as a cutoff value of non-fasting serum TG levels, Kaplan–Meier plots revealed that the difference in the progression-free survival rate between carotid arteries with and without hypertriglyceridemia was much greater than that in a cutoff value of 175 mg/dL (Supplementary Fig. 8).

To assess the relationships between the degree of baseline carotid artery stenosis and non-fasting TG levels on carotid stenosis progression, the ROC curve was analyzed separately for less than 50% stenosis and 50–99% stenosis. The ROC curve demonstrated that the area under the curve was 0.752, and that the cutoff value of non-fasting TG was 169.5 mg/dL with a sensitivity of 0.640 and a specificity of 0.789 in ≤50% carotid artery stenosis (Fig. 2b). In 50–99% carotid artery stenosis, the area under the curve was 0.775, and the cutoff value of non-fasting TG was 154.5 mg/dL with a sensitivity of 0.833 and a specificity of 0.739 (Fig. 2c).

Discussion

This study for the first time reported that patients with carotid stenosis progression were associated with non-fasting TG levels of greater than or equal

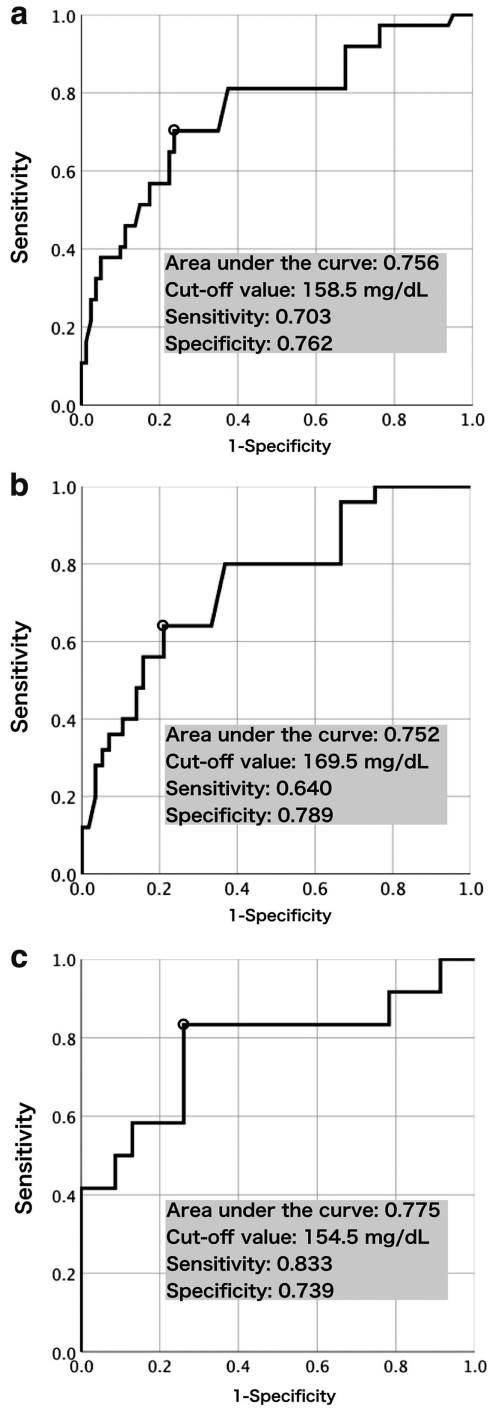

Fig. 2 ROC curves for non-fasting TG levels in the reference population by carotid stenosis progression in all carotid arteries (a), carotid arteries with less than 50% stenosis (b), and with 50–99% stenosis (c). ROC: receiver operating characteristic, TG: triglyceride.

to 175 mg/dL when fasting LDL-C levels were controlled to less than 140 mg/dL, suggesting the importance of controlling non-fasting TGs at least within normal limits in patients with carotid artery stenosis. In addition, the ROC curve demonstrated that cutoff values of non-fasting TGs associated with carotid stenosis progression were 169.5 mg/dL in carotid arteries with less than 50% stenosis and 154.5 mg/dL in those with 50–99% stenosis in carotid artery-based analyses. These findings may indicate that non-fasting serum TG levels are useful to monitor and predict a risk of carotid stenosis progression, and that more strict control of non-fasting TG levels is necessary to prevent carotid stenosis progression in carotid arteries with greater stenosis.

The risk factors for carotid artery stenosis are similar to those for other atherosclerotic vascular diseases, but the relationships between hypertriglyceridemia and carotid artery stenosis are not well known. Recently, a few studies reported higher fasting TG levels as one of the risk factors for carotid stenosis progression.[1,2] Vouillarmet et al.[1] analyzed a retrospective cohort of 342 patients with a mean of 13.6±10.6-year duration of diabetes mellitus, and reported that the carotid atherosclerosis progression tended to be associated with higher fasting TG levels at the first duplex ultrasound. Kitagami et al.[2] revealed that fasting TG levels greater than or equal to 150 mg/dL is an independent risk factor for carotid stenosis progression in a retrospective study consisting of 71 patients with moderate to severe carotid stenosis under normal fasting LDL-C levels irrespective of medical treatment, treatment with CAS or CEA. As to non-fasting TG levels, elevated non-fasting TG levels have been associated with an increased risk of ischemic heart disease[7,8] and ischemic stroke.[9] Freiberg et al.[9] revealed that the cumulative incidences of ischemic stroke increased, as non-fasting TG levels were elevated in 13956 cases (6375 males and 7581 females) including 1529 patients (779 males and 750 females) who had ischemic stroke. In the report, age-adjusted hazard ratios for ischemic stroke ranged from 1.4 for non-fasting TG levels of 89–176 mg/dL to 3.2 for those of greater or equal to 443 mg/dL versus those of less than 89 mg/dL in males; and ranged from 1.3 for non-fasting TG levels of 89–176 mg/dL to 5.1 for those of greater or equal to 443 mg/dL versus those of less than 89 mg/dL in females, showing a previously unnoticed relationship between linear increases in levels of non-fasting TG and stepwise increases in the risk of ischemic stroke.[9]

TGs and TG-rich lipoproteins are known to accelerate atherogenesis via direct and indirect mechanisms.[12] TG is a major component of TG-rich lipoproteins that include chylomicrons, very low-density lipoproteins (LDLs) and their remnants created during metabolism of TG, and elevated non-fasting TG levels indicate the presence of increased levels of TG-rich

remnant particles from chylomicrons and very LDLs.[7] Atherogenic dyslipidemia, a cardiovascular risk factor for atherosclerosis, is an imbalance between pro-atherogenic apolipoprotein B-containing lipoproteins (chylomicrons and very LDL remnants) and anti-atherogenic apolipoprotein A1-containing HDL.[13] In contrast to larger sizes of chylomicrons and very LDL particles, their remnants can infiltrate into sub-endothelial space.[13] The cholesterol-containing TG-rich lipoproteins and its lipolytic products including TG-rich lipoprotein remnants are easy to get deposited on the wall of artery, and may damage the endothelium via increasing the production of reactive oxygen species and expression of cell adhesion molecules.[13,14] Then, TG-rich lipoproteins and its products penetrate in intima and get trapped within the subendothelial space,[15–17] inducing recruitment and attachment of monocytes.[13] The monocytes can take up TG or cholesterol contents of TG-rich lipoprotein remnants to form foam cells, and develop into fatty streak and core of atherosclerotic plaque.[13,14,18,19] TG-rich lipoprotein remnants may have a stronger atherogenic effect compared with LDL because their particles contain approximately 40 times more cholesterol than LDL due to their larger size, do not need to be modified or oxidized to become atherogenic, and are taken up directly by macrophages.[13] In addition, TG-rich lipoproteins take part in the development and progression of atherosclerosis by stimulating inflammatory reactions and increasing the production of various cytokines including tumor necrosis factor-α via activating nuclear factor-κB signaling pathways.[14,19] In human apolipoprotein E2 knock-in mice, a TG-lowering agent pemafibrate decreased aortic atherosclerotic lesion burden and Oil-red-O-stained fatty streak in the atherosclerotic lesions associated with anti-inflammatory properties.[20] Lehti et al.[21] analyzed the ultrastructure of the accumulated lipids in endarterectomized human carotid atherosclerotic plaques using three-dimensional electron microscopy and revealed that apolipoprotein B is their main protein component, indicating their origin from LDL, intermediate-density lipoprotein, very LDL, lipoprotein (a), or chylomicron remnants. Moerman et al.[22] visualized the distribution of approximately 200 different lipid signals in endarterectomized human carotid atherosclerotic plaques using matrix-assisted laser desorption/ionization mass spectrometry imaging, and revealed that TGs were spatially correlated to areas containing the coagulation protein fibrin, providing a possible marker for intraplaque bleeding. Although the proatherogenic mechanisms associated with TGs and TG-rich lipoproteins seem rather complicated and need to be further explored, it may be reasonable to measure non-fasting TG levels, which may reflect the levels of TG-rich lipoproteins and the remnants. The clinical use of non-fasting levels of lipids, particularly TGs, has been limited due to concerns about effects of a meal on lipid particles, but this study suggests that non-fasting TG assessment can reduce a barrier to lipid testing and facilitate a more convenient assessment of vascular risks including carotid stenosis progression.

In this study, symptomatic cases were not significantly associated with carotid stenosis progression in univariate analyses in the patient-based analyses. However, symptomatic carotid stenosis had a significant association with the progression in univariate analyses in the carotid artery-based analyses. This may be because most of the patients with symptomatic unilateral moderate to severe carotid stenosis underwent CAS or CEA early, and the data were not analyzed due to shorter follow-up periods in both patient-based and carotid artery-based analyses in this study; on the other hand, the contralateral asymptomatic carotid lesion continued to be followed up and was analyzed as the data of patients with symptomatic lesions in the patient-based analyses and as the data of asymptomatic lesions in the carotid artery-based analyses. Thus, carotid artery-based analyses might be more accurate in this study compared with patient-based analyses.

This report showed that higher non-fasting glucose values were an independent predictor of carotid stenosis progression in patients with moderate to severe carotid artery stenosis under normal fasting LDL-C levels. The findings are consistent with previous studies.[23,24] Hu et al.[23] reported that post-challenge glucose spikes were the strongest determinant of intima-media thickening of common carotid artery in patients with type 2 diabetes, independent of other risk factors. They suggested two major deteriorated metabolic events, the hyperglycemia-induced excessive glycation and the generation of oxidative stress, as the possible mechanisms of the progression of carotid atherosclerosis in diabetes.[23] Esposito et al.[24] reported that progression of carotid atherosclerosis could be prevented by the control of postprandial hyperglycemia in type 2 diabetic patients by measuring carotid intima-media thickening. Our study also showed that antihypertensive treatment with CCB was negatively associated with carotid stenosis progression on univariate analyses, although the significance disappeared on multivariate analyses. With regard to the effect of CCB on carotid atherosclerosis, several studies have reported that CCB reduced the rate of carotid intima-media thickening compared with ACE inhibitors, β-blockers, or diuretics in the presence

of similar blood pressure reductions in patients with coronary heart disease or diabetes mellitus.[25] However, this study showed that higher non-fasting values of TG and glucose were more important determinants of carotid stenosis progression.

There are some limitations in this study including no rigid timing of postprandial blood sampling. Non-fasting TG levels may vary to some extent depending on the time passing from the last meal as well as the contents. It may be useful to determine the optimal timing of measuring non-fasting TG levels for assessing a risk of carotid stenosis progression in future researches. However, the blood sampling data in this study were obtained under actual clinical practice, and therefore we think that the findings in this study can be applied to a clinical setting.

This study for the first time revealed that higher non-fasting TG levels were associated with carotid stenosis progression, and that non-fasting TG levels can be a marker to assess a risk of carotid stenosis progression in patients with moderate to severe carotid stenosis and normal fasting LDL-C. Each analysis of the ROC curve suggested that more strict control of non-fasting TG levels may be necessary to prevent carotid stenosis progression for more severe carotid artery stenosis. According to these findings, we hypothesize that TG lowering medications suppress carotid stenosis progression in patients with moderate to severe carotid artery stenosis, and that the therapeutic levels should be changed based on the degree of carotid artery stenosis. Thus, further large-scale prospective studies are needed to confirm the effect of non-fasting TG levels on carotid stenosis progression and to clarify if TG lowering medications reduce or block carotid stenosis progression.

Conclusion

This study revealed that a higher non-fasting TG level was an important independent risk factor for the progression of carotid artery stenosis in patients with ≥50% stenosis of at least unilateral cervical internal carotid artery and normal fasting LDL-C.

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Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest. All authors have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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