**Evaluation of the common carotid artery and carotid bulb plaque: A population-based study from Japan**

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**Abstract:**

**Background:** To investigate factors associated with the maximal intima-media thickness (max-IMT) of the carotid artery, particularly plaques of an max-IMT of >1.5 mm, in a geographically coherent population in Japan. **Methods:** A total of 1,073 residents underwent carotid artery ultrasonography during the health screening conducted in Tochigi Prefecture, Japan, from October 2015 to March 2019. The observable visual field of max-IMT was evaluated in 929 participants without stroke or coronary artery disease. The results of a self-administered questionnaire survey examining risk factors for vascular disease were assessed, and factors associated with a max-IMT of >1.5 mm were analyzed. **Results:** Overall, 15.1% of the participants had a max-IMT of >1.5 mm. There were more elderly male patients and hypertensive patients (47.9% vs. 30.8%) in the max-IMT >1.5-mm group than in the max-IMT ≤1.5-mm group. The prevalence of dyslipidemia and diabetes mellitus was higher in the max-IMT >1.5-mm group than in the max-IMT ≤1.5-mm group. Logistic regression analysis after adjusting for age and sex revealed that hypertension (odds ratio, 1.54; 95% confidence interval, 1.05-2.26; p = 0.0284) was the sole predictor of a max-IMT of >1.5 mm. **Conclusion:** Among residents in a relatively high stroke-related mortality region, hypertension was associated with a max-IMT of >1.5 mm. For prevention of stroke, screening tests, including carotid artery ultrasonography, must be employed for arteriosclerosis in patients with hypertension.

**Key words:** Hypertension, Intima-media thickness, Carotid artery plaque, Carotid ultrasonography, Stroke

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**Introduction**

Malignant neoplasia is the most common cause of death in Japan, followed by heart diseases, senility, and stroke. The mortality rate of malignant neoplasia is 300.7 persons per 100,000, compared with the 167.6 persons of heart diseases and 87.1 persons of stroke\(^3\). The combined mortality rate for heart diseases and stroke is similar to the mortality rate of malignant neoplasia alone\(^1\). Stroke is the second most common causal factor necessitating nursing care, and it accounts for >30% of bedridden cases in Japan\(^2\); therefore, prevention of stroke is crucial.

In Tochigi Prefecture, the mortality rate per 100,000 persons of malignant neoplasms is well below the national average mortality rate in Japan, whereas the average incidence of heart disease is almost 184.9 people per 100,000 persons\(^2\). However, the mortality rate of stroke is 110.3 people per 100,000 persons, which is well above the national average of 100.5 people per 100,000 persons, and this rate is the 14th lowest rate among the 47 Japanese prefectures\(^2\).

Measurement of the carotid artery intima-media thickness (IMT) by ultrasonography is noninvasive and simple. IMT is widely used as a predictive marker for stroke and myocardial infarction because of its known association with cardiovascular disease and stroke onset\(^7\). A plaque is characterized when the maximal IMT (max-IMT) exceeds 1.5 mm,
with a visible protrusion exceeding 0.5 mm, and when the protrusion is >50% of the surrounding IMT. Plaques exceeding 1.5 mm require detailed assessments of their characteristics.

IMT research involving residents of Tochigi Prefecture who have high age-adjusted stroke-related mortality rates demonstrated that the max-IMT of the common carotid artery (CCA) is associated with hypertension and smoking; however, that study failed to investigate plaques of a max-IMT of >1.5 mm.

This study aimed to evaluate the max-IMT of the carotid artery, including the carotid bulbs (CB), and determine factors associated with plaques of a max-IMT of >1.5 mm.

Materials and methods

The survey was conducted among 1,073 individuals who underwent carotid artery ultrasonography during a health screening assessment between October 2015 and March 2019. Almost all participants are general citizens living in Tochigi Prefecture. Examinations were conducted at a public hall or citizen center. A self-administered survey assessing factors such as age, sex, and vascular disease risk factors was administered and completed prior to carotid artery ultrasonography (Table 1).

Carotid artery ultrasonography was performed by AI, RO, HT, AS, YT, and MO, with the patient placed in a sitting position. One of the following ultrasonic diagnostic machines was used: LOGIQ e Expert, LOGIQ e Premium (GE Healthcare Japan, Co., Ltd., Tokyo, Japan); CX 50 (Philips, Co., Ltd., Tokyo, Japan); ACUSON Freestyle (SIEMENS Japan, Co., Ltd., Tokyo, Japan); Noblus (Hitachi, Co., Ltd., Tokyo, Japan); Aplio 300, Viamo, Xario 100, and Xario 200 (Toshiba Medical Systems, Co., Ltd., Tochigi, Japan).

The IMT of the CCA and CB was evaluated on the long axis cross-section using a linear-array probe (7.5 MHz or higher), with B-mode imaging, color Doppler imaging, and power Doppler imaging. A total of 929 cases were analyzed with consent; 69 cases were excluded due to incomplete questionnaires and 75 due to the presence of known concomitant stroke or a coronary artery disease. No cases of suspected Takayasu’s arteritis or circumferential intima-media thickening were reported. Statistical analysis was conducted using IBM SPSS for Mac, version 27 (Tokyo, Japan) in addition to the Mann-Whitney U test, Pearson’s chi-square test, and logistic regression. Inter-rater errors and max-IMT inter-rater errors were evaluated using intra-class correlation coefficients (ICCs) of five patient cases admitted to our University Hospital.

All p-values were two-tailed, and p-values of <0.05 were considered statistically significant.

Results

Data reliability tests

Both intra-rater and inter-rater reliability were satisfactory (ICC = 0.85 and 0.83, respectively).

Background characteristics

Table 2 lists the demographic details of the study participants: the median age was 66.0 (20-89) years, and 29.7% (n = 276) were men. Overall, 104 participants (11.2%) were smokers and 169 (18.2%) consumed alcohol daily. Hypertension was present in 33.4% of the participants (n = 310), dyslipidemia in 45.9% (n = 426), and diabetes mellitus in 12.7% (n = 118); the median max-IMT was 1.0 (0.4-5.0) mm.

Of the 929 cases, 140 (15.1%) had a max-IMT of >1.5 mm. A max-IMT of >1.5 mm for the CCA and CB were noted in nine (1%), whereas a max-IMT of >1.5 mm for the CB was noted in 140 cases (15.1%).

Factors associated with a max-IMT of >1.5 mm

Participants were classified into two groups: max-IMT > 1.5-mm group and max-IMT ≤ 1.5-mm group.

The median age of participants in the max-IMT > 1.5-mm group was 71.5 years compared with the 65 years in the max-IMT ≤ 1.5-mm group. In the max-IMT > 1.5-mm group, 38.6% were male, whereas in the max-IMT ≤ 1.5-mm group, 28.1% were male. Hypertension was more common in the max-IMT > 1.5-mm group than in the max-IMT ≤ 1.5-mm group (47.9% vs. 38.6%). Dyslipidemia and diabetes mellitus were more likely to be found in the max-IMT > 1.5-mm group, but these differences were not significant.
and no significant differences were noted in other factors between these groups (Table 2).

A logistic regression analysis was performed to analyze dyslipidemia, diabetes mellitus, and hypertension, and a significant difference or trends was noted in these factors in the univariate analysis. Results indicated that hypertension (odds ratio 2.06, p < 0.0001) and diabetes mellitus (odds ratio 1.63, p < 0.05) were associated with a max-IMT of >1.5 mm in the univariate analysis. However, the result for dyslipidemia alone was not significant (p = 0.0720) (Table 3, Model 1). The age-adjusted results indicated a relationship with hypertension (odds ratio 1.61, p = 0.0139) (Table 3, Model 2). However, although an association was suggested, diabetes mellitus (odds ratio 1.61, p = 0.0630) was not identified as a significant factor, whereas dyslipidemia showed no association. Results after adjustment for sex (Table 3, Model 3) indicated that hypertension (odds ratio 2.04, p < 0.001) was a significant factor and was associated with diabetes mellitus (p = 0.0649) and dyslipidemia (p = 0.0503). In contrast, results after adjustments for age and sex indicated that hypertension (odds ratio 1.54, p < 0.05) was the only significant factor. Although diabetes mellitus tended to show an association with IMT (p = 0.0713), dyslipidemia showed no such association (p = 0.151) (Table 3, Model 4).

### Discussion

This study investigated factors, such as plaque characteristics, that are associated with a max-IMT of >1.5 mm in a Japanese prefectural population who underwent carotid artery ultrasonography, i.e., individuals with relatively high levels of health consciousness. We investigated possible associations of IMT of >1.5 mm with hypertension and diabetes mellitus, both of which have been previously reported, particularly in the case of hypertension.

As reported by the Framingham study, hypertension is widely known to promote atherosclerosis, and a 4.4-year follow-up study of 11,547 hypertensive patients reported that increases in the IMT and mean blood pressure correlate with the onset of the first stroke. Another report of 1,781 cases indicated that age, systolic blood pressure, and fasting blood glucose were independent factors associated with IMT. Hypertension from childhood has also been strongly associated with IMT.

On the surface of vascular endothelial cells damaged by hypertension, the number of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and chemokines such as monocyte chemoattractant protein-1 increases. These molecules are produced to increase vascular permeability and allow monocytes and low-density lipoproteins (LDLs) to migrate under the intima. LDL forms foam cells with LDL oxide, thus contributing to plaque growth. The production of free oxygen radicals following activation of

### Table 2. Background characteristics of the study participants

| Age (years; median, range) | Total (n = 929) | max-IMT ≤ 1.5 mm (n = 789) | max-IMT > 1.5 mm (n = 140) | p value |
|---------------------------|----------------|---------------------------|---------------------------|---------|
| Male (n; %)               | 276 (29.7)     | 222 (28.1)                | 54 (38.6)                 | 0.0158  |
| Smoking (n; %)            | 104 (11.2)     | 87 (11.0)                 | 17 (12.1)                 | 0.665   |
| Daily drinking (n; %)     | 169 (18.2)     | 137 (17.4)                | 32 (22.9)                 | 0.123   |
| Hypertension (n; %)       | 310 (33.4)     | 243 (30.8)                | 67 (47.9)                 | 0.000135|
| Dyslipidemia (n; %)       | 426 (45.9)     | 352 (44.6)                | 74 (52.9)                 | 0.0803  |
| Diabetes mellitus (n; %)  | 118 (12.7)     | 93 (11.8)                 | 25 (17.9)                 | 0.0537  |
| Snore (n; %)              | 396 (42.6)     | 335 (42.5)                | 61 (43.6)                 | 0.853   |
| Sleep apnea (n; %)        | 95 (10.2)      | 77 (9.76)                 | 18 (12.9)                 | 0.288   |
| Max-IMT (mm; median, range)| 1.0 (0.4–5.0) | 1.0 (0.4–1.5)             | 2.0 (1.6–5.0)             | <0.0001 |

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nicotinamide adenine dinucleotide phosphate oxidase via angiotensin II receptor stimulation and the deterioration of endothelial cell function due to hypertension from blood vessel aging and mechanical stress are also thought to promote atherosclerosis. In addition, in our study, CB plaques were more frequent than CCA plaques and concomitant hypertension was more frequent in the max-IMT > 1.5-mm group than in the max-IMT ≤ 1.5-mm group, suggesting that variations in wall shear stress at the bifurcation of the internal carotid artery and external carotid artery causes CB plaque thickening. In previous studies, carotid bifurcation has been associated with a high risk of arteriosclerosis due to specific hemodynamics and decreased wall shear stress has shown to promote arteriosclerosis, resulting from the decreased expression of VCAM-1 and reduced binding strength of endothelial cells. These reports indicate that changes in wall shear stress at the carotid bifurcation promote plaque formation in the CB.

The multivariate analysis results of a previous study indicated a correlation of age, systolic blood pressure, and smoking with IMT in both men and women. Fasting blood glucose levels, high-density lipoprotein-cholesterol levels in men, and total cholesterol levels in women were also associated with IMT. Thus, in addition to hypertension, vascular disease risk factors, such as smoking, diabetes mellitus, and dyslipidemia, are considered to contribute to IMT.

Smoking induces the production of reactive oxygen species, causing vascular endothelial cell disorders, vascular smooth muscle proliferation, and inflammatory cell invasion. It is associated with an increased IMT and plaque formation. In other previous report, smoking was associated with CCA thickening. In such a previous study, 15% of participants were smokers, as opposed to the 10% in our study, possibly why no association of smoking with a max-IMT of >1.5 mm was noted.

Diabetes mellitus and dyslipidemia are known to increase IMT and are risk factors for cardiovascular events. An association between very low LDL-cholesterol levels and IMT has been reported in postmenopausal women. Oral administration of statins for dyslipidemia has been suggested to reduce IMT. The present study found that the associations between diabetes mellitus, dyslipidemia, and a max-IMT of >1.5 mm were not statistically significant, although diabetes mellitus was nearly so.

In our study, males comprised 38.6% of the participants in the max-IMT > 1.5-mm group. Although enlargement of the intravascular space is associated with an increase in IMT, the CCA diameter is known to be larger in males than in females. We did not evaluate CCA diameters, but this could explain the preponderance of males in the max-IMT > 1.5-mm group. A correlation between alcohol consumption and IMT has been indicated previously. Furthermore, an association between alcohol consumption and plaque formation has been suggested in smokers. In our study, daily drinking was not associated with a max-IMT of >1.5 mm. However, if accurate daily alcohol intake could be evaluated, daily alcohol consumption might have been a significant factor of a max-IMT of >1.5 mm.

Snoring may reportedly cause arteriosclerosis. In particular, snoring is strongly associated with arterial effects in females, and prolonged snoring at night has been associated with an increase in CCA diameter. Sleep apnea, especially obstructive sleep apnea, induces a cascade of events, such as increasing sympathetic tone and renin-angiotensin-aldosterone system activation, due to hypoxemia and hypercapnia. This is postulated to result in the development of endothelial dysfunction, vasoconstriction, myocardial and vascular remodeling, and hypertension. Thereafter, increased oxidative stress, inflammatory substance release, and enhanced lipolysis and insulin resistance occur, resulting in left and right ventricular hypertrophy, left atrial dilation, cardiomyopathy, and microvascular retinal changes, and microalbuminuria. However, the CCA IMT differs according to severity of sleep apnea or the apnea hypopnea index (AHI). Given that our study did not assess snoring duration or AHI, it is possible that snoring and sleep apnea were not factors associated with a max-IMT of >1.5 mm.

The study has limitations, including the use of a self-administered survey. In addition, blood pressure, lipids, blood glucose control, orally administered medication status, and treatment period were unclear. This may have influenced our results, particularly with respect to the effects of daily drinking, dyslipidemia, diabetes mellitus, snoring, and sleep apnea. The difference in IMT between the treated and untreated groups is also unknown. Furthermore, intima-media thickening due to arteriosclerosis may not have been accurately excluded.

In addition, a selection bias occurred because participants were from a health-conscious population, who requested carotid artery ultrasonography at a health screening.

Because we performed carotid ultrasonography along the long axis image in the sitting position, it was difficult to make precise CB evaluation in cases of high-level branching. Furthermore, we did not assess the form and surface properties of plaques. Nevertheless, vulnerable atherosclerotic plaques, such as echolucent plaque or jellyfish plaque, must be examined for prevention of stroke.

Conclusion

In a population with relatively high stroke-related mortality rate, carotid artery ultrasonography should be employed as a screening method to help prevent stroke, as individuals with hypertension may have a max-IMT of >1.5 mm.

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Conflicts of Interest
There are no financial or other relations that could lead to conflicts of interest.

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