Original Article

Initial Progressions of Carotid Artery Plaque Are Associated with Risk Factors of Cardiovascular Disease

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Abstract

Background: Carotid artery plaque, white matter disease (WMD), and silent lacunae infarcts (initial indicators) are associated with symptomatic cerebral infarction (CI) caused by atherosclerosis. We retrospectively examined the association between the initial indicators and risk factors for cerebrovascular disease, considering the primary prevention of symptomatic CI. **Methods:** We divided 1503 individuals who were neurologically healthy and enrolled in a brain screening program (brain dock) at our institution, into three initial plaque grades (grade 0, 1, and 2) based on having no plaques, having plaques on the right or left carotid artery, or having plaques on both carotid arteries, respectively. We analyzed the risk factors according to the presence/absence of the initial indicators. **Results:** WMD and the risk factors (low-density lipoprotein [LDL], hemoglobin A1c, systolic blood pressure [BP], and smoking cigarettes) were positively correlated with the initial plaque grades, even when their laboratory values were within normal ranges. Systolic BP (116.5 ± 14.0 mmHg) was significantly lower in group 00 (without carotid plaque and WMD) than that in age-adjusted others (with carotid plaque or WMD). In young participants aged between 40 and 52 years, LDL (132.8 ± 24.5 mg/dl) was significantly higher in subgroup ++ (with carotid plaque and WMD) compared to others (without carotid plaque or WMD). **Conclusion:** Initial plaque grade and WMD grade as clinical initial indicators of symptomatic CI are associated with risk factors. To avoid deterioration of the initial indicators, it was suggested that the risk factors should be maintained at the lower ends of normal ranges and smoking cessation should be recommended.

Keywords: Cerebral infarction, intima-media thickness, leukoaraiosis, plaque, risk factors

Introduction

Carotid endarterectomy (CEA) or carotid artery stenting (CAS) has conferred benefits on patients with severe stenosis of a carotid artery in terms of preventing the likelihood of further cerebral infarction (CI). Even if a cerebral artery is not stenosed or occluded, CI with neurological deficits can often arise as a result of atherosclerotic changes, such as lacunae infarction in smaller arteries within the skull. We previously reported the clinical significance of carotid artery plaque and concurrent WMD in patients with symptomatic CI without severe steno-occlusive disease of a main cerebral artery.[1] Numerous reports indicate that an increase in the carotid intima-media thickness (IMT) and an increase in plaque scores, plaque numbers, and maximum plaque IMT (MPIMT) of the carotid arteries are helpful for risk assessment of CI.[2-11] White matter disease (WMD) is also reportedly associated with carotid plaque[12-14] and increased risk of ischemic stroke.[15] The WMD and silent brain infarct are associated with future symptomatic stroke risk.[15,16]

It is impossible to cure and promote recovery from the neurological deficits of CI induced by established atherosclerotic changes. Therefore, according to numerous risk assessment of CI,[1-16] plaque and WMD as indicators of symptomatic CI have been reported and should be maintained at low level in terms of prevention of CI. We investigated relationships between initial changes of carotid artery plaque and WMD and risk factors for cardiovascular disease among patients who were enrolled in a brain screening program referred to as the brain dock[17]

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and were in the early stages of the atherosclerotic disease, to identify plaque and WMD and prevent their progression before symptomatic CI.[1] Participation in the brain dock is becoming popular in Japan.[17] Here, we examined relationships between the initial progression of plaque and WMD and the risk factors for cardiovascular disease, to find a way to prevent initial progression of plaque and WMD, considering the primary prevention of symptomatic CI. In older participants without plaque and WMD and younger participants with both plaque and WMD, we also examined the risk factors for cardiovascular disease.

Materials and Methods

We extracted data about 1503 persons who were confirmed as being neurologically healthy and enrolled in the brain dock for disease screening at the International University of Health and Welfare between March 2008 and July 2012. We excluded patients who developed cerebrovascular or cardiovascular disease and received antiplatelet or anticoagulant therapy. All participants underwent blood tests and blood pressure checks in the morning before breakfast, magnetic resonance imaging (MRI), and carotid ultrasonography. The institutional review board at the International University of Health and Welfare approved the study with a waiver of informed consent (Approval No. 13-B-322).

Initial plaque grades

We subclassified participants into the initial plaque grade 0, 1, and 2, depending on whether they had no evidence of plaque, plaque in the right or left carotid artery, or plaque in both carotid arteries, respectively [Table 1]. We analyzed data in 1503 participants and included 927 participants after excluding the 576 participants aged <45 and >75 years to balance the three age-adjusted three initial plaque grade groups and to examine risk factors for cardiovascular disease.

Risk factors according to the presence/absence of plaques on both sides, white matter disease, and silent lacunae infarcts in 1503 participants

The risk factors for cardiovascular disease were compared between participants with plaques on both sides (group 2) and others (group 0 and 1), between no WMD group and WMD group, and between no lacunae group and lacunae group [Tables 2-5].

Subgroup 00 (without plaque and white matter disease)

We defined subgroup 00 as having no evidence of plaque and WMD. We assigned participants to age-adjusted subgroups 00 (plaque− and WMD−) and others (plaque+ and WMD+, plaque+ and WMD−, and plaque− and WMD+) and analyzed blood parameters, BP, and the number of smoking cigarettes [Tables 6 and 7].

Subgroup ++ (with plaque and white matter disease) aged between 40 and 52 years

We defined subgroup ++ as having evidence of plaque and WMD. We divided 455 participants to age-adjusted subgroup ++ (plaque+ and WMD+) and others (plaque− and WMD−, plaque+ and WMD−, plaque− and WMD+) between 40 and 52 years and compared blood parameters, blood pressure, and number of cigarette smoking between them [Tables 8 and 9].

Carotid ultrasonography

The extracranial carotid arteries in the neck were evaluated using high-resolution B-mode ultrasonography with linear array transducers (NEMIO XG SSA-580A, Toshiba, Otawara, Japan). Bilateral images were acquired from comfortably lying participants in three longitudinal and transverse projections. A lesion was defined as plaque [Figure 1] when the distance between the plaque thickness was >1.0 mm. Plaque scores, plaque numbers, and maximum plaque IMT (MPIMT) were calculated. The carotid arteries were divided into four 15-mm sections starting 15 mm distal to the internal carotid artery and extending to 45 mm proximal to the common carotid artery bifurcation. Plaque scores were calculated by summing the largest plaque IMT of each section on both sides of the carotid artery.[18] The MPIMT was derived from the single section with the thickest plaque. The number of plaques (plaque number) was similarly determined based on thickness >1.0 mm.

Magnetic resonance imaging

Standard T1- and T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion images were acquired using a 1.5 T MRI scanner (Philips Intera, Amsterdam, Netherlands). The severity of periventricular hyperintensity and deep and subcortical white matter hyperintensity (DSWMH) was graded from 0 to 4 from FLAIR images [Figure 1].[19]

Risk factors

We measured systolic and diastolic blood pressure (BP), blood parameters (glucose blood sugar [BS]), hemoglobin A1c (HbA1c), total cholesterol, triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total protein, and γ-glutamyl transpeptidase. Smoking habit also

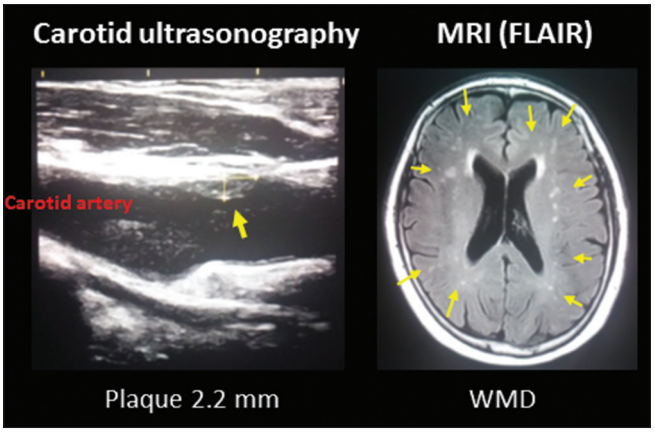

Figure 1: Representative images of carotid plaque (2.2 mm) and WMD. Arrows: plaque or WMD. MRI: magnetic resonance image, FLAIR: fluid-attenuated inversion recovery, WMD: White matter disease

Table 1: Clinical characteristics in Group 0, 1, and 2

	No plaque (Group 0)	Plaques on one side (Group 1)	Plaques on both sides (Group 2)	Total	*P*		
					Group	Group 1 versus 2	Group 0 versus 2
Age (years)	48.6±10.4	56.6±9.5	61.3±9.3	53.1±11.3	<0.0001*	<0.0001*	<0.0001*
AA	59.0±5.6	58.9±7.8	59.8±8.0	59.2±7.2	0.96	0.26	0.37
n	845	344	314	1503			
AA	339	300	288	927			
Gender, male (%)	445 (53)	209 (61)	229 (73)	883 (59)			
AA (%)	159 (47)	175 (58)	213 (74)	547 (59)			
Plaque							
Score (mm)	0	1.78±0.95	4.94±2.95	2.03±2.40	<0.0001*	<0.0001*	<0.0001*
AA	0	1.80±0.99	4.65±2.38	2.03±2.40	<0.0001*	<0.0001*	<0.0001*
Number	0	1.16±0.39	3.17±1.70	1.32±1.48	<0.0001*	<0.0001*	<0.0001*
AA	0	1.17±0.40	3.02±1.33	1.32±1.48	<0.0001*	<0.0001*	<0.0001*
Maximum IMT (mm)	0.63±0.33	1.60±0.53	2.16±0.73	1.43±0.83	<0.0001*	<0.0001*	<0.0001*
AA	0.67±0.11	1.61±0.54	2.13±0.82	1.43±0.83	<0.0001*	<0.0001*	<0.0001*
WMD							
PVH (grade)	0.12±0.34	0.25±0.48	0.43±0.62	0.31±0.52	<0.0001*	<0.0001*	<0.0001*
AA	0.28±0.48	0.28±0.51	0.38±0.58	0.31±0.52	1.00	0.04*	0.04*
DSWMH (grade)	0.38±0.60	0.66±0.70	0.82±0.76	0.72±0.71	<0.0001*	0.0051*	<0.0001*
AA	0.66±0.70	0.74±0.70	0.77±0.73	0.72±0.71	0.34	0.86	0.13
Lacunae (number)	0.08±0.32	0.14±0.59	0.24±0.54	0.13±0.45	0.09	0.02*	<0.0001*
AA	0.15±0.43	0.15±0.63	0.23±0.54	0.17±0.54	0.99	0.23	0.19
Laboratory data							
TP	7.11±0.37	7.14±0.38	7.14±0.41	7.13±0.38	0.63	0.96	0.45
AA	7.12±0.38	7.13±0.37	7.12±0.39	7.13±0.38	0.92	0.94	0.99
GTP	35.0±34.1	40.4±64.0	42.3±56.5	37.7±40.6	0.18	0.87	0.06
AA	35.2±31.2	36.2±37.5	42.2±51.8	37.7±40.6	0.07	0.17	0.94
Tcho (mg/dl)	205.9±33.1	211.4±35.0	215.8±30.5	214.3±32.7	0.02*	0.20	<0.0001*
AA	212.4±32.9	214.3±34.6	216.6±30.2	214.3±32.7	0.25	0.68	0.74
LDL (mg/dl)	120.7±29.6	125.7±29.2	129.8±27.9	126.9±28.4	0.02*	0.17	<0.0001*
AA	124.1±28.3	126.4±28.7	130.3±27.7	126.9±28.4	0.41	0.32	0.02*
HDL (mg/dl)	60.5±16.2	58.8±15.8	57.0±13.9	59.5±16.2	0.20	0.30	0.0018*
AA	61.1±18.1	59.7±15.6	57.3±14.1	59.5±16.2	0.54	0.18	0.01*
TG (mg/dl)	109.4±66.3	112.7±64.8	127.2±76.4	117.4±68.8	0.73	0.02*	0.0002*
AA	114.2±66.5	112.4±63.3	126.5±75.9	117.4±68.8	0.94	0.03*	0.06
HbA1c (%)	5.24±0.46	5.35±0.58	5.54±0.72	5.43±0.59	0.0067*	<0.0001*	<0.0001*
AA	5.39±0.44	5.38±0.58	5.53±0.73	5.43±0.59	0.93	0.01*	0.01*
BS	99.2±12.1	102.7±16.4	107.6±21.0	103.9±17.0	0.0010*	0.0001*	<0.0001*
AA	101.6±13.2	103.3±15.6	107.3±21.3	103.9±17.0	0.40	0.01*	<0.0001*
BP							
Systolic (mmHg)	115±15	121±15	125±17	121.8±15.7	<0.0001*	0.0004*	<0.0001*
AA	119±14	122±15	125±18	121.8±15.7	0.18	0.02*	<0.0001*
Diastolic (mmHg)	72±11	74±9.9	76±11	75.2±10.1	0.01	0.15	<0.0001*
AA	75±9.9	75±9.7	76±11	75.2±10.1	0.94	0.11	0.19
Smoking cigarettes	6.6±10.4	8.9±13.2	12.9±15.0	8.8±13.1	0.0069*	0.0001*	<0.0001*
AA	5.8±9.8	8.9±13.6	12.2±14.9	8.8±13.1	0.01*	0.001*	<0.0001*

AA: Age-adjusted, IMT: Intima-media thickness, WMD: White matter disease, PVH: Periventricular hyperintensity, DSWMH: Deep and subcortical white matter hyperintensity, GTP: γ-glutamyl transpeptidase, Tcho: Total cholesterol, TG: Triglycerides, TP: Total protein, BP: Blood pressure, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BS: Blood sugar

included former smokers, and current smoking was taken as the estimated number of cigarettes smoked per day.

Statistical analyses

Data were statistically analyzed using JMP for Windows, Version 9 (SAS Institute Inc., Cary, NC, USA). Values for plaque in grade 0, 1, and 2 groups were assessed using analysis of variance [Table 1]. Risk factors between participants with plaques on both sides (group 2) and others (group 0 and 1), between no WMD group and WMD group, between no lacunae group and lacunae group, between subgroup 00 and others, and between subgroup ++ and others were analyzed by logistic

Table 2: Logistic regression analysis between Group 0 and 1 and Group 2 from 1503 participants (lack of fit test: *P*>0.05)

Discriminants	Group 0 and 1	Group 2	OR	95% CI	*P*
Number	1190	313			
Gender, male (%)	654 (55)	230 (73)	2.415	1.702-3.450	<0.0001*
Age (years)	50.9±10.8	61.3±10.9	1.098	1.079-1.117	<0.0001*
PVH (grade)	0.16±0.39	0.43±0.62	1.035	0.757-1.414	0.827
Lacunae	0.08±0.32	0.14±0.59	1.177	0.866-1.548	0.284
LDL (mg/dl)	122.1±29.6	129.8±27.9	1.012	1.003-1.022	<0.0001*
BP sys. (mmHg)	116±15	125±17	1.012	1.003-1.022	0.012*
HbA1c (%)	5.28±0.50	5.54±0.72	1.319	1.057-1.644	0.015*
Smoking cigarettes	7.3±11.4	12.9±15.1	1.014	1.003-1.026	0.014*

The model fit the data, determined by an LOF test (>0.05). LOF: Lack of fit test, CI: Confidence interval, OR: Odds ratio, PVH: Periventricular hyperintensity, LDL: Low-density lipoprotein, BP: Blood pressure, HbA1c: Hemoglobin A1c

Table 3: Logistic regression analysis between no white matter disease group and white matter disease group from 1503 participants (lack of fit test: *P*>0.05)

Discriminants	No WMD group	WMD group	OR	95% CI	*P*
Number	829	674			
Gender, male (%)	392 (60)	391 (58)	0.937	0.699-1.257	0.665
Age (years)	48.0±9.9	59.3±9.7	1.103	1.087-1.121	<0.0001*
Plaque (grade)	0.46±0.73	0.87±0.84	1.025	0.863-1.216	0.779
Lacunae	0.01±0.12	0.27±0.63	11.79	6.278-24.81	<0.0001*
LDL (mg/dl)	122.4±29.5	125.4±29.1	1.001	0.997-1.005	0.641
BP sys. (mmHg)	114±15	123±16	1.015	1.006-1.024	0.001*
HbA1c (%)	5.24±0.48	5.44±0.63	1.312	0.906-1.422	0.275
Smoking cigarettes	8.1±11.3	9.0±13.7	0.998	0.987-1.009	0.694

The model fit the data, determined by an LOF test (>0.05). WMD: White matter disease, LOF: Lack of fit test, CI: Confidence interval, OR: Odds ratio, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein, BP: Blood pressure

Table 4: Logistic regression analysis between no lacunae group and lacunae group from 1503 participants (lack of fit test: *P*>0.05)

Discriminants	No lacunae group	Lacunae group	OR	95% CI	*P*
n	1349	154			
Gender, male (%)	796 (59)	86 (56)	0.766	0.489-1.197	0.242
Age (years)	52.1±11.1	61.6±9.8	1.026	1.003-1.050	0.024*
Plaque grade	0.60±0.79	1.00±0.87	1.053	0.816-1.357	0.689
PVH (grade)	0.15±0.38	0.81±0.67	5.795	4.044-8.443	<0.0001*
LDL (mg/dl)	123.6±29.2	124.6±31.2	1.002	0.995-1.008	0.611
BP sys. (mmHg)	117±15	126±18	1.015	1.002-1.027	0.020*
HbA1c (%)	5.32±0.55	5.46±0.68	0.962	0.662-1.342	0.828
Smoking cigarettes	8.4±12.4	8.9±13.2	0.997	0.980-1.014	0.726

The model fit the data, determined by an LOF test (>0.05). LOF: Lack of fit test, CI: Confidence interval, OR: Odds ratio, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein, BP: Blood pressure, PVH: Periventricular hyperintensity

regression analysis [Tables 2-4, 7 and 9]. These discriminants were clinically meaningful variables. We determined whether the model fit the data by a lack of fit test. Characteristics and risk factors between subgroup 00 and others and between subgroup ++ and others were analyzed using an unpaired two-tailed *t*-test ($P > 0.05$) or a Welch *t*-test ($P < 0.05$) and determined by a Levene's test to assess homogeneity of variance [Tables 5, 6 and 8]. Data are presented as means ± standard deviation. Statistical significance was taken at $P < 0.05$.

Results

Plaque progression and risk factors

Data from 927 participants who had been assessed by carotid ultrasonography and MRI were analyzed, and their characteristics are summarized in Table 1. Among age-adjusted three groups, there were significant differences of plaque scores, plaque numbers, and MPIMT. Notably, LDL, HDL, TG, HbA1c, BS, and systolic BP and smoking cigarettes differed between group 2 and all other groups [Table 1].

Table 5: Characteristics of no lacunae group and lacunae group from 1503 participants

	No lacunae group	Lacunae group	Levene		*t*-test	*P*	Total
			P	*t*	Df		
Number	1349	154					1503
Gender, Male	796 (59%)	86 (56%)					646 (59%)
Age (years)	52.1±11.1	61.6±9.8	0.034	11.33	200	<0.0001*	56.7±8.4
Plaque (grade)	0.60±0.79	1.00±0.87	0.121	5.844	1501	<0.0001*	
PVH (grade)	0.15±0.38	0.81±0.67	<0.0001	11.98	165	<0.0001*	
DSWMH (grade)	0.44±0.62	1.37±0.68	0.188	17.40	1501	<0.0001*	0.16±0.51
Lab data							
TP	7.11±0.38	7.21±0.40	0.297	2.903	1501	0.004*	7.13±0.39
GTP	37.4±45.0	41.1±66.3	0.166	0.931	1501	0.352	39.2±51.4
Tcho (mg/dl)	209.0±33.0	210.9±35.3	0.459	0.683	1501	0.495	212.8±33.3
LDL (mg/dl)	123.6±29.2	124.6±31.2	0.398	0.407	1501	0.684	126.2±29.0
HDL (mg/dl)	59.3±14.9	60.1±21.1	0.208	0.587	1501	0.557	59.3±16.1
TG (mg/dl)	113.9±69.3	113.1±61.9	0.600	-0.138	1501	0.890	117.1±70.8
HbA1c (%)	5.32±0.55	5.46±0.68	0.019	2.503	175	0.013*	5.40±0.60
BS	101.2±15.3	107.0±19.9	0.0004	3.485	173	0.0006*	103.2±17.1
BP							
Systolic (mmHg)	117.3±15.3	126.0±17.5	0.385	6.562	1501	<0.0001*	120.6±15.6
Diastolic (mmHg)	73.2±10.7	76.4±10.4	0.242	3.462	1501	0.0006*	74.9±10.5
Smoking cigarettes	8.4±12.4	8.9±13.2	0.395	0.442	1501	0.659	8.7±13.0

Subgroup 00: no evidence of plaque or WMD. Others: plaque + and WMD+, plaque + and WMD-, plaque- and WMD+.

Table 6: Characteristics of subgroup 00 and others in 1089 participants

	Subgroup 00	Others	Levene (*P*)	*t*	*T*-test Df	*P*	Total
n	184	905					1089
Gender, male (%)	102 (55)	544 (60)					646 (59)
Age (years)	56.0±4.9	56.9±7.5	<0.0001	1.899	467	0.058	56.7±8.4
Lacune (number)	0.03±0.19	0.19±0.55	<0.0001	6.953	820	<0.0001*	0.16 ± 0.51
Laboratory data							
TP	7.11±0.36	7.13±0.39	0.119	0.555	1087	0.579	7.13±0.39
GTP	34.8 ± 30.9	40.1 ± 54.6	0.197	1.286	1087	0.199	39.2±51.4
Tcho (mg/dl)	214.2±33.8	212.5±33.2	0.520	−0.635	1087	0.526	212.8±33.3
LDL (mg/dl)	125.1±29.3	126.5±29.0	0.675	0.569	1087	0.570	126.2±29.0
HDL (mg/dl)	61.9±16.3	58.8±16.1	0.438	−2.402	1087	0.017*	59.3±16.1
TG (mg/dl)	116.3±67.8	117.3±71.4	0.950	0.175	1087	0.861	117.1±70.8
HbA1c (%)	5.39±0.44	5.40±0.63	0.115	0.267	1087	0.790	5.40±0.60
BS	101.5±15.1	103.5±17.5	0.240	1.485	1087	0.138	103.2±17.1
BP							
Systolic (mmHg)	116.5±14.0	121.4±15.8	0.231	3.933	1087	<0.0001*	120.6±15.6
Diastolic (mmHg)	73.8±10.0	75.1±10.5	0.763	1.478	1087	0.140	74.9±10.5
Smoking cigarettes	6.4±10.7	9.2±13.4	0.002	3.076	307	0.002*	8.7±13.0

Subgroup 00: No evidence of plaque or WMD. Others: plaque + and WMD+, plaque+ and WMD−, plaque- and WMD+. WMD: White matter disease, Df: Degree of freedom, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BS: Blood sugar, TP: Total protein, BP: Blood pressure, TG: Triglycerides, Tcho: Total cholesterol, GTP: γ-glutamyl transpeptidase

Risk factors according to the presence/absence of plaques on both sides, white matter disease, and silent lacunae infarcts in 1503 participants

Logistic regression analysis revealed that gender, age, LDL, systolic BP, HbA1c, and smoking cigarettes correlated with carotid plaques on both sides [Table 2]. Logistic regression analysis revealed that age, lacunae, and systolic BP correlated with WMD [Table 3] and that age, DSWMH, and systolic BP correlated with lacunae [Table 4]. The variables were found using an unpaired two-tailed *t*-test [Table 5].

Subgroup 00 (no plaque and no white matter disease)

Lacunae, HDL, systolic BP, and smoking cigarettes significantly differed between subgroups 00 and others

Table 7: Logistic regression analysis between subgroup 00 and others from 1089 participants (lack of fit test: *P*>0.05)

Discriminants	Subgroup 00	Others	OR	95% CI	*P*
Gender, male	102 (55%)	544 (60%)	1.383	0.922-2.082	0.118
Age (years)	56.0±4.9	56.9±7.5	1.001	0.980-1.022	0.943
Lacunae	0.03±0.19	0.19±0.55	5.233	2.415-14.70	<0.0001*
HDL (mg/dl)	61.9±16.3	58.8±16.1	0.992	0.982-1.003	0.171
BP sys. (mmHg)	116.5±14.0	121.4±15.8	1.019	1.007-1.031	0.002*
HbA1c (%)	5.39±0.44	5.40±0.63	0.915	0.695-1.246	0.555
Smoking cigarettes	6.4±10.7	9.2±13.4	1.008	0.992-1.027	0.321

The model fit the data, determined by an LOF test (>0.05). Subgroup 00: no evidence of plaque or WMD. Others: plaque+ and WMD+, plaque+ and WMD−, plaque- and WMD+. LOF: lack of fit test, LOF: Lack of fit test, CI: Confidence interval, OR: Odds ratio, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, BP: Blood pressure, WMD: White matter disease

Table 8: Characteristics of subgroup ++ and others from 40 to 52 years old

	Plaque and white matter disease		Levene (*P*)	*t*	*t*-test Df	*P*	Total
	Others	Subgroup ++					
Number	412	43					455
Gender, male (%)	247 (60)	31 (72)					278 (61)
Age (years)	46.8±3.5	47.7±3.1	0.119	−1.689	453	0.092	46.9±3.4
Lacunae (number)	0.04±0.23	0.19±0.39	<0.0001	2.331	45	0.024*	0.06±0.25
Laboratory data							
TP	7.09±0.37	7.09±0.41	0.145	−0.077	453	0.939	7.09±0.37
GTP	38.0±34.9	73.1±148.8	<0.0001	1.542	43	0.130	41.4±57.1
Tcho (mg/dl)	207.9±33.0	217.1±29.5	0.480	−1.768	453	0.077	208.7±32.8
LDL (mg/dl)	122.9±30.1	132.8±24.5	0.148	−2.051	453	0.041*	123.8±29.7
HDL (mg/dl)	60.3±15.4	56.3±12.8	0.088	1.634	453	0.103	59.9±15.2
TG (mg/dl)	117.1±75.5	137.5±95.2	0.039	−1.638	453	0.102	119.1±77.7
HbA1c (%)	5.22±0.53	5.19±0.29	0.168	0.424	453	0.672	5.22±0.51
BS	98.9±13.4	99.0±8.7	0.397	−0.010	453	0.992	98.9±13.0
BP							
Systolic (mmHg)	114.1±13.7	121.6±16.5	0.021	2.859	48	0.006*	114.8±14.1
Diastolic (mmHg)	72.9±11.2	77.7±12.3	0.404	−2.611	453	0.009*	73.4±11.4
Smoking cigarettes	7.98±11.6	10.8±13.1	0.078	−1.520	453	0.129	8.25±11.8

Subgroup ++: Evidence of plaque and WMD. Others: plaque− and WMD−, plaque+ and WMD−, plaque− and WMD+. WMD: White matter disease, Df: Degree of freedom, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, BS: Blood sugar, TP: Total protein, BP: Blood pressure, TG: Triglycerides, Tcho: Total cholesterol, GTP: γ-glutamyl transpeptidase

Table 9: Logistic regression analysis between subgroup ++ and others from 40 to 52 years old (lack of fit test: *P*>0.05)

Discriminants	Others	Subgroup ++	OR	95% CI	*P*
Gender (%)	247 (60)	31 (72)	1.443	0.644-3.370	0.377
Age (years)	46.8±3.5	47.7±3.1	1.070	0.968-1.188	0.188
Lacunae (*n*)	0.04±0.23	0.19±0.39	4.217	1.691-10.32	0.003*
LDL (mg/dl)	122.9±30.1	132.8±24.5	1.013	1.001-1.025	0.025*
BP sys. (mmHg)	114.1±13.7	121.6±16.5	1.033	1.010-1.057	0.005*
HbA1c (%)	5.22±0.53	5.19±0.29	0.607	0.249-1.134	0.131
Smoking cigarettes	7.98±11.6	10.8±13.1	1.010	0.982-1.037	0.458

Subgroup ++: Evidence of plaque and WMD. Others: plaque− and WMD−, plaque+ and WMD−, plaque− and WMD+. The model fit the data, determined by an LOF test (>0.05). LOF: Lack of fit test, CI: Confidence interval, OR: Odds ratio, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein, BP: Blood pressure, WMD: White matter disease

comprising age-adjusted 1089 participants [Table 6]. Logistic regression analysis of subgroup 00 and others revealed significant differences in lacunae and systolic BP [Table 7].

Subgroup ++ (younger participants with plaque and white matter disease)

Among 455 participants aged 40–52 years, lacunae, LDL, and systolic and diastolic BP were significantly increased

[Table 8]. Logistic regression analysis of the two groups also revealed significant differences in lacunae, LDL, and systolic BP [Table 9].

Discussion

In atherosclerosis, the inside of an artery narrows in not only main cerebral arteries (internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and so on) but also small arteries due to building up of the plaque, which is one of the main causes of CI. Numerous reports indicate that development of IMT and plaque of carotid arteries is helpful for risk assessment of CI[2-11] and that WMD and silent brain infarcts increased risk of ischemic stroke independently of each other.[15,16] We previously reported the clinical significance of carotid artery plaque and concurrent WMD in patients with symptomatic CI.[1] Considering the primary prevention of symptomatic CI, we should avoid development of carotid artery plaque, WMD, and silent lacunae infarcts as initial indicators. Therefore, we examined association between the initial indicators and risk factors for cardiovascular diseases in participants without symptomatic CI and cardiovascular disease in the brain dock.[17]

Among 1503 participants, plaque and WMD were identified in 658 and 674 participants, respectively, although silent lacunae infarcts were in 154 participants. We determined the initial indicators of deterioration among these risk factors with assessment of plaque and WMD in this report.

Participants without symptomatic CI in the brain dock were divided into three initial plaque grades that clearly reflected degrees of atherosclerosis. Grade 0 (apparently normal) had no atherosclerosis, grade 1 had atherosclerosis in one carotid artery (beginning of atherosclerosis), and grade 2 had atherosclerosis in both carotid arteries (atherosclerotic progression). Plaque scores, plaque number, and MPIMT significantly differed among these grades, indicating that clinical degrees of carotid artery atherosclerosis can be easily differentiated. Our findings might also indicate progression from having no evidence of atherosclerosis to initial atherosclerosis.

WMD, BP, LDL, HDL, TG, BS, HbA1c, and cigarette smoking, as well as age, were significantly associated with the development of carotid plaque. If the elderly could maintain no or minimal values for risk factors, plaques might not progress. Risk factors should be maintained as low as possible or at least close to the middle, but not the high end of the normal range before initial plaque progresses in carotid arteries. We found a significant difference among risk factors, especially systolic BP, between older participants in subgroup 00 (with no plaque and no WMD) and others, and between younger participants in subgroup ++ (with plaque and WMD) and others, even though the measured values were within normal ranges. Minimizing the risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking through exercise, nutrition management, medication, and smoking cessation should be a priority because carotid artery plaque, WMD, and silent lacunae infarcts as initial indicators are difficult to cure.

The most significant and important risk factor was systolic BP in both older and younger persons. Therefore, BP should be kept as low as possible to avoid initial progression of carotid plaque, WMD, and small lacunae infarcts. Among the younger participants in subgroup ++ (plaque + and WMD +), LDL was in the high level of the normal range. Hyperlipidemia might be an important risk factor in younger persons for plaque, WMD, and silent lacunae infarcts. Our experimental studies showed that hyperlipidemia induced by a high cholesterol diet causes deterioration of the cerebral microcirculation and induces inflammation and CI in young adult mice.[20,21] These findings in normal mice might reflect those in young humans.

The aims of the brain dock in Japan are to detect early asymptomatic brain conditions such as WMD, silent brain infarction, microbleeds, unruptured intracranial aneurysms, and stenosis of the carotid and cerebral arteries and to try to prevent the development of symptomatic CI, subarachnoid and intracranial hemorrhage, and other cerebrovascular pathologies. Individuals with no or minimal plaque registered in the brain dock should be able to prevent the growth and spread of carotid artery plaque. If, for example, carotid artery stenosis, an aneurysm or a brain tumor is diagnosed by the brain dock, patients will be referred to the neurosurgical department within a few days for the treatment by CEA, CAS, aneurysm – clipping or coiling, tumor removal, or follow-up without treatment. If people have a lot of plaque, WMD, and risk factors, they can attend neurosurgical or internal medicine departments or clinics for treatment.[1]

Further clinical and experimental investigations into the microcirculatory mechanism of symptomatic CI are needed to determine the most effective treatment to achieve the primary prevention of symptomatic CI. Furthermore, the Japanese brain dock should perhaps be publicized more and discussed to prevent or minimize brain disease worldwide.

Conclusion

We found a significant difference of risk factors among the three initial plaque grades, between subgroup 00 (without plaque and WMD) and others, and between younger participants in subgroup ++ (with plaque and WMD) and others, even though the measured values were within normal ranges. Efforts should be directed at maintaining risk factors for cardiovascular disease, namely systolic BP, LDL, TG, HbA1c, and BS at the lower ends of normal ranges, and avoiding smoking cigarettes, particularly hyperlipidemia in young persons, to prevent progression of initial indicator (plaque grade and WMD grade), considering the primary prevention of symptomatic CI.

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Conflicts of interest

There are no conflicts of interest.

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