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Original Article

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# The Atherogenic Index of Plasma is Associated With Cerebral Small Vessel Disease: A Cross-Sectional Study

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## ABSTRACT

**Objective:** Recently, the lipid profile of atherogenic dyslipidemia has become important in cerebrovascular diseases. Atherogenic index of plasma (AIP), an index that reflects this lipid profile as a single number, has been proposed, but there are still few related studies in cerebrovascular disease. In this study, we evaluated the relationship between AIP and cerebral small vessel disease (cSVD) in health check-up participants.
**Methods:** We assessed consecutive health check-ups participants between 2006 and 2013. cSVD was measured including the following three subtypes: white matter hyperintensity (WMH), lacuens, and cerebral microbleeds (CMBs). WMH quantitatively measured the volume, and lacunes and CMBs qualitatively evaluated the presence. AIP was calculated according to the following formula based on blood test results: AIP=log [triglyceride (mg/dL)/high-density lipoprotein cholesterol (mg/dL)].
**Results:** A total of 3,170 participants were evaluated (mean age: 56.5 years, male sex: 53.8%). In multivariable linear regression analysis, AIP ($\beta$=0.129, 95% confidence interval [CI]=0.003–0.255) was associated with WMH. Age, hypertension, diabetes, lipid-lowering agents, and intracranial atherosclerosis were also associated with WMH volume. In multivariable logistic regression analysis, AIP (adjusted odds ratio=1.72 1.79, 95% CI=1.03–2.90) showed close association with lacunes. Age and intracranial atherosclerosis were also related to lacunes. CMBs did not show a statistically significant association with AIP.
**Conclusion:** High AIP was associated with cSVD in health check-up participants. Since this close relationship was only seen in WMH and lacunes, these subtypes may have arisen from a more atherosclerosis-related pathology.

**Keywords:** Dyslipidemia; Triglyceride; Cholesterol; Atherosclerosis; Cerebrovascular disease

## INTRODUCTION

Cerebral small vessel disease (cSVD) is a spectrum of cerebrovascular diseases, including subtypes with various pathologies (e.g. white matter hyperintensity [WMH], lacunes, and cerebral microbleeds [CMBs]).[1,2] The prevalence of cSVD is gradually increasing due to the aging population and the advancement of brain imaging technology.[3] In addition, cSVD has high clinical importance because it increases the risk of ischemic stroke or dementia.[3-5]

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Recently, it has been found that cSVD causes cognitive impairment, gait disturbance, and dysphagia by itself, beyond acting as a simple risk factor.[6-8] As a result, studies to elucidate the mechanisms of occurrence and risk factors of cSVD has been actively conducted, and various mechanisms have been proposed as hypotheses so far.

Atherosclerosis is one of the major pathological mechanisms of cerebrovascular diseases that has been traditionally well known.[9] The role of cholesterol, especially low-density lipoprotein (LDL) cholesterol, in the development of atherosclerosis (i.e., atherogenesis) is important.[10] Therefore, many international guidelines, including the American Heart Association/American Stroke Association guideline, have long recommended to strictly control the level of LDL cholesterol to avoid vascular complications.[11] Nevertheless, hypercholesterolemia is gradually increasing in Korea due to westernized diet and lifestyle.[12]

On the other hand, gradually, the opinion that it is necessary to properly evaluate the lipid profiles beyond the LDL cholesterol level is gaining strength.[13-15] Atherogenic dyslipidemia represented by high triglyceride, low high-density lipoprotein (HDL) cholesterol, and small/dense LDL cholesterol is an example.[14,15] Atherogenic index of plasma (AIP) was developed as an index to reflect this lipid profile as one numerical value.[16] Since it was first proposed, AIP has been closely associated with atherosclerosis and cardiovascular diseases in several studies to date.[17-19] However, relatively few studies have been conducted on cerebrovascular diseases, particularly cSVD.

In this study, we evaluated the association between AIP and cSVD lesions in health check-up participants. Furthermore, by comparing the associations between AIP and each subtype of cSVD, it was also evaluated whether atherogenic dyslipidemia is a common mechanism penetrating all cSVD pathologies or a mechanism related only to a specific pathology.

## MATERIALS AND METHODS

### 1. Study population

From a registry at Seoul National University Hospital Health Promotion Center, we included consecutive health check-up participants underwent brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) aged 30–79 years between 2006 and 2013 (n=3,224). Among them, we excluded participants 1) having a history of stroke or severe neurological diseases (n=31), 2) missing data regarding covariates (n=19), and 3) impaired brain imaging data (n=4). Finally, a total of 3,170 health check-up participants were included in the final analyses (**Fig. 1**). The current study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (number: 1502-026-647). The requirement to obtain informed consent from participants was waived by the IRB due to the retrospective study design using de-identified information. All experiments were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. All data and materials related to this article are presented in the main text and in **Tables 1-5**.

### 2. Demographic, clinical, and laboratory assessments

Demographic and clinical factors were broadly evaluated, including age, sex, body mass index, hypertension, diabetes, hyperlipidemia, ischemic heart disease, current smoking, and use of antiplatelet agents, antihypertensives, and glucose- and lipid-lowering agents.[3] These factors were assessed by participants answering questionnaires about medical history and treatment.


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Laboratory examinations were conducted after 12 hours of overnight fasting, including fasting glucose, total/LDL/HDL cholesterol, and triglyceride.[3] The AIP was calculated by taking the log transformation of the ratio of triglyceride and HDL cholesterol as follows: AIP=log [triglyceride (mg/dL)/HDL cholesterol (mg/dL)][16]

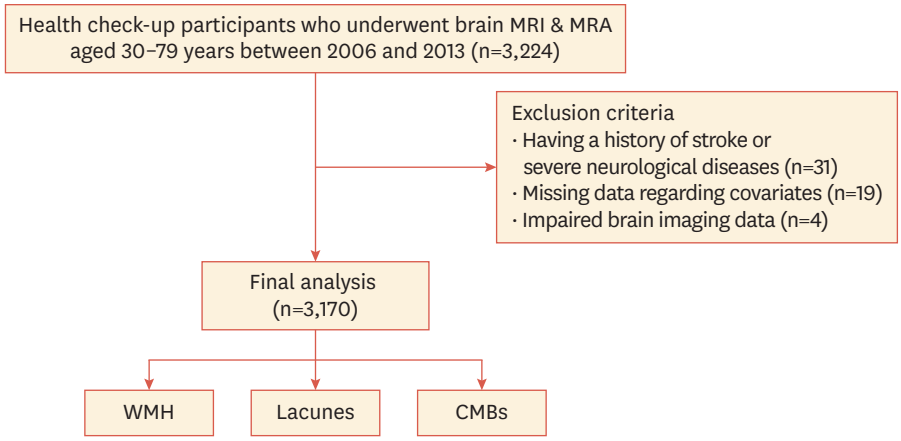


**Fig. 1.** Flow chart of the participants.
WMH, white matter hyperintensity; CMB, cerebral microbleed; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography.

**Table 1.** Baseline characteristics of the study population (n=3,170)

| Demographic & clinical factors | Values |
|---|---|
| Age (yr) | 56 [50–63] |
| Sex, male | 1,706 (53.8) |
| Body mass index (kg/m$^2$) | 24.02 [22.12–25.94] |
| Hypertension | 712 (22.5) |
| Diabetes | 436 (13.8) |
| Hyperlipidemia | 807 (25.5) |
| Ischemic heart disease | 122 (3.8) |
| Current smoking | 490 (15.5) |
| Antiplatelet agents | 344 (10.5) |
| Antihypertensives | 712 (22.5) |
| Glucose-lowering agents | 219 (6.9) |
| Lipid-lowering agents | 270 (8.5) |
| Laboratory factors | |
| Fasting glucose (mg/dL) | 91 [85–101] |
| Total cholesterol (mg/dL) | 197 [174–222] |
| LDL cholesterol (mg/dL) | 125 [101–148] |
| HDL cholesterol (mg/dL) | 53 [45–63] |
| Triglyceride (mg/dL) | 100 [73–144] |
| Atherogenic index of plasma | 0.27 [0.09–0.48] |
| Radiological factors | |
| White matter hyperintensity volume (mL) | 1.07 [0.20–2.60] |
| Lacunes | 232 (7.3) |
| Cerebral microbleeds | 131 (4.1) |
| Intracranial atherosclerosis | 95 (3.0) |
| Extracranial atherosclerosis | 36 (1.1) |

Values are presented as number (%) or number [interquartile range].
LDL, low-density lipoprotein; HDL, high-density lipoprotein.


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**Table 2.** Simple linear regression analysis between Atherogenic index of plasma and demographic, clinical, and laboratory risk factors

| Variables | β (95% CI) | *p*-value |
|---|---|---|
| Age | −0.001 (−0.002 to 0.000) | 0.106 |
| Sex, male | 0.143 (0.124 to 0.161) | <0.001 |
| Body mass index | 0.029 (0.026 to 0.032) | <0.001 |
| Hypertension | 0.051 (0.028 to 0.075) | <0.001 |
| Diabetes | 0.108 (0.080 to 0.136) | <0.001 |
| Hyperlipidemia | 0.036 (0.014 to 0.058) | 0.001 |
| Ischemic heart disease | 0.015 (−0.035 to 0.066) | 0.555 |
| Current smoking | 0.176 (0.150 to 0.203) | <0.001 |
| Fasting glucose* | 0.744 (0.630 to 0.857) | <0.001 |
| Antiplatelet agents | 0.029 (−0.003 to 0.060) | 0.075 |
| Antihypertensives | 0.051 (0.028 to 0.075) | <0.001 |
| Glucose-lowering agents | 0.055 (0.017 to 0.094) | 0.005 |
| Lipid-lowering agents | 0.036 (0.001 to 0.071) | 0.044 |
| White matter hyperintensity volume† | 0.010 (0.001 to 0.019) | 0.026 |
| Lacunes | 0.045 (0.008 to 0.082) | 0.018 |
| Cerebral microbleeds | 0.032 (−0.017 to 0.081) | 0.202 |
| Intracranial atherosclerosis | 0.068 (0.011 to 0.124) | 0.020 |
| Extracranial atherosclerosis | 0.091 (0.000 to 0.183) | 0.050 |

CI, confidence interval.
*These variables were transformed into log scales; †These variables were transformed into square root scales.

**Table 3.** Univariate and multivariable linear regression analyses between possible predictors and the square root of white matter hyperintensity volume*

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | β (95% CI) | *p*-value | β (95% CI) | *p*-value |
| Age | 0.053 (0.049 to 0.057) | <0.001 | 0.050 (0.046 to 0.053) | <0.001 |
| Sex, male | 0.005 (−0.070 to 0.079) | 0.904 | 0.003 (−0.068 to 0.075) | 0.930 |
| Body mass index | 0.004 (−0.008 to 0.016) | 0.500 | - | - |
| Hypertension | 0.464 (0.377 to 0.552) | <0.001 | 0.214 (0.129 to 0.299) | <0.001 |
| Diabetes | 0.461 (0.355 to 0.568) | <0.001 | 0.138 (0.014 to 0.262) | 0.029 |
| Hyperlipidemia | 0.062 (−0.023 to 0.148) | 0.150 | - | - |
| Ischemic heart disease | 0.243 (0.051 to 0.436) | 0.013 | −0.038 (−0.213 to 0.138) | 0.674 |
| Current smoking | −0.206 (−0.308 to −0.104) | <0.001 | 0.008 (−0.091 to 0.107) | 0.877 |
| Antiplatelet agents | 0.314 (0.194 to 0.435) | <0.001 | −0.021 (−0.134 to 0.093) | 0.723 |
| Antihypertensives | 0.464 (0.377 to 0.552) | <0.001 | - | - |
| Glucose-lowering agents | 0.510 (0.365 to 0.655) | <0.001 | - | - |
| Lipid-lowering agents | 0.192 (0.059 to 0.324) | 0.005 | −0.147 (−0.271 to −0.023) | 0.020 |
| Fasting glucose† | 1.685 (1.246 to 2.125) | <0.001 | 0.171 (−0.343 to 0.685) | 0.513 |
| Total cholesterol | −0.001 (−0.002 to 0.000) | 0.011 | - | - |
| LDL cholesterol | −0.002 (−0.003 to −0.001) | 0.002 | - | - |
| HDL cholesterol | −0.002 (−0.004 to 0.001) | 0.183 | - | - |
| Triglyceride† | 0.201 (0.027 to 0.376) | 0.024 | - | - |
| Intracranial atherosclerosis | 0.680 (0.464 to 0.896) | <0.001 | 0.301 (0.106 to 0.496) | 0.002 |
| Extracranial atherosclerosis | 0.808 (0.459 to 1.156) | <0.001 | 0.299 (−0.013 to 0.611) | 0.061 |
| Atherogenic index of plasma | 0.151 (0.018 to 0.283) | 0.026 | 0.129 (0.003 to 0.255) | 0.046 |

CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*These variables were transformed into square root scales; †These variables were transformed into log scales.

## 3. Radiological assessments

We performed brain MRI on all visiting participants using 1.5-T MR scanners (Signa; GE Healthcare, Milwaukee, WI, USA or Magnetom SONATA; Siemens, Munich, Germany). As part of the health check-ups, brain imaging was performed on the same day as the history taking and laboratory examinations. The detailed MRI acquisitions were as follows: The basic slice thickness was 5mm, except for time-of-flight MRA images. T1-weighted images (repetition time [TR]/echo time [TE]=500/11 ms), T2-weighted images (TR/TE=5,000/127 ms), T2-gradient echo images (TR/TE=57/20 ms), T2 fluid-attenuated inversion recovery


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**Table 4.** Differences of characteristics between patients with and without lacune

| Variables | No lacune (n=2,938) | Lacunes (n=232) | *p*-value |
|---|---|---|---|
| Age (yr) | 56 [50–62] | 63 [58–69] | <0.001 |
| Sex, male | 1,579 (53.7) | 127 (54.7) | 0.769 |
| Body mass index (kg/m$^2$) | 24.00 [22.13–25.94] | 24.11 [22.07–26.13] | 0.547 |
| Hypertension | 629 (21.4) | 83 (35.8) | <0.001 |
| Diabetes | 381 (13.0) | 55 (23.7) | <0.001 |
| Hyperlipidemia | 743 (25.3) | 64 (27.6) | 0.447 |
| Ischemic heart disease | 110 (3.7) | 12 (5.2) | 0.276 |
| Current smoking | 460 (15.7) | 30 (12.9) | 0.269 |
| Antiplatelet agents | 296 (10.1) | 38 (16.4) | 0.003 |
| Antihypertensive | 629 (21.4) | 83 (35.8) | <0.001 |
| Glucose-lowering agents | 193 (6.6) | 26 (11.2) | 0.007 |
| Lipid-lowering agents | 242 (8.2) | 28 (12.1) | 0.044 |
| Fasting glucose (mg/dL) | 91 [85–101] | 94 [85–110] | 0.005 |
| Total cholesterol (mg/dL) | 198 [175–223] | 190 [165–217] | 0.002 |
| LDL cholesterol (mg/dL) | 125 [102–148] | 115 [89–150] | 0.007 |
| HDL cholesterol (mg/dL) | 53 [45–63] | 51 [43–61] | 0.054 |
| Triglycerides (mg/dL) | 99 [73–144] | 108 [76–147] | 0.036 |
| ICAS | 77 (2.6) | 18 (7.8) | <0.001 |
| ECAS | 33 (1.1) | 3 (1.3) | 0.744 |
| AIP | 0.27 [0.09–0.48] | 0.33 [0.12–0.53] | 0.021 |

Values are presented as number (%) or number [interquartile range].
LDL, low-density lipoprotein; HDL, high-density lipoprotein; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis; AIP, atherogenic index of plasma.

**Table 5.** Multivariable logistic regression analysis of possible predictors for lacunes*

| Variables | Crude HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
|---|---|---|---|---|
| Age | 1.09 (1.08–1.11) | <0.001 | 1.09 (1.07–1.10) | <0.001 |
| Male sex | 1.04 (0.80–1.36) | 0.769 | 1.00 (0.76–1.33) | 0.987 |
| Hypertension | 2.05 (1.54–2.71) | <0.001 | 1.36 (0.99–1.86) | 0.055 |
| Diabetes | 2.09 (1.51–2.88) | <0.001 | 1.31 (0.85–2.02) | 0.227 |
| Antiplatelet agents | 1.75 (1.21–2.53) | 0.003 | 1.06 (0.72–1.58) | 0.759 |
| Lipid-lowering agents | 1.53 (1.01–2.32) | 0.046 | 0.91 (0.58–1.43) | 0.690 |
| Fasting glucose† | 11.39 (2.86–45.34) | 0.001 | 0.98 (0.14–6.95) | 0.987 |
| ICAS | 3.13 (1.84–5.32) | <0.001 | 1.78 (1.01–3.15) | 0.045 |
| AIP | 1.76 (1.10–2.83) | 0.018 | 1.72 (1.03–2.90) | 0.040 |

HR, hazard ratio; CI, confidence interval; ICAS, intracranial atherosclerosis; AIP, atherogenic index of plasma.
*Adjusted for variables with $p<0.10$ in univariate analysis; †These variables were transformed into log scales.

images (TR/TE=8,800/127 ms), and three-dimensional time of flight MRA images (TR/TE=24/3.5 ms, slice thickness=1.2 mm).

In this study, we evaluated a total of three cSVD subtypes: WMH, lacunes, and CMBs.[1] WMH was quantitatively measured using the Medical Imaging Processing, Analysis, and Visualization (MIPAV, version 7.3.0; National Institutes of Health, Bethesda, MD, USA) program as in our previous studies.[3] For these measurements, T2 fluid-attenuated inversion recovery images were obtained from a converted DICOM files. Then, after specifying the boundary line of the lesion in a semi-automated method, the volume was calculated through the sum of the areas of each slide.[3] We defined lacunes as asymptomatic 3–15 mm well-defined lesions in the territory of perforating arterioles, with same signal characteristics as those of the cerebrospinal fluid on T1- or T2-weighted images.[1] CMBs were defined as a < 10 mm in size focal round lesion with low signal on T2-gradient echo images (**Fig. 2**).[1] Intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS) were defined as occlusion or ≥ 50% stenosis of the intracranial and extracranial vessels on the time-of-flight MRA images.[20,21] All radiological parameters were rated by two neurologists (K.-W.N. and H.-Y.J.), and disagreements were resolved by discussion with a third rater (H.-M.K.).


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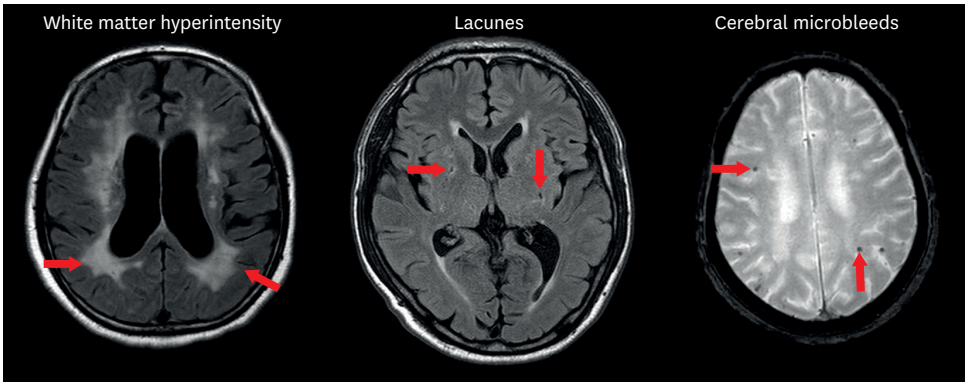


**Fig. 2.** Representative cases of cerebral small vessel disease subtypes.
Red arrows indicate each pathology.

### 4. Statistical analysis

All statistical analyses were performed using SPSS version 23.0 (IBM SPSS, Chicago, IL, USA). Continuous variables with normal distributions were showed as the mean ± standard deviation, while the others were presented as the median + interquartile range. Continuous variables with skewed data were transformed into a log scale, except for WMH volume. The WMH volume was calibrated on a square root scale because the data contained a large number of zero values. AIP is a rather unfamiliar index. Therefore, we tried to show the characteristics of AIP through associations with already familiar variables. For this analysis, simple linear regression analysis was used. Among cSVD subtypes, only WMH volume and lacunes showed statistical associations with AIP, so subsequent univariate and multivariable analyses were performed on these only.

To identify possible predictors of WMH volume, we performed univariate and multivariable linear regression analyses. On the other hand, the presence of lacunes is a binary outcome. Therefore, to perform univariate analysis, Student *t*-test and Mann-Whitney *U*-test were used for continuous variables, and chi-square test was used for categorical variables. For multivariable analysis, logistic regression analysis was used. To perform multivariable analyses of WMH volume and lacunes, variables with a result of $p<0.10$ in univariate analyses were introduced into the multivariable analysis along with age and sex as confounders. Considering multicollinearity with AIP, we did not introduce lipid profile values together with AIP to multivariable analysis. All variables with a $p<0.05$ were considered statistically significant.

## RESULTS

A total of 3,170 participants were assessed. The mean age of the population was 56.5±9.1 years, and the male sex ratio was 53.8%. The mean value of WMH volume was 2.50±5.62 mL, and the prevalence of lacunes and CMBs were 232 (7.3%) and 131 (4.1%), respectively. The mean AIP value of the entire population was 0.29±0.28. Other detailed characteristics are described in **Table 1**. In our data, AIP was strongly associated with male sex, body mass index, hypertension, diabetes, hyperlipidemia, current smoking, fasting glucose, use of antihypertensives, glucose- and lipid-lowering agents, WMH volume, lacunes, and ICAS. CMBs did not have statistical significance with AIP (**Table 2**).


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In univariate linear regression analysis, WMH volume was associated with age, hypertension, diabetes, ischemic heart disease, current smoking, antiplatelet agents, antihypertensives, glucose- and lipid-lowering agents, fasting glucose, total and LDL cholesterol, triglyceride, ICAS, ECAS, and AIP. In multivariable analysis, AIP ($\beta$=0.129, 95% confidence interval [CI]=0.003–0.255) was significantly related to WMH volume after adjusting confounders. Age ($\beta$=0.050, 95% CI=0.046–0.053), hypertension ($\beta$=0.214, 95% CI=0.129–0.299), diabetes ($\beta$=0.138, 95% CI=0.014–0.262), lipid-lowering agents ($\beta$=−0.147, 95% CI=−0.271 to −0.023), and ICAS ($\beta$=0.301, 95% CI=0.106–0.496) were also associated with WMH volume, being independent from AIP (**Table 3**).

In univariate analysis, participants with lacunes showed positive correlation with age, hypertension, diabetes, use of antiplatelet agents, use of antihypertensives, use of glucose- and lipid-lowering agents, level of fasting glucose, triglyceride, ICAS, and AIP. On the other hand, they showed a negative correlation with total- and LDL cholesterol (**Table 4**). In multivariable logistic regression analysis, AIP was closely associated with the presence of lacunes (adjusted odds ratio [aOR]=1.72, 95% CI=1.01–3.15) after adjusting for confounders. Age (aOR=1.09, 95% CI=1.07–1.10) and ICAS (aOR=1.78, 95% CI=1.01–3.15) were also related to lacunes (**Table 5**).

## DISCUSSION

We found that high AIP was associated with cSVD in a neurologically healthy population. This close association was pronounced only in WMH and lacunes. Therefore, dyslipidemia and atherosclerosis are thought to be more closely involved in the generation of these pathologies.

Although evident in our data, the exact pathophysiological mechanisms that could explain the close relationship between AIP and cSVD are unclear. However, the authors could suggest several plausible hypotheses. First, atherosclerosis may be the main mechanism linking the AIP and cSVD. As previously described, AIP reflects an atherogenic dyslipidemia profile.[16] Small/dense LDL cholesterol, which is abundantly present in this state, is easily oxidized and is also involved in foam cell formation, promoting atherogenesis.[22,23] Of course, high triglyceride and low HDL cholesterol were also closely related to atherogenesis in several studies, respectively.[24,25] In fact, in our **Table 2**, AIP showed a close correlation with ICAS, and showed a statistical trend with ECAS. The resulting ICAS or ECAS induces diffuse hypoperfusion of the brain, which can develop cSVD.[26] In addition, the formation of micro-atheroma of the perforating artery rather than the large vessel or the formation of branch atheromatous disease at the origin of the perforating artery may also contribute to the development of cSVD.[26] Second, endothelial dysfunction is also a mechanism to consider. Ischemic dyslipidemia is often accompanied by insulin resistance (IR). In fact, the TG/HDL ratio has been used as an indicator of IR and also correlates well with other IR markers.[27,28] In other words, participants with high AIP can be considered as having subclinical inflammation with a high burden like IR. Under these conditions, lipid peroxidation or cellular/DNA damage occurs, and it affects the endothelium, causing dysfunction.[29,30] Then, endothelial dysfunction causes blood-brain-barrier breakdown, impaired clearance through the glymphatic pathway, and arteriosclerosis, which leads to cSVD lesion progression.[1,26] Last, it may simply be the result of AIP and cSVD sharing common risk factors. In our **Table 2**, AIP showed a close association with various vascular risk factors, which are also well-known risk factors for cSVD.


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Among the three cSVD subtypes, only CMBs had no statistical significance with AIP. Of course, this may be the result of a statistical bias due to the relatively low prevalence of CMBs. The mean age of our study population was 56 years, and the prevalence of CMBs was only 4.1%. However, rather than this hypothesis, the interpretation that the pathophysiological mechanism of CMBs was fundamentally far from dyslipidemia or atherosclerosis seems more correct. Although not separated in this study, CMBs are divided into lobar CMBs and deep CMBs according to their locations.[1] Lobar CMBs are known to be mainly caused by amyloid angiopathy, whereas deep CMBs are known to be related to hypertensive injury.[1,26] Of course, the blood-brain-barrier breakdown can help rupture of microvessels caused by hypertensive injury, and impaired glymphatic clearance may accelerate the accumulation of amyloid. However, these influences are not expected to be large. In short, atherogenic dyslipidemia and accompanying macro/micro-atherosclerosis are interpreted not as a common mechanism penetrating all cSVD subtypes, but as a mechanism related to a specific cSVD pathology close to an ischemic mechanism.

In previous studies, a negative correlation between hypercholesterolemia and cSVD was also reported.[31] At first glance, this may seem contradictory to our major finding indicating a positive correlation between AIP and cSVD. However, the two studies have distinct differences in the study subjects and the definition of cSVD. In addition, in the corresponding study, cSVD lesions were evaluated only qualitatively and analyzed as a single variable without subtype classification. Therefore, this may lead to differences between our results and our results. Also, in our data, total cholesterol was negatively correlated with WMH volume and lacune univariate analysis. However, when introduced to multivariable analysis instead of AIP, total cholesterol did not show statistical significance with either WMH volume or lacune. In other words, it could be suggested that atherogenic dyslipidemia is more important than hypercholesterolemia in the development and progression of cSVD.

There are several limitations to consider in interpreting our results. First, this study is a retrospective cross-sectional study. Due to the limitations of cross-sectional analyses, we can only suggest associations, not causal relationships. Second, our study population is a relatively young and has few cardiovascular risk factors. In our data, only 8.5% of participants taking lipid-lowering agents. If there were a sufficient number of participants taking lipid-lowering agents, it might be possible to analyze the effects of biological interaction of AIP with lipid-lowering agents on cSVD development. Last, we used a single measure of AIP. Because cSDV is a chronic, slowly forming pathology, it is unclear when it generated. If we analyze in AIP measured at various time points and the change of cSVD therebetween, we will be able to more accurately prove the causal relationship between the two. In addition, lipid-lowering agents showed a negative correlation with WMH volume in our data. Therefore, analyzing the changes in AIP and the development of cSVD according to the use of lipid-lowering agents will be helpful in understanding their causal relationship and pathophysiology. This is a topic that needs to be confirmed through subsequent studies.

In conclusion, we found that AIP was closely related to cSVD, especially WMH and lacunes, in a neurologically healthy population. In our data, most participants had triglyceride and HDL cholesterol within the “normal ranges.” Nevertheless, our results that even at this subclinical level, dyslipidemia profiles may influence cSVD formation. And, AIP can be calculated quickly through a simple blood test. Therefore, if verified through future studies, the authors think that AIP can be used as an inexpensive and convenient indicator to predict the occurrence and progression of cSVD. By classifying this high-risk group for cSVD, we may be able to identify people who need brain imaging.


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