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Serum gamma-glutamyl transferase is associated with silent brain infarcts in a healthy population

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HIGHLIGHTS

- Serum gamma-glutamyl transferase (GGT) is associated with silent brain infarcts (SBI) in a healthy population.
- This relationship was more prominent in male subjects.
- Oxidative stress, atherosclerosis, or sharing vascular risk factors may have a role between serum GGT and SBIs.

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ABSTRACT

Background and aims: Although there is substantial evidence that serum gamma-glutamyl transferase (GGT) is associated with cerebrovascular diseases, its role in silent brain infarcts (SBIs) has not been addressed. In this study, we evaluated the relationship between serum GGT and the presence of SBI in a neurologically healthy population.

Methods: We evaluated a consecutive series of healthy volunteers recruited between January 2006 and December 2013. We conducted broad examinations in the form of health check-ups, which included brain magnetic resonance imaging and laboratory examinations including assessment of GGT levels. SBI was defined as asymptomatic, well-defined lesions with a dimeter of ≥3 mm with the same signal characteristics as cerebrospinal fluid on T1- or T2-weighted images.

Results: A total of 3145 healthy subjects were assessed, and 260 SBI cases were identified. In multivariate analysis, the highest GGT tertile was independently associated with SBI [adjusted OR (aOR) = 1.48, 95% confidence interval (CI) = 1.02 to 2.15, $p = 0.040$] in a dose-response manner (p for trend = 0.037). Age and hypertension were also found to be significant factors for SBI. In a stratified analysis by sex, these positive associations of GGT levels with SBI became more prominent in the male group (aOR = 2.14, 95% CI = 1.15 to 4.00, $p = 0.017$), with a significantly increasing trend (p for trend = 0.028), while there was no association among female participants.

Conclusions: Increased serum GGT levels were found to be associated with higher SBI prevalence in a neurologically healthy population.

1. Introduction

Silent brain infarct (SBI) is a preclinical pathology that originates from vascular lesions [1]. With the increased use of magnetic resonance imaging (MRI), the prevalence of SBI has increased in the elderly prior to symptomatic ischemic stroke [2,3]. As recovery from neurological symptoms is limited following ischemic stroke, SBI has been evaluated in previous studies as an intermediate stage of stroke [3]. Several

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possible pathophysiological mechanisms for SBI have been suggested (e.g., atherosclerosis, lipohyalinosis, and endothelial dysfunction); however, there is still a lack of evidence-based knowledge in this area [4–6].

Gamma-glutamyl transferase (GGT), a catalytic enzyme that is involved in the metabolism of extracellular glutathione (GSH) [7,8], has typically been used as a clinical marker of excessive alcohol consumption or liver disease [9–12]. Recently, there has been evidence that serum GGT is related to the risk and prognosis of symptomatic cardiovascular or cerebrovascular diseases [7,13–17]. In addition, serum GGT is also associated with asymptomatic atherosclerosis [18] and various vascular risk factors (e.g., hypertension, diabetes, obesity, and metabolic syndrome) [8,9,11,19]. Being spectrums of cerebrovascular diseases, serum GGT may be associated with SBI, however, no studies have been conducted to determine a direct relationship.

In this study, we investigated the relationship between serum GGT levels and SBI in a neurologically healthy adult population.

2. Materials and methods

2.1. Participating subjects

As a part of a consecutive registry of health check-ups in the Seoul National University Hospital Health Promotion Center between January 2006 and December 2013, subjects who were older than 29 years were evaluated (n = 3317). All participants who visited our center underwent a broad screening examination, including brain MRI, magnetic resonance angiography, and laboratory examinations as a part of a health check-up. Of these participants, 57 subjects, who had a history of stroke or severe neurological deficit, were excluded. Participants without GGT data (n = 19), or those who had suffered active hepatitis, liver cirrhosis, or other cholestatic diseases (n = 96), were also excluded. Finally, a total of 3145 neurologically healthy subjects were included in the final analyses (Supplemental Fig. 1). This study was approved by the Institutional Review Board at the Seoul National University Hospital (IRB number: H-1502-026-647) and any data not published within the article will be available from the corresponding author upon reasonable request.

2.2. Clinical assessment

We evaluated demographic factors, cardiovascular risk factors, and laboratory factors of the participants, including age, sex, body mass index (BMI), hypertension (≥140 mmHg systolic blood pressure, ≥ 90 mmHg diastolic blood pressure, or use of anti-hypertensives), diabetes (≥6.5% hemoglobin A1c levels, or use of glucose lowering agents), hyperlipidemia (≥240 mg/dL total cholesterol levels, ≥ 160 mg/dL low-density lipoprotein cholesterol levels, or use of lipid lowering agents), ischemic heart disease, current smoking, current alcohol use, use of antiplatelet medication, antihypertensive and statin [20]. Blood pressure was measured after 5 min rest in the sitting position. We also defined heavy alcohol drinking according to the guideline of National Institute on Alcohol Abuse and Alcoholism (> 14 standard drinks/week for male, and > 7 standard drinks/week for female). Laboratory examinations were performed after 12 h of overnight fasting, and included glucose profiles, lipid profiles, GGT levels, alkaline phosphatase levels, high-sensitivity C-reactive protein (hs-CRP) levels, and white blood cell (WBC) counts.

2.3. Radiological assessment

All participants underwent brain MRI using 1.5-Tesla MR scanners (Signa, GE Healthcare, Milwaukee, WI, USA or Magnetom SONATA, Siemens, Munich, Germany). MRI scans were acquired as follows: basic slice thickness = 5 mm; T1-weighted images [repetition time (TR)/echo time (TE) = 500/11 ms]; T2-weighted images (TR/TE = 5000/127 ms); T2-gradient echo images (TR/TE = 57/20 ms); T2 fluid-attenuated inversion recovery images (TR/TE = 8800/127 ms).

SBI was defined as an asymptomatic, well-defined lesion of ≥3 mm, with the same signal characteristics as cerebrospinal fluid on T1- or T2-weighted images [1]. We defined cerebral microbleeds as focal round lesions with a size smaller than 10 mm, with low signal on T2-Gradient echo images [1]. White matter hyperintensity lesions were rated by quantitative methods using Medical Imaging Processing, Analysis, and Visualization (MIPAV, version 7.3.0, National Institutes of Health, Bethesda, MD), according to our previous studies [20,21]. All radiological markers were rated by two neurologists (K.-W.N. and H.-Y.J.). Disagreements were resolved by discussion with a third rater (H.-M.K.).

2.4. Statistical analysis

Continuous variables were displayed as the mean [± standard deviation] when they met the criteria for a normal distribution, and as the median [+ interquartile range] for the others. To compare baseline characteristics between groups with and without SBI, we used Student's *t*-test or the Mann-Whitney *U* test for continuous variables, and the Chi-squared test or Fisher's exact test for categorical variables. Variables with p values < 0.10 in the univariate analysis, as well as sex, BMI, current alcohol use, and use of antihypertensive and statin were used as confounding factors in the multivariate logistic regression analysis. We also conducted additional multivariable analyses using heavy drinking as a variable instead of current alcohol use as a sensitivity analysis. As serum GGT levels have shown sexual differences with regards to clinical importance or sensitivity in previous studies, we conducted additional subgroup analyses in both male and female groups [22–24].

To understand the pathophysiologic mechanism connecting GGT and SBI, we compared the distribution of risk factors according GGT burden. We divided the cohort into GGT tertiles, and compared differences among tertiles using analyses of variance, the Kruskal-Wallis test, and the Jonckheere-Terpstra test for continuous variables. For categorical variables, we used chi-squared test and linear-by-linear association analyses to confirm differences and tendencies among tertiles. All statistical analyses in the study were performed using SPSS version 23 (IBM SPSS, Chicago, IL, USA), and statistical significance was considered to be $p < 0.05$.

3. Results

A total of 3145 healthy participants were included (median age = 56 years, male sex = 54%, median BMI = 24.04 kg/m^2). The median GGT value was 26 [17–41] IU/L, and the prevalence of SBI was 8% (206/3145). The baseline characteristics of the cohort are displayed in Table 1. In the comparison among GGT tertiles, GGT was associated with younger age, the male sex, hypertension, diabetes, hyperlipidemia, ischemic heart disease, current smoking, current alcohol use, heavy drinking, antiplatelet medication, SBI, higher BMI, hs-CRP, and WBC counts (Table 2). White matter hyperintensity volume ($p = 0.728$) and the presence of cerebral microbleeds ($p = 0.626$) were not related to GGT.

In univariate analysis, the SBI group presented with older age; higher rates of hypertension, diabetes, antiplatelet medication; higher levels of alkaline phosphatase, and hs-CRP; and WBC counts (Table 3). Patients with SBI also had a tendency toward a higher GGT tertile ($p = 0.058$, Table 3). In multivariate analysis, the highest GGT tertile remained a significant predictor of SBI, after adjustment for confounders [adjusted odds ratio (aOR) = 1.48, 95% confidence interval (CI) = 1.02 to 2.15, $p = 0.040$, Table 4], in a dose-response manner (p for trend = 0.038). Older age (aOR = 2.39, 95% CI = 2.04 to 2.81, $p < 0.001$) and hypertension (aOR = 1.35, 95% CI = 1.01 to 1.81, $p = 0.044$) were also significant predictors of SBI, independent of GGT (Table 4). The highest GGT tertile still remained significant when we conducted additional sensitivity analysis using heavy drinking as a

Table 1
Baseline characteristics of the cohort (n = 3145).

	Total	Male (n = 1693)	Female (n = 1452)
Age, y [IQR]	56 [50–63]	56 [50–63]	57 [51–63]
Sex, male, n (%)	1693 (54)	N/A	N/A
Body mass index, kg/m^2 [IQR]	24.04 [22.11–25.97]	24.48 [22.74–26.35]	23.46 [21.54–25.45]
Hypertension, n (%)	708 (23)	416 (25)	292 (20)
Diabetes, n (%)	436 (14)	288 (17)	148 (10)
Hyperlipidemia, n (%)	803 (26)	400 (24)	403 (28)
Ischemic heart disease, n (%)	123 (4)	71 (4)	52 (4)
Current smoking, n (%)	486 (15)	441 (26)	45 (3)
Current alcohol use, n (%)	1525 (48)	1135 (67)	390 (27)
Heavy drinking, n (%)	552 (18)	479 (28)	73 (5)
On antiplatelet medication, n (%)	325 (10)	208 (12)	117 (8)
On antihypertensive, n (%)	695 (22)	370 (22)	325 (22)
On statin, n (%)	476 (15)	143 (8)	110 (8)
GGT, IU/L [IQR]	26 [17–41]	33 [23–53]	19 [15–28]
Alkaline phosphatase, IU/L	62 [52–74]	61 [53–72]	63 [52–77]
hs-CRP, mg/dL [IQR]	0.04 [0.01–0.15]	0.06 [0.01–0.16]	0.04 [0.01–0.13]
White blood cell, x 10^3/μL [IQR]	5.31 [4.40–6.38]	5.60 [4.66–6.83]	5.03 [4.15–5.98]
White matter hyperintensity volume, mL [IQR]	1.08 [0.20–2.60]	1.10 [0.18–2.75]	1.00 [0.21–2.51]
Cerebral microbleeds, n (%)	129 (4)	75 (4)	54 (4)
Silent brain infarct, n (%)	260 (8)	144 (9)	116 (8)

GGT = gamma-glutamyl transferase, hs-CRP = high-sensitivity C-reactive protein.

Table 2
Comparison of characteristics among GGT tertiles.

	GGT Tertile 1	GGT Tertile 2	GGT Tertile 3	*p*-value[a]	*p*-trend[b]
Number, n	990	1077	1078		
Age, y [IQR]	56 [50–63]	58 [52–64]	55 [49–61]	< 0.001	0.001
Sex, male, n (%)	231 (23)	624 (58)	838 (78)	< 0.001	< 0.001
BMI, kg/m^2 [IQR]	23.08 [21.26–24.83]	23.92 [22.23–25.95]	25.00 [23.17–26.84]	< 0.001	< 0.001
Hypertension, n (%)	169 (17)	257 (24)	282 (26)	< 0.001	< 0.001
Diabetes, n (%)	71 (7)	160 (15)	205 (19)	< 0.001	< 0.001
Hyperlipidemia, n (%)	212 (21)	275 (26)	316 (29)	< 0.001	< 0.001
Ischemic heart disease, n (%)	27 (3)	47 (4)	49 (5)	0.066	0.035
Current smoking, n (%)	49 (5)	128 (12)	309 (29)	< 0.001	< 0.001
Current alcohol use, n (%)	312 (32)	509 (47)	704 (65)	< 0.001	< 0.001
Heavy drinking, n (%)	52 (5)	132 (12)	368 (34)	< 0.001	< 0.001
On antiplatelet medication, n (%)	78 (8)	119 (11)	128 (12)	0.007	0.003
On antihypertensive, n (%)	229 (23)	222 (21)	244 (23)	0.337	0.814
On statin, n (%)	76 (8)	86 (8)	91 (8)	0.812	0.522
hs-CRP, mg/dL [IQR]	0.02 [0.01–0.08]	0.04 [0.01–0.14]	0.10 [0.01–0.20]	< 0.001	< 0.001
White blood cell, x 10^3/μL [IQR]	4.82 [4.00–5.75]	5.32 [4.46–6.32]	5.75 [4.81–7.05]	< 0.001	< 0.001
WMH volume, mL [IQR]	1.00 [0.20–2.55]	1.14 [0.20–2.99]	1.10 [0.20–2.41]	0.158	0.728
SBI, (%)	68 (7)	87 (8)	105 (10)	0.058	0.018
CMBs, (%)	36 (4)	49 (5)	44 (4)	0.578	0.626

GGT = gamma-glutamyl transferase, BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, WMH = white matter hyperintensity, SBI = silent brain infarct, CMBs = cerebral microbleeds.
[a] These values were obtained with the Kruskal-Wallis test or Chi-squared test.
[b] These values were obtained with the Jonckheere-Terpstra test or linear-by-linear association analysis.

variable (aOR = 1.47. 95% CI = 1.01 to 2.14, $p = 0.046$) (Table 4).

In the subgroup analyses, which stratified sexual difference, the highest GGT tertile remained an independent predictor of SBI (aOR = 2.14, 95% CI = 1.15 to 4.00, $p = 0.017$) in only the male group, in a dose-response manner (p for trend = 0.028). In contrast, the female group showed no association between GGT and SBI (OR = 1.28, 95% CI = 0.75 to 2.18, $p = 0.365$). These results were also confirmed in additional sensitivity analyses (Table 5).

4. Discussion

In this study, we found that high serum GGT was associated with SBI in a neurologically healthy population. Since SBI showed a dose-response relationship with GGT levels, our findings suggest clues for the underlying pathophysiology of SBI. These relationships were more prominent in male subjects, while serum GGT was not related to SBI in female subjects.

We suggest several possible explanations for the close relationship between serum GGT and SBI. First, inflammation and oxidative stress may play a role. The main role of cellular GGT is degradation of extracellular GSH [8,25], and thus, serum GGT reflects underlying oxidative stress and depletion of GSH [14,26–28]. Furthermore, several studies have reported that serum GGT itself can also generate reactive oxygen species [8,15]. Therefore, whether via direct generation or indirect reflection of underlying oxidative stress, systemic oxidative stress and subclinical inflammation may lead to downstream of lipid peroxidation, cellular and DNA damage, and defects of endothelial vasodilation [9,29–31]. This endothelial dysfunction, consequently, could trigger SBI through chronic hypoperfusion or leakage of toxic metabolites into perivascular neural spaces [5,6]. Second, atherosclerosis might connect serum GGT levels and SBI. Catalytically active GGT interacts with low-density lipoprotein (LDL), and this GGT-LDL complex and foam cells can be taken up by atherosclerotic lesions [7,8,15,27], where they impair plaque stability and consequently lead to plaque

Table 3
Differences of characteristics between patients with and without SBI.

	No SBI (n = 2885)	SBI (n = 260)	*p*-value
Age, y [IQR]	56 [50–62]	64 [57–69]	< 0.001
Sex, male, n (%)	1549 (54)	144 (55)	0.600
Body mass index, kg/m^2 [IQR]	24.02 [22.11–25.96]	24.28 [22.05–26.18]	0.299
Hypertension, n (%)	616 (21)	92 (35)	< 0.001
Diabetes, n (%)	377 (13)	59 (23)	< 0.001
Hyperlipidemia, n (%)	733 (25)	70 (27)	0.600
Ischemic heart disease, n (%)	110 (4)	13 (5)	0.344
Current smoking, n (%)	452 (16)	34 (13)	0.268
Current alcohol use, n (%)	1406 (49)	119 (46)	0.359
Heavy drinking, n (%)	504 (17)	48 (18)	0.478
On antiplatelet medication, n (%)	285 (10)	40 (15)	0.005
On antihypertensive, n (%)	633 (22)	62 (24)	0.796
On statin, n (%)	231 (8)	22 (8)	0.687
Alkaline phosphatase, IU/L	62 [52–74]	65 [56–79]	< 0.001
GGT tertile, n (%)			0.058
Tertile 1	992 (32)	68 (26)	
Tertile 2	990 (34)	87 (33)	
Tertile 3	973 (34)	105 (40)	
hs-CRP, mg/dL [IQR]	0.04 [0.01–0.15]	0.08 [0.01–0.17]	0.024
White blood cell, x 10^3/μL [IQR]	5.30 [4.40–6.36]	5.49 [4.48–6.77]	0.036

SBI = silent brain infarct, GGT = gamma-glutamyl transferase, hs-CRP = high-sensitivity C-reactive protein.

Table 4
Multivariable analysis of possible predictors of silent brain infarct.

	Model 1		Model 2	
	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age[b]	2.39 [2.04 to 2.81]	< 0.001	2.36 [2.01 to 2.76]	< 0.001
Sex	0.88 [0.65 to 1.21]	0.433	0.93 [0.69 to 1.25]	0.631
BMI[b]	1.04 [0.91 to 1.18]	0.582	1.03 [0.91 to 1.17]	0.642
Hypertension	1.35 [1.01 to 1.81]	0.044	1.35 [1.01 to 1.81]	0.044
Diabetes	1.18 [0.84 to 1.65]	0.334	1.16 [0.83 to 1.62]	0.379
Current alcohol use	1.35 [0.99 to 1.83]	0.060	…	…
Heavy drinking	…	…	1.37 [0.94 to 2.00]	0.100
On antiplatelet medication	1.02 [0.69 to 1.49]	0.936	1.03 [0.70 to 1.51]	0.891
On antihypertension	1.08 [0.78 to 1.49]	0.659	1.07 [0.77 to 1.47]	0.695
On statin	0.95 [0.58 to 1.56]	0.850	0.95 [0.58 to 1.55]	0.827
hs-CRP[b]	1.08 [0.98 to 1.18]	0.116	1.07 [0.98 to 1.18]	0.136
ALP[b]	1.11 [0.98 to 1.24]	0.098	1.10 [0.98 to 1.23]	0.123
GGT		0.038[a]		0.062[a]
Tertile 1	Ref	Ref	Ref	Ref
Tertile 2	1.01 [0.71 to 1.44]	0.948	1.04 [0.73 to 1.48]	0.849
Tertile 3	1.48 [1.02 to 2.15]	0.040	1.47 [1.01 to 2.14]	0.046

BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, ALP = alkaline phosphatase, GGT = gamma-glutamyl transferase.
[a] *p* values are for linear trend across GGT tertiles.
[b] These variables were standardized by division with standard deviation.

rupture [7,8,25,27]. Since intraplaque GGT activity is determined by serum GGT levels [15], high serum GGT could indicate higher burden of unstable atherosclerotic plaques, resulting in plaque rupture and development of SBI [4]. Finally, it could be a simple surrogate marker of various vascular risk factors. We already knew that serum GGT is associated with many well-known vascular risk factors that are also risk factors for SBI [8,10,11,19]. Thus, subjects who had higher serum GGT may have additional vascular risk factors that contribute to SBI.

Notably, our results were pronounced in male participants, contrary to losing statistical powers in females. The mechanism of this discrepancy is unclear; however, we here speculate on the underlying causes of these findings. In this cohort, we observed that male subjects had a greater frequency of vascular risk factors and higher levels of inflammatory markers, and all these factors were significantly correlated with serum GGT levels (Supplemental Table 1). According to these findings, serum GGT in male groups might reflect underlying systemic oxidative stress, subclinical inflammation, and metabolic diseases, which are all causal factors for vascular damage. In contrast, the female group had lower occurrence of these risk factors, except for older age. Thus, the effects of age on SBI may mask influence of other factors, excluding current alcohol use, which was negatively correlated with age (Pearson coefficient = −0.252, $p < 0.001$). The difference between alcohol consumption in these groups could be another reason for the sex-based difference, as most of male group (67%) was a current alcohol user. Thus, although serum GGT is more sensitive to alcohol consumption in males than females [23,24], the power of alcohol consumption as a variable may be underestimated in this study.

Although we adjusted for well-known factors about increasing serum GGT levels such as alcohol use status or BMI, participants with high serum GGT values independently showed high prevalence of SBI. Thus, more strategic and intensive preventive health care plan should be made in this high-risk group by both the patients and their primary care physicians. Most importantly, the periodic screening and early preventive intervention on modifiable risk factors of SBI (e.g., hypertension, diabetes, hyperlipidemia, and smoking) should be included in these health care plans.

Table 5
Multivariable analysis according to sexual differences.

	Model 1		Model 2	
	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Male				
Age[b]	2.67 [2.14 to 3.32]	< 0.001	2.74 [2.20 to 3.42]	< 0.001
BMI[b]	1.11 [0.92 to 1.33]	0.280	1.11 [0.92 to 1.33]	0.276
Hypertension	1.48 [1.01 to 2.18]	0.047	1.46 [0.99 to 2.15]	0.057
Diabetes	1.07 [0.69 to 1.65]	0.768	1.06 [0.69 to 1.64]	0.778
Current alcohol use	1.12 [0.75 to 1.67]	0.584	…	…
Heavy drinking	…	…	1.49 0.97 2.28]	0.069
On antiplatelet medication	1.18 [0.74 to 1.90]	0.483	1.20 [0.75 to 1.93]	0.441
On antihypertension	1.10 [0.70 to 1.71]	0.686	1.09 [0.70 to 1.69]	0.715
On statin	0.74 [0.37 to 1.48]	0.393	0.73 [0.37 to 1.47]	0.382
hs-CRP[b]	1.12 [0.99 to 1.25]	0.063	1.12 [1.00 to 1.26]	0.058
ALP[b]	1.08 [0.91 to 1.28]	0.391	1.09 [0.92 to 1.29]	0.342
GGT		0.028[a]		0.068[a]
Tertile 1	Ref	Ref	Ref	Ref
Tertile 2	1.44 [0.77 to 2.69]	0.255	1.48 [0.79 to 2.76]	0.221
Tertile 3	2.14 [1.15 to 4.00]	0.017	2.01 [1.08 to 3.77]	0.028
Female				
Age[b]	2.13 [1.67 to 2.72]	< 0.001	2.01 [1.59 to 2.55]	< 0.001
BMI[b]	1.01 [0.84 to 1.21]	0.926	1.00 [0.84 to 1.20]	0.982
Hypertension	1.18 [0.74 to 1.87]	0.481	1.18 [0.75 to 1.87]	0.478
Diabetes	1.50 [0.87 to 2.59]	0.147	1.43 [0.83 to 2.47]	0.193
Current alcohol use	1.67 [1.05 to 2.65]	0.031	…	…
Heavy drinking	…	…	1.18 [0.45 to 3.10]	0.732
On antiplatelet medication	0.76 [0.38 to 1.52]	0.441	0.75 [0.38 to 1.49]	0.407
On antihypertension	1.05 [0.66 to 1.70]	0.828	1.05 [0.65 to 1.69]	0.850
On statin	1.28 [0.63 to 2.60]	0.500	1.27 [0.63 to 2.59]	0.504
hs-CRP[b]	0.96 [0.72 to 1.29]	0.796	0.96 [0.72 to 1.28]	0.788
ALP[b]	1.14 [0.97 to 1.35]	0.110	1.13 [0.96 to 1.34]	0.141
GGT		0.464[a]		0.455[a]
Tertile 1	Ref	Ref	Ref	Ref
Tertile 2	0.91 [0.57 to 1.45]	0.680	0.92 [0.58 to 1.47]	0.732
Tertile 3	1.28 [0.75 to 2.18]	0.365	1.30 [0.76 to 2.22]	0.334

BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, ALP = alkaline phosphatase, GGT = gamma-glutamyl transferase.
[a] *p* values are for linear trend across GGT tertiles.
[b] These variables were standardized by division with standard deviation.

There are several caveats in our current study. First, this study was designed as a retrospective, single-center study. Although we included a large number of participants with broad evaluations, the problem of selection bias remained. Second, due to the nature of cross-sectional study, we could not suggest causality between serum GGT and SBI. Further large prospective studies on the pathophysiologic mechanisms behind SBI and the contribution of GGT are needed. Third, since we included only neurologically healthy volunteers, the prevalence of SBI was lower than in the general population. However, by removing those with a history of stroke and other neurologic diseases, we could describe more pure association between serum GGT and SBI.

In conclusion, we found that high serum GGT levels were associated with increased prevalence of SBI in a neurologically healthy population. Since SBI is an independent risk factor for subsequent ischemic stroke, conducting brain MRI in high-risk groups may be beneficial. However, our results should be confirmed with further large prospective studies.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Conceptualization: K.-W.N., H.-M.K, J.-H.P.
Data curation: K.-W.N., H.-Y.J., S.H.K.
Formal analysis: K.-W.N., S.-M.J.
Writing: K.-W.N., H.-M.K.
Supervision: H.-M.K., J.-H.P.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.11.005.

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