Association Between Periodontitis and Hemorrhagic Stroke Among Koreans: A Case-Control Study

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Background: Several studies suggested that periodontitis is a risk factor for stroke, but the relationship between periodontitis and hemorrhagic stroke has not been widely reported. This study aims to evaluate the association between periodontitis and hemorrhagic stroke and to identify the risk group for this association.

Methods: We recruited 165 patients who were diagnosed via computed tomography brain imaging as having had a hemorrhagic stroke and 214 non-stroke control subjects for a case-control study. All participants underwent a clinical periodontal examination using clinical attachment level (CAL) as a marker. Information about sociodemographic factors, behavioral factors, systemic health, and a familial history of systemic health was gathered through an interview using structured questionnaires. The association between periodontitis and hemorrhagic stroke was evaluated using multivariate logistic regression analyses with adjustment for age, gender, income, education, hypertension, diabetes, body mass index, cardiac disease, familial hypertension history, familial diabetes history, familial cardiac disease history, smoking, and alcohol consumption. Subgroup analyses were also performed to investigate potential risk groups.

Results: After controlling for potential confounders, periodontitis (CAL ≥6 mm) was found to be significantly associated with hemorrhagic stroke (odds ratio: 2.5; 95% confidence interval: 1.1 to 5.6), but this association did not exhibit a dose-dependent response for periodontitis (percentile of sites of periodontal pockets with CAL ≥5 mm among total probed pockets). The association between periodontitis (CAL ≥6 mm) and hemorrhagic stroke was significant for males, patients who had a lower income than control subjects, obese patients, and patients without diabetes.

Conclusions: Periodontitis may be an independent risk factor for hemorrhagic stroke. Risk groups include males, patients without diabetes, and obese subjects. *J Periodontol 2010;81:658-665.*

KEY WORDS

Cardiovascular diseases; epidemiology; periodontitis.

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Periodontitis results from a complex interplay between chronic bacterial infection and the inflammatory host response, which leads to irreversible destruction of tooth-supporting tissues and tooth loss.[1] There are two main types of stroke: ischemic stroke is the most common type that occurs when an artery in the brain is blocked, usually because of atherosclerosis, and the second type is a hemorrhagic stroke that occurs when a portion of the arterial wall weakens and bursts. The known risk factors for stroke do not fully explain its high prevalence among patients with periodontitis.[2] Inflammation, including periodontitis, is thought to be one of the risk factors for stroke.[3]

Periodontitis and stroke share risk factors including age,[4] smoking,[5,6] diabetes,[7] hypertension,[8] and cardiovascular disease.[9-13] Although periodontitis is associated with elevated markers for inflammation that are themselves indicators of stroke risk,[14,15] the epidemiologic association between periodontitis and a stroke is still controversial. Some studies[10,16-21] demonstrated positive associations between a stroke and periodontitis, whereas other studies[22,23] found no associations. Moreover, there has been only one article[18] examining the relationship between periodontal inflammation and hemorrhagic stroke in particular. However, Wu et al.[18] demonstrated that periodontitis was significantly associated with an increased risk

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for a total cerebrovascular accident and non-hemorrhagic (ischemic) stroke but not for hemorrhagic stroke. Additional evidence is needed to clarify whether periodontitis is independently associated with hemorrhagic stroke. The aim of this study is to evaluate the relationship between periodontal inflammation and hemorrhagic stroke among subgroups based on age, gender, and other established common risk factors.

MATERIALS AND METHODS

Study Design and Subjects

The hypothesis tested in this case-control study was that periodontitis is independently associated with hemorrhagic stroke. Hemorrhagic stroke was the output variable, and periodontitis was the main explanatory variable. To test the hypothesis, the necessary sample size for this frequency-matched study (one case subject versus two control subjects) was estimated using the statistics generated through a preliminary pilot study. Under the condition of type I error at 0.05 and type II error at 0.8 and a severe periodontitis prevalence of 22% for case subjects and 10% for control subjects, the number of subjects needed for the analysis was estimated to be 104 case subjects and 208 control subjects. Assuming an attrition rate of 10%, we planned to recruit 348 subjects (116 case subjects and 232 control subjects). The Institutional Review Board for Human Subjects at the School of Dentistry, Seoul National University, approved the study (approval number: LO605-02). Written informed consent was obtained from all participants or appointed guardians when warranted.

We obtained sufficient information for the final analysis for a total of 332 subjects, which included 118 case subjects who had a hemorrhagic stroke that occurred within the previous year and a non-stroke population of 214 control subjects (Table 1). Subjects were between the ages of 40 and 79 years and resided in the metropolitan area of Seoul (12 million residents) or the neighboring province of GyungGi-Do (10 million residents). All case subjects were recruited among patients who had a hemorrhagic stroke who were hospitalized for convalescence at the National Rehabilitation Center, Seoul, Korea, from June 2005 to May 2006. Age- and gender-matched control subjects were recruited at random from the general population through an advertisement in churches, temples, and social-welfare institutions. Although we attempted to recruit the control subjects matched by age and gender, there was a difference in age between case and control subjects. The exclusion criteria for case and control subjects included pregnancy, antibiotic therapy within the previous 3 months, and subjects with <6 remaining teeth.

Ascertainment of Hemorrhagic Stroke

Medical specialists at the National Rehabilitation Center diagnosed hemorrhagic stroke based on the presence of hemorrhagic brain lesions by computed tomography (CT) and comprehensive systemic examinations. The stage of stroke for each patient was classified as follows according to the time elapsed since the occurrence of the stroke: hyperacute (<12 hours), acute (~1 week), and chronic (>4 weeks). For hemorrhagic stroke, the acute stage was usually subdivided into acute (1 to 3 days), early subacute (1 week), and late subacute (2 weeks). All patients included in this study who had a hemorrhagic stroke were categorized as non-fatal chronic: i.e., they suffered permanent disabilities and were hospitalized for rehabilitation ~6 months after the first occurrence.

Assessment of Periodontitis and Oral Health Status

A single dentist (SJS) performed comprehensive oral examinations for all patients in a dental unit or a mobile dental unit chair under blue light. The exam included periodontal probing, oral hygiene, a dental examination for caries/non-carious tooth lesions, and a mucosal evaluation. The clinical attachment level (CAL), which was defined as the distance between the cemento-enamel junction (CEJ) and the probed base of the periodontal pocket, was selected as a marker, because periodontal bone loss represents chronic periodontal inflammation. The probing depth (PD) was defined as the distance between the gingival crest and the probed base of the periodontal pocket, and gingival recession (GR) was defined as the distance from the gingival crest to the CEJ (+ = visible CEJ; – = invisible CEJ). The CAL was calculated using the PD and GR (PD + GR = visible CEJ; PD – GR = invisible CEJ). Measurements were made to the nearest millimeter without rounding off using a periodontal probe# at six sites (mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual, and mesio-lingual) on each tooth. In instances of a full dentition, 12 teeth were designated. Two teeth per sextant were selected: a second molar and second premolar from the upper right sextant, a right lateral incisor and left central incisor from the upper anterior sextant, a first premolar and first molar from the upper left sextant, a second molar and second premolar from the lower left sextant, a left lateral incisor and right central incisor from the lower anterior sextant, and a first premolar and first molar from the lower right sextant. In instances of missing teeth or implants, an adjacent tooth was selected. The 1-week interval test-retest reliability of CAL had an intraclass correlation coefficient of 0.98 using a dataset of 3,672 probed sites replicated from 51 subjects.

PCP-UNC15 Color-Coded Probe, Hu-Friedy, Chicago, IL.

Table 1.

Sociodemographic Variables and Risk Factors

Variable	Patients With Hemorrhagic Stroke (n = 118)	Control Subjects (n = 214)	*P**
Age (years; mean ± SD)	55.19 ± 9.21	60.06 ± 11.70	<0.001†
40 to 59 years (n [%])	84 (71.2)	110 (51.4)	
60 to 79 years (n [%])	34 (28.8)	104 (48.6)	<0.001
Males (n [%])	65 (55.1)	99 (46.3)	0.124
Income ≥$1,000/month (n [%])	50 (42.4)	115 (53.7)	0.047
Duration of education ≥9 years (n [%])	58 (49.2)	97 (45.3)	0.504
Smoking (ever) (n [%])	42 (35.6)	49 (22.9)	0.013
Alcohol consumption (ever) (n [%])	43 (36.4)	86 (40.2)	0.503
Hypertension (n [%])	94 (79.7)	55 (25.7)	<0.001
DM (n [%])	21 (17.8)	29 (13.6)	0.301
Cardiac disease (n [%])	3 (2.5)	9 (4.2)	0.437
BMI ≥25 kg/m^2 (n [%])	35 (29.7)	57 (26.6)	0.555
Family hypertension history (n [%])	45 (38.1)	58 (27.1)	0.038
Family DM history (n [%])	21 (17.8)	36 (16.8)	0.822
Family cardiac disease history (n [%])	5 (4.2)	16 (7.5)	0.246

* Obtained from χ^2 statistics, unless otherwise indicated.
† Obtained from *t* test statistics without the assumption of equal variances.

Assessment of Covariates

Interviews using structured questionnaires were administered to assess potential confounders. Selected potential confounders included sociodemographic factors (age, gender, income, and education), cardiovascular risk factors (hypertension, diabetes mellitus [DM], body mass index [BMI]), cardiac disease, familial cardiovascular risk factors (familial hypertension history, familial diabetic mellitus history, and familial cardiac disease history), behaviors (smoking and alcohol consumption) (Table 1), and oral health behaviors (frequency of daily toothbrushing and annual dental visits) (Table 2). Approximately one-half of the case patients were unable to be interviewed directly; we interviewed caregivers to obtain information regarding confounders. We reviewed admission records to compensate for incomplete information caused by the inability to communicate with some stroke patients.

Statistical Analyses

Periodontitis was evaluated in two ways (Table 2). First, we assessed the presence of deep periodontitis (CAL ≥6 mm). Subjects were dichotomized as having normal (CAL<6 mm) or deep periodontitis (CAL ≥6 mm). Second, we assessed the amount of periodontitis to evaluate dose-dependent effects according to the percentile of sites of periodontal pockets with CAL ≥5 mm among the total probed pockets (percentage of CAL ≥5 mm). Subjects were grouped by a three-category ordinal scale for periodontitis: no/mild = 0% to <48.6%, moderate = 48.6% to <73%, and severe ≥73%.

We defined two groups for the analysis of age subgroups: adults were classified as subjects aged 40 to 59 years, and elderly subjects were classified as subjects aged 60 to 79 years (Table1). Income, duration of education, and BMI were also dichotomized. Frequencies of daily toothbrushing and annual dentist visits were dichotomized, and the number of missing teeth and the decayed, missing, and filled teeth index were categorized by ordinal scales (Table 2). For a crude association, *t* and χ^2 tests were applied. Multivariate logistic regression analyses were used to evaluate the adjusted associations between periodontitis and hemorrhagic stroke. For fitting the final model, we considered the basic model first including only the sociodemographic variables, and then

Table 2.

Oral Health Variables

Variable	Patients With Hemorrhagic Stroke (n = 118)	Control Subjects (n = 214)	*P**
Toothbrushing ≥2 times/day (n [%])	76 (64.4)	96 (44.9)	0.001
Annual dentist visit ≥1 (n [%])	21 (17.8)	41 (19.2)	0.760
Number of missing teeth (n [%])			
None: 0	31 (26.3)	65 (30.4)	–
Low: 1 to 7	60 (50.8)	109 (50.9)	–
High: ≥8	27 (22.9)	40 (18.7)	0.576
DMFT index (n [%])			
Low: <4	31 (26.3)	59 (27.6)	–
Medium: 4 to 11	63 (53.4)	117 (54.7)	–
High: ≥12	24 (20.3)	38 (17.8)	0.843
CAL (n [%])			
<6 mm	80 (67.8)	175 (81.8)	–
≥6 mm	38 (32.2)	39 (18.2)	0.004
% CAL ≥5 mm (n [%])			
No/mild: <48.6%	59 (50.0)	141 (65.9)	–
Moderate: 48.6% to <73%	33 (28.0)	43 (20.1)	–
Severe: ≥73%	26 (22.0)	30 (14.0)	0.017

– = not applicable; DMFT = decayed, missing, and filled teeth.
* Obtained from χ^2 statistics.

we included the health-related variables and oral health-related variables one by one while comparing the explanatory power of the model, and finally we included the systemic risk factors to evaluate their independent association. The fitness of the model was evaluated by a change of –2 log likelihood and a 10% change of the odds ratio (OR).

Additional analyses were performed among the subgroups to assess whether different factors could modify the associations found. Subgroups were defined according to established risk factors including age group, gender, smoking, hypertension, DM, and BMI. We treated the confounding factor of age as a continuous variable in the age-subgroup analyses because age was distributed widely with a maximum difference of 20 years in age subgroups. The interactions between periodontitis and two well-known risk factors for stroke (hypertension and BMI ≥25 kg/m^2) were also assessed. The extent of the interaction effect (IE) was also estimated using the following equation: $IE = OR_{interaction}/OR_{total}$; $OR_{interaction}$ between A and B = $OR_{total} - OR_A - OR_B + OR_{background}$. $OR_{interaction}$ = the part of the OR in the association with hemorrhagic stroke that was attributable to the interaction between periodontitis and risk factor (hypertension or BMI ≥25 kg/m2); OR_{total} = the part of the OR of the periodontitis with risk factor (hypertension or BMI ≥25 kg/m2) for hemorrhagic stroke; OR_A = the part of the OR of the periodontitis without risk factor (hypertension or BMI ≥25 kg/m2) for hemorrhagic stroke; OR_B = the part of the OR of the risk factor (hypertension or BMI ≥25 kg/m2) without periodontitis for hemorrhagic stroke; and $OR_{background}$ = the OR of the reference = 1.

RESULTS

Case subjects who had a hemorrhagic stroke were younger than the control subjects (Table 1). Case subjects who had a stroke had less income than control subjects, but the education level was the same for both groups. The stroke group had 13% more smokers than the control group. In terms of cardiovascular risk factors, the stroke group exhibited a 54% higher prevalence of hypertension and 11% higher prevalence of familial history of hypertension than control subjects.

In bivariate analyses, we found that a stroke was significantly associated with both types of periodontitis (CAL ≥6 mm and percentage of CAL ≥5 mm) (Table 2). A stroke was not associated with the number of missing teeth, the experience of dental caries, or annual dentist visits. Patients who had a stroke brushed their teeth more frequently than the population control subjects as a result of having guardian assistance.

In multivariate analyses, a stroke was found to be strongly associated with periodontitis after controlling for confounders (Table 3). The OR was 2.5 (95% confidence interval [CI]: 1.1 to 5.5) for CAL ≥6 mm, whereas there was no significant dose-dependent association for percentage of CAL ≥5 mm. In these models, the impact of periodontitis to the hemorrhagic stroke (OR = 2.5) was 19% higher compared to the impact of DM (OR = 2.1) for CAL ≥6 mm. Alcohol consumption and cardiac disease history had a very strong negative association with stroke.

In the subgroup analyses, the association between periodontitis and stroke was moderate to strong across subgroups (Table 4). For the model of CAL ≥6 mm, we found a positive association with male gender, monthly income <$1,000, non-DM, and obese subjects. For percentage of CAL ≥5 mm, we did not

Table 3.

ORs (95% CIs) for Periodontitis and Other Risk Factors

Variable	CAL ≥6 mm Model (n = 332)	% CAL ≥5 mm Model (n = 332)
Periodontitis		
CAL ≥6 mm	**2.53 (1.14 to 5.61)**	–
CAL ≥5 mm Percent		
Low	–	1
Medium	–	1.88 (0.82 to 4.30)
High	–	1.72 (0.73 to 4.08)
Toothbrushing ≥2 times/day	**3.50 (1.80 to 6.83)**	**3.38 (1.74 to 6.56)**
Annual dentist visit ≥1	0.86 (0.33 to 2.22)	0.86 (0.33 to 2.24)
Number of missing teeth*	1.73 (0.86 to 3.50)	1.74 (0.85 to 3.55)
DMFT index*	1.00 (0.51 to 1.94)	1.03 (0.53 to 2.02)
Income ≥$1,000/month	0.54 (0.26 to 1.10)	0.50 (0.25 to 1.03)
Duration of education ≥12 years	0.95 (0.42 to 2.15)	0.94 (0.42 to 2.12)
Smoking (ever)	1.48 (0.63 to 3.47)	1.49 (0.64 to 3.48)
Alcohol consumption (ever)	**0.41 (0.18 to 0.94)**	**0.43 (0.19 to 0.98)**
Hypertension	**22.11 (10.57 to 46.26)**	**20.08 (9.76 to 41.29)**
DM	2.08 (0.82 to 5.28)	2.28 (0.90 to 5.79)
Cardiac disease	**0.19 (0.04 to 0.98)**	0.20 (0.04 to 1.03)
BMI ≥25 kg/m^2	0.94 (0.46 to 1.90)	0.91 (0.45 to 1.85)
Family history of:		
Hypertension	0.61 (0.29 to 1.27)	0.64 (0.31 to 1.33)
DM	0.80 (0.31 to 2.09)	0.81 (0.31 to 2.09)
Cardiac disease	0.51 (0.12 to 2.11)	0.50 (0.12 to 2.08)

– = not applicable; DMFT = decayed, missing, and filled teeth.
ORs for variables were adjusted for age (continuous), gender, frequency of toothbrushing, dentist visit, number of missing teeth, DMFT index, monthly income, education, smoking, alcohol consumption, hypertension, DM, cardiac disease, BMI, family history of hypertension, family history of DM, and family history of cardiac disease. **Bold** denotes statistically significant (P <0.05).
* Ordinal scale according to the information presented in Table 2.

find a significant dose-dependent effect in any of the subgroups.

In subsequent analysis of the interactions (Table 5), the interaction between periodontitis (CAL ≥6 mm) and hypertension showed a significant association with hemorrhagic stroke (model I): the adjusted OR was 48.7 (95% CI: 14.6 to 162.9) when periodontitis with hypertension was compared to non-periodontitis with non-hypertension. The background component was 1.0, which was the reference value. Periodontitis without hypertension had an OR of 3.7, and non-periodontitis with hypertension had an OR of 27.6. The part of the OR in the association with hemorrhagic stroke that was attributable to the interaction between periodontitis and hypertension was 18.4: 18.4 = (47.7 – 1.0) – ([3.7 – 1.0] + [27.6 – 1.0]). The amount of the IE was 37.8%: $OR_{interaction}/OR_{total}$ = 18.4/48.7. Similarly, the interaction between periodontitis and obesity (BMI ≥25 kg/m^2) on hemorrhagic stroke (model II) was significant: the adjusted OR was 5.7 (95% CI: 1.3 to 25.3) when periodontitis with obesity was compared to non-periodontitis with non-obesity. The OR attributable to the interaction between periodontitis and obesity was 4.2: 4.2 = (5.7 – 1.0) –([1.8 – 1.0] + [0.7 – 1.0]). The amount of the IE was 73.7%: $OR_{interaction}/OR_{total}$ = 4.2/5.7.

DISCUSSION

Syrjänen et al.[3] suggested that periodontal inflammation could be a risk factor for stroke, and subsequently, there have been a number of studies[10,16-23] addressing this possibility. Of these studies, only Wu et al.[18] analyzed data from the first National Health and Nutrition Examination Survey and its follow-up study. They found a significant association between periodontitis and total cerebrovascular accidents, in particular non-hemorrhagic (ischemic) stroke, but not between periodontitis and hemorrhagic stroke. However, our results provide evidence that periodontitis is independently associated with a non-fatal hemorrhagic stroke (OR = 2.4; 95% CI = 1.1 to 5.5) after controlling for possible potential confounders including familial cardiovascular risk factors. To our knowledge, this is the first evidence that periodontitis is positively associated with hemorrhagic stroke.

Our study has some major strengths. First, we selected control subjects from the population matched to the valid case subjects hospitalized at the National

Table 4.

Periodontitis in Subgroups

Subgroup	n	OR (95% CI)			
			CAL ≥5 mm Percent		
		CAL ≥6 mm	No/Mild	Moderate	Severe
Age (years)*					
40 to 59	194	2.35 (0.61 to 9.04)	1	2.87 (0.69 to 11.97)	2.97 (0.72 to 12.29)
60 to 79	138	3.03 (0.87 to 10.49)	1	1.01 (0.28 to 3.70)	1.74 (0.40 to 7.50)
Gender					
Male	164	**4.10 (1.29 to 13.09)**	1	1.74 (0.54 to 5.64)	1.69 (0.44 to 6.50)
Female	168	1.68 (0.46 to 6.19)	1	2.09 (0.55 to 7.98)	2.60 (0.74 to 9.11)
Income					
<$1,000/month	167	**3.09 (1.03 to 9.27)**	1	3.06 (0.89 to 10.53)	3.37 (0.90 to 12.68)
≥$1,000/month	165	3.26 (0.73 to 14.55)	1	1.65 (0.38 to 7.23)	1.54 (0.35 to 6.73)
Smoking					
Ever	91	6.00 (0.95 to 38.00)	1	1.41 (0.18 to 10.97)	1.39 (0.25 to 7.68)
Never	241	2.36 (0.85 to 6.56)	1	2.35 (0.86 to 6.45)	2.29 (0.73 to 7.12)
Alcohol consumption					
Ever	129	3.99 (0.94 to 17.00)	1	1.12 (0.26 to 4.86)	1.15 (0.25 to 5.43)
Never	203	2.20 (0.76 to 6.36)	1	3.00 (1.00 to 8.98)	2.03 (0.64 to 6.42)
Missing teeth					
None: 0	96	0.35 (0.02 to 7.38)	1	4.75 (0.35 to 64.23)	2.01 (0.12 to 35.03)
Low: 1 to 7	169	**8.70 (2.53 to 29.86)**	1	2.03 (0.57 to 7.28)	**4.27 (1.29 to 14.18)**
High: ≥8	67	2.03 (0.13 to 31.49)	1	0.33 (0.02 to 5.32)	0.46 (0.02 to 13.61)
Hypertension					
Yes	149	2.15 (0.59 to 7.88)	1	1.05 (0.28 to 3.98)	1.57 (0.42 to 5.94)
No	183	3.20 (0.95 to 10.75)	1	2.20 (0.62 to 7.78)	3.27 (0.80 to 13.32)
DM					
Yes	50	0.13 (0.00 to 52.97)	1	–	–
No	282	**2.84 (1.16 to 6.99)**	1	1.65 (0.68 to 4.01)	1.65 (0.61 to 4.42)
BMI (kg/m^2)					
<25	240	1.51 (0.60 to 3.79)	1	1.69 (0.62 to 4.65)	1.33 (0.46 to 3.78)
≥25	92	**74.47 (3.48 to 1,592.87)**	1	2.26 (0.27 to 19.11)	4.55 (0.60 to 34.64)

ORs for covariables were adjusted for age, gender, frequency of toothbrushing, dentist visit, number of missing teeth, DMFT index, monthly income, education, smoking, alcohol consumption, hypertension, DM, cardiac disease, BMI, family history of hypertension, family history of DM, and family history of cardiac disease. **Bold** denotes statistically significant (P <0.05).
– = not applicable.
* Controlled for continuous age.

Rehabilitation Center. Second, we used the direct measurement method of CAL for evaluating periodontitis and CT assessment of brain imaging for hemorrhagic stroke. Thirdly, we controlled for various potential confounders including sociodemographic variables, lifestyle factors, cardiovascular risk factors, and familial cardiovascular history. Finally, we used two models for the main explanatory variable, one for the presence of the periodontitis (CAL ≥6 mm) and another for the amount of periodontitis according to the percentile of sites of periodontal pockets with CAL ≥5 mm among the total probed pockets.

The study by Wu et al.[18] was a secondary study based on an existing data set and did not demonstrate a significant association between periodontitis and hemorrhagic stroke. Hence, we conducted a primary study to test the original hypothesis using case-control study data and demonstrated a positive association between periodontitis and hemorrhagic stroke. Future primary, prospective, cohort studies using clinical information will help further explain the link between periodontitis and hemorrhagic stroke.

When periodontal intervention is proposed as a method for reducing the risk of stroke, it is important

Table 5.

Interaction Among Periodontitis, Hypertension, and Obesity for Hemorrhagic Stroke

Model and Interaction	n	OR (95% CI)	*P*
I*			
CAL ≥6 mm (–) hypertension (–)	145	1	
CAL ≥6 mm (–) hypertension (+)	110	**27.55 (11.50 to 65.98)**	**<0.001**
CAL ≥6 mm (+) hypertension (–)	38	**3.71 (1.25 to 11.05)**	**0.018**
CAL ≥6 mm (+) hypertension (+)	39	**48.73 (14.58 to 162.88)**	**<0.001**
		Trend *P* <0.001	
II†			
CAL ≥6 mm (–) BMI ≥25 kg/m^2 (–)	185	1	
CAL ≥6 mm (–) BMI ≥25 kg/m^2 (+)	70	0.67 (0.30 to 1.51)	0.333
CAL ≥6 mm (+) BMI ≥25 kg/m^2 (–)	55	1.79 (0.73 to 4.37)	0.200
CAL ≥6 mm (+) BMI ≥25 kg/m^2 (+)	22	**5.73 (1.30 to 25.30)**	**0.021**
		Trend *P* = 0.043	

Bold denotes statistically significant ($P<0.05$).
* Adjusted for covariables as in Table 3 except for CAL ≥6 mm and hypertension.
† Adjusted for covariables as in Table 3 except for CAL ≥6 mm and BMI ≥25 kg/m^2.

to investigate the supporting epidemiologic evidence. Therefore, we established evidence that the association between periodontitis and hemorrhagic stroke is stronger among males, patients without DM, and obese patients. Because hypertension and obesity are commonly related factors for hemorrhagic stroke and periodontitis, the IEs between periodontitis and hypertension and between periodontitis and obesity were scrutinized. Although the amount of the IE was higher for the periodontitis group with obesity (73.7%) than for the periodontitis group with hypertension (37.8%), hypertension was an effect modifier on the association between periodontitis and hemorrhagic stroke but obesity was not. These results are suggestive of future prospective epidemiologic studies including biologic perspectives regarding the links among periodontitis and hypertension and obesity for elucidating the causative mechanism of periodontitis on hemorrhagic stroke.

We did not show that the link between periodontitis and hemorrhagic stroke was stronger in elderly subjects (>60 years), which disagrees with previous evidence on ischemic strokes.[19,20] Moreover, our results suggest that there is no gender difference in the association between periodontitis and hemorrhagic stroke, which is similar to the findings of Wu et al.[18] that showed a positive association between periodontitis and an ischemic stroke in both genders. The results from our subgroup analysis did not show a significant dose-response effect for the percentage of CAL ≥5 mm model. The interaction terms between periodontitis and hypertension/obesity for hemorrhagic stroke were statistically significant. Therefore, we interpret our results with caution. Gender differences, DM, and obesity should be carefully considered to correctly interpret the results of further studies.

The limitations of our case-control study are as follows: lack of causality, possible selection bias for control subjects, and potential misclassification and/or information biases. Although control subjects were recruited voluntarily from the non-stroke general population, volunteers tend to pay more attention to their health than the general population, which may have positively distorted the association. The examiner (SJS) was not masked to the case or control status, which could have potentially led to a misclassification bias for periodontitis. However, the high standard of reliability for the periodontal examination probably reduced this potential bias. Because we could not measure the periodontal status of subjects before the occurrence of stroke, the possibility of deterioration of the periodontal status as a result of functional limitations after a stroke could have lead to a positive bias.[24] Considering the confounders, we asked the patients who had a stroke about their current toothbrushing exposure as a surrogate of their toothbrushing habits before the stroke because the case subjects could not recall the exact frequencies of toothbrushing before the onset of stroke. Ideally, the information about hygiene activities that occurred before a stroke should have been obtained. Similarly, we met difficulties in getting information on the amount of smoking and alcohol consumption before a stroke. More detailed information about the consumption could have been more useful. In addition, the lack of confounders such as physical activity added to this limitation. Our results show that those with monthly incomes <$1,000.00 USD had a strong association with stroke. We speculated that income might have conflated the influence of various types of preventive factors such as physical activity and prophylactic medication, resulting in a negative association. Despite these possible limitations, our data are sufficient to fulfill the aims of this study. Future systemically designed prospective studies will reduce these limitations and will help to clarify the causality between periodontitis and hemorrhagic stroke.

CONCLUSIONS

Overall, our results support the hypothesis that periodontal inflammation is associated independently with

hemorrhagic stroke. The association may be stronger among males, individuals without DM, and obese adults. Although our results do not provide evidence of a causal relationship between periodontitis and hemorrhagic stroke, these findings have valuable clinical implications in considering the importance of periodontal health as a promoter of general health.

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