

Periodontitis and the Risk for Non-Fatal Stroke in Korean Adults

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Background: The association between periodontal inflammation and non-fatal stroke is still controversial and limited to evidence in Western countries. The aim of this study was to investigate whether periodontitis is independently associated with non-fatal stroke in Korean adults.

Methods: A case-control study was conducted on 265 non-fatal chronic stroke cases at the National Rehabilitation Center, Seoul, Korea, and 214 non-stroke population controls. Medical specialists diagnosed stroke by using brain imaging from magnetic resonance imaging and/or computerized tomography. A dentist recorded the clinical attachment level (CAL), the distance between the cemento-enamel junction and the probed base of the periodontal pocket, using a University of North Carolina-15 manual probe. An interview assessed 17 sociodemographic, behavioral, systemic/oral health-related possible confounders. Multiple logistic regression analysis was used to evaluate the association between periodontitis and stroke while controlling for age, gender, income, education, smoking, drinking, history of systemic disease, body mass index, familial cardiovascular risk factors, and oral health behaviors. Subgroup analyses were also performed.

Results: Stroke was strongly associated with periodontitis (presence of CAL ≥ 6 mm): the odds ratio was 4.0 (95% confidence interval: 2.3 to 7.0) after controlling for all possible confounders. The association with periodontitis (tertiary percentage of CAL ≥ 5 mm) had a dose-response effect. The association between periodontitis and stroke was higher among adults younger than age 60 (6.0 versus 2.6) and normotensives (4.8 versus 3.2).

Conclusion: Our data suggested that periodontitis is independently associated with non-fatal stroke, and its impact seems to be greater among younger or normotensive Korean adults. *J Periodontol* 2008;79:1652-1658.

KEY WORDS

Association; Korean; periodontitis; stroke.

Because stroke is a significant cause of death among individuals with cardiovascular disease, its risk factors should be identified and clarified.¹ Inflammation, including periodontitis, has been proposed as one such risk factor.²

Periodontal disease is a major oral disease causing tooth loss, and it is associated with systemic disease and inflammatory biomarkers.^{3,4} Periodontitis and stroke have several common risk factors, such as age,⁵ smoking,^{6,7} diabetes,⁸ and hypertension.⁹ Periodontitis is also associated with elevated markers of inflammation that are themselves indicators of stroke risk.^{10,11} One cross-sectional study,¹² four case-control studies,¹³⁻¹⁶ and five cohort studies¹⁷⁻²¹ have investigated the associations between periodontal inflammation and stroke in the United States, Canada, Germany, and Finland. Of these studies, most^{12-17,19,21} showed positive results, whereas two others^{18,20} did not. Additional studies are needed to clarify the association between periodontal inflammation and stroke, especially in non-Western countries. Hence, we performed a case-control study of hospital stroke cases and population non-stroke controls in Korea. The aim of this study was to investigate whether periodontitis is independently associated with stroke among Korean adults. We also analyzed this association within age and gender subgroups as well as other established risk factors.

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MATERIALS AND METHODS

This case-control study was approved by the Institutional Review Board for Human Subjects at the School of Dentistry, Seoul National University (approval number: LO605-02), and all of the participants, or appointed guardians when warranted, provided written informed consent.

Sample-Size Estimation and Subjects

The sample size of this 1:1 frequency-matched, case-control study was estimated by using the statistics generated from a pilot study. Under the condition of type I error at 0.05, type II error at 0.2, and a prevalence of severe periodontitis of 25% for cases and 10% for controls, the number of subjects needed for the analysis was estimated at 100 per group. For analysis of age-specific subgroups (40 to 59 years and 60 to 79 years), the final cases needed to be doubled for a total of 200 cases. We estimated that the total sample required for the final analysis should be 400: 200 cases and 200 controls. Because of the missing information due to an attrition rate of 10% from the pilot survey, we decided to recruit 446 subjects (223 cases and 223 controls).

There were 503 initial subjects, comprising 284 stroke cases and 219 non-stroke controls, recruited for the survey from June 2005 to May 2006. There were 479 subjects with complete information (Table 1): 265 non-fatal chronic stroke cases, which occurred within the previous year, and 214 non-stroke controls. Subjects were limited to 40- to 79-year-old residents of Seoul and the neighboring province of Kyunggi-Do. These two areas include half of the total population of South Korea. Stroke cases were recruited from the National Rehabilitation Center, Seoul, Korea. The controls were recruited randomly from the general population through an advertisement in social institutions, such as churches and temples, and social welfare institutions and were frequency matched to cases within each age group. Exclusion criteria for the cases and controls were pregnancy, antibiotic therapy within the last 3 months, and fewer than six remaining teeth.

Assessment of Stroke

At the National Rehabilitation Center, medical specialists diagnosed stroke as a hemorrhagic or ischemic lesion using brain images taken by computerized tomography (CT) or magnetic resonance imaging (MRI) along with a comprehensive systemic examination. Based on the time lapsed since the occurrence,

Table 1.
Sociodemographic Variables and Risk Factors

Variable	Non-Fatal Stroke Cases (n = 265)	Population Controls (n = 214)	P Value*
Age (years; mean \pm SD)	58.87 \pm 9.39	60.06 \pm 11.70	0.227†
40 to 59 (n [%])	136 (51.4)	110 (51.3)	
60 to 79 (n [%])	129 (48.6)	104 (48.7)	0.986
Male (n [%])	150 (56.6)	99 (46.3)	0.024
Income \geq \$1,000/month (n [%])	106 (48.0)	115 (53.7)	0.003
Education \geq 12 years (n [%])	124 (46.8)	97 (45.3)	0.749
Smoking (ever) (n [%])	105 (39.6)	49 (22.9)	<0.001
Alcohol drinking (ever) (n [%])	113 (42.6)	86 (40.2)	0.588
Hypertension (n [%])	195 (73.6)	55 (25.7)	<0.001
DM (n [%])	72 (27.2)	29 (13.6)	<0.001
Cardiac disease (n [%])	9 (3.4)	9 (4.2)	0.643
BMI \geq 25 kg/m ² (n [%])	73 (27.5)	57 (26.6)	0.823
Family history of hypertension (n [%])	106 (40.0)	58 (27.1)	0.003
Family history of DM (n [%])	61 (23.0)	36 (16.8)	0.093
Family history of cardiac disease (n [%])	15 (5.7)	16 (7.5)	0.422

* P value obtained from χ^2 test.

† P value obtained from t test without the assumption of equal variances.

the stage of stroke was classified into 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). The final diagnosis of stroke was confirmed by the medical records of the patients. All patients who had experienced a stroke were hemiplegic with permanent disability and were hospitalized for rehabilitation after 6 months from the first attack. There were 265 non-fatal chronic strokes comprising 118 ischemic cases, 143 hemorrhagic cases, and four cases having both.

Assessment of Periodontitis and Oral Health Status

A dentist performed comprehensive oral examinations in a dental unit or a mobile dental chair under blue light. The time elapsed between stroke and dental examination was from 3 months to 1 year. The examination included periodontal probing, oral hygiene, examination for dental caries, and mucosal evaluation. Clinical attachment level (CAL), defined as the distance between the cemento-enamel junction and the probed base of the periodontal pocket, was

selected as the measure for a history of periodontal inflammation, because periodontal bone loss represents the effects of chronic periodontal inflammation. Measurements were made to the nearest millimeter without rounding off using a University of North Carolina-15 manual probe at six sites (mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual, and mesio-lingual) per tooth. Twelve teeth, two per sextant, were selected for the periodontal examination. In case of a missing tooth or an implant, the adjacent tooth was selected instead. A 1-week interval test-retest reliability of CAL had an intraclass correlation coefficient of 0.98 using a dataset of 3,672 probing sites replicated from 51 subjects.

Assessment of Covariates

To assess potential confounders, we interviewed subjects using structured questionnaires. Selected potential confounders were sociodemographic factors (age, gender, income, and education), cardiovascular risk factors (hypertension, diabetes mellitus [DM], cardiac disease, and body mass index [BMI = weight in kilograms/height in meters squared]), familial cardiovascular risk factors (familial hypertension history, familial DM history, and familial cardiac disease history), behaviors (smoking and alcohol drinking) (Table 1), and oral health behaviors (frequency of daily toothbrushing and annual dentist visit) (Table 2). For patients who had experienced a stroke, we reviewed the admission records to compensate for the incomplete information that resulted from a lack of communication.

Statistical Analysis

Stroke was the outcome variable, and periodontitis measured by CAL was the main explanatory variable. For age subgroup analysis, age was dichotomized into two sets: the adult group, aged 40 to 59 years, and the elderly group, aged 60 to 79 years. The periodontitis was evaluated in two ways (Table 2). First, we assessed the presence of deep periodontitis by site-specific CAL ≥ 6 mm (periodontitis [+]). Subjects were dichotomized into negative or positive severe periodontitis by the presence of any periodontal sulcus of CAL ≥ 6 mm. There were 134 periodontitis-negative and 131 periodontitis-positive subjects among stroke cases and 175 periodontitis-negative and 39 periodontitis-positive subjects among controls. Second, we assessed the extent of periodontitis to test for a dose-response effect by the percentile of sites of periodontal pockets with CAL ≥ 5 mm among total probed pockets (periodontitis [%]). Subjects were categorized into three periodontitis

Table 2.
Oral Health Variables

Variable	Non-Fatal Stroke Cases (n = 265)	Population Controls (n = 214)	P Value*
Daily toothbrushing ≥ 3 (n [%])	174 (65.7)	96 (44.9)	<0.001
Annual dental visit ≥ 1 (n [%])	47 (17.7)	41 (19.2)	0.698
Missing teeth (n [%])			
None: 0	62 (23.4)	65 (30.4)	
Low: 1 to 7	128 (48.3)	109 (50.9)	
High: ≥ 8	75 (28.3)	40 (18.7)	0.032
DMFT index (n [%])			
Low: <4	74 (27.9)	59 (27.5)	
Medium: 4 to 11	127 (47.9)	117 (54.7)	
High: ≥ 12	64 (24.2)	38 (17.8)	0.189
Presence of periodontitis (n [%])			
CAL <6 mm	134 (50.6)	175 (81.8)	
CAL ≥ 6 mm	131 (49.4)	39 (18.2)	<0.001
Percentage of periodontitis (n [%])			
CAL ≥ 5 mm [%] [†] :			
No/mild: $<48.6\%$	92 (34.7)	141 (65.9)	
Moderate: 48.6% to $<73\%$	74 (27.9)	43 (20.1)	
Severe: $\geq 73\%$	99 (37.4)	30 (12.0)	<0.001

* P value obtained from χ^2 test.

[†] CAL ≥ 5 mm [%] = pockets with CAL ≥ 5 mm/total probed pockets $\times 100$.

groups: no/mild, 0% to $<48.6\%$; moderate, 48.6% to $<73\%$; and severe, $\geq 73\%$. There were 92 subjects with no/mild periodontitis, 74 subjects with moderate periodontitis, and 99 subjects with severe periodontitis among stroke cases, and 141 subjects with no/mild periodontitis, 43 subjects with moderate periodontitis, and 30 subjects with severe periodontitis among controls.

Income, the duration of education, and BMI were dichotomized (Table 1). The frequencies of daily toothbrushing and dentist visits were also dichotomized, and the number of missing teeth and decayed, missing, and filled teeth due to dental caries (DMFT index) were categorized into three ordinal scales (Table 2). Multivariate logistic regression analyses in a statistical software program* were used to evaluate the adjusted odds ratio (ORs) estimates between periodontitis and stroke. For fitting the final model, we considered the basic model first including only the sociodemographic variables, then entered the health-related variables and oral health-related variables step-by-step while comparing the explanatory power of model and finally included the systemic risk factors to evaluate their independent association. Fitness of the model was evaluated by a change of -2 log likelihood and 10% change of OR. After comparing multiple multivariate

* SPSS 12 for Windows, SPSS, Chicago, IL.

Table 3.
ORs of Periodontitis and Other Risk Factors for Stroke

Variable	OR (95% confidence interval)	
	Model I (n = 479)	Model II (n = 479)
Periodontitis		
Presence of periodontitis	3.97 (2.26 to 6.97)	
Percentage of periodontitis		
No/mild		Referent
Moderate		2.58 (1.39 to 4.81)
Severe		4.30 (2.27 to 8.16)
		Trend P <0.001
Annual dental visit ≥ 1	0.95 (0.44 to 2.05)	1.06 (0.49 to 2.31)
Number of missing teeth*	1.36 (0.79 to 2.35)	1.39 (0.80 to 2.42)
DMFT index*	0.86 (0.51 to 1.44)	0.89 (0.52 to 1.50)
Income $\geq \$1,000$ /month	0.15 (0.08 to 0.28)	0.14 (0.08 to 0.26)
Duration of education ≥ 12 years	1.33 (0.69 to 2.56)	1.29 (0.67 to 2.47)
Smoking (ever)	1.81 (0.92 to 3.58)	1.72 (0.87 to 3.40)
Alcohol drinking (ever)	0.60 (0.31 to 1.15)	0.62 (0.32 to 1.18)
Hypertension	9.40 (5.44 to 16.26)	8.37 (4.89 to 14.32)
DM	2.56 (1.28 to 5.11)	2.55 (1.28 to 5.10)
Cardiac disease	0.36 (0.12 to 1.09)	0.44 (0.14 to 1.32)
BMI ≥ 25 kg/m ²	0.85 (0.48 to 1.49)	0.88 (0.50 to 1.55)
Family history of hypertension	0.91 (0.53 to 1.59)	0.92 (0.53 to 1.59)
Family history of DM	1.50 (0.76 to 2.98)	1.43 (0.72 to 2.83)
Family history of cardiac disease	0.59 (0.19 to 1.87)	0.64 (0.20 to 2.02)

ORs for stroke (yes versus no) were adjusted for age (continuous), gender, daily toothbrushing ≥ 3 , and all variables in Table 3 mutually.

Bold type denotes statistical significance.

* Ordinal scale according to the information in Table 2.

models, we decided that the final model should encompass all potential confounders (Table 3). Interaction terms were also assessed.

Additional subgroup analyses were performed to assess whether different risk factors could modify the association. Subgroups included established risk factors, such as age, gender, smoking, hypertension, and DM and BMI groups. In the age subgroup analyses, age was distributed in a wide range spanning 20 years, so we decided to add the age variable in a continuous scale to covariates.

RESULTS

There was no difference in the mean ages and the distribution of age groups between stroke cases and non-stroke controls (Table 1). Stroke cases included more males and slightly fewer subjects with higher incomes than controls, whereas they had the same education level as controls. There were 17% more smokers among stroke cases compared to population controls but the same proportion of drinkers (~40%). With regard to cardiovascular risk factors, stroke cases exhibited a higher prevalence of hypertension and DM

than controls, whereas there was no difference in cardiac disease and BMI. In terms of family history, more patients who had experienced a stroke had a family history of hypertension than did normal controls.

From the bivariate analyses, stroke was associated with any type of periodontitis, such as periodontitis (+) and periodontitis (%) (Table 2). Stroke was associated with the number of missing teeth, whereas it was not associated with dental caries or with making an annual dentist visit. Patients who experienced a stroke brushed their teeth more frequently than population controls.

From multivariate analyses, stroke was strongly and significantly associated with periodontitis (Table 3). The OR was 4.0 (95% confidence interval [CI]: 2.26 to 6.97) for periodontitis (+) and 4.3 (95% CI: 2.27 to 8.16) for periodontitis (%) after controlling for all possible confounders. The OR of periodontitis (+) was 5.7 (95% CI: 3.1 to 10.7) for ischemic stroke and 2.4 (95% CI: 1.1 to 5.5) for hemorrhagic stroke. The association for periodontitis (%) (severe versus moderate versus no/mild) had a dose-response effect (trend, $P < 0.001$). Compared to cardiovascular risk factors, the association of peri-

odontitis was ~30% higher than that of DM (4.0 versus 2.6) but ~60% less than that of hypertension (4.0 versus 9.4). In contrast to the crude models, the two final multivariate models showed that the number of missing teeth, smoking, and family history of hypertension lost the significant association after controlling for covariates. Income had a very strong negative association with stroke (adjusted OR: 0.15; 95% CI: 0.08 to 0.28). Among the familial cardiovascular risk factors, family hypertension history was the only variable positively associated with stroke, although it was not significant.

No interaction terms among periodontitis and other risk factors were found in this analysis. In subgroup analyses, the association between periodontitis and stroke changed dramatically (Table 4). For the model of periodontitis (+), the association was higher among younger adults (5.96 versus 2.58), men, ever smokers, normotensives, those without DM, and obese adults. For the other model of periodontitis (%), the association of periodontitis (severe versus no/mild) had the same trend as that of periodontitis (+) in subgroups such as younger adults and normotensives.

Table 4.

ORs of Periodontitis for Stroke in Subgroups

Subgroup	n	OR (95% confidence interval)			
		CAL ≥ 6 mm (yes versus no)	CAL ≥ 5 mm (%)		
			No/Mild	Moderate	Severe
Age* (years)					
40 to 59	246	5.96 (2.12 to 16.75)	I	7.94 (2.19 to 28.73)	5.67 (1.88 to 17.14)
60 to 79	233	2.58 (1.21 to 5.50)	I	1.44 (0.64 to 3.21)	2.28 (0.90 to 5.78)
Gender					
Male	249	5.38 (2.35 to 12.33)	I	2.23 (0.90 to 5.51)	6.43 (2.42 to 17.08)
Female	230	3.79 (1.60 to 9.00)	I	3.75 (1.42 to 9.90)	4.12 (1.60 to 10.61)
Smoking					
Ever	154	7.35 (2.38 to 22.75)	I	1.78 (0.45 to 7.14)	6.81 (1.95 to 23.84)
Never	325	3.34 (1.67 to 6.70)	I	3.39 (1.61 to 7.14)	3.75 (1.65 to 8.51)
Hypertension					
Yes	250	3.15 (1.24 to 8.03)	I	1.95 (0.74 to 5.15)	2.69 (0.99 to 7.27)
No	229	4.76 (2.24 to 10.12)	I	3.68 (1.50 to 9.03)	6.71 (2.69 to 16.77)
DM					
Yes	101	1.06 (0.21 to 5.39)	I	29.62 (2.31 to 397.57)	2.25 (0.31-16.41)
No	378	4.96 (2.58 to 9.55)	I	1.95 (0.97 to 3.91)	4.93 (2.37-10.24)
BMI (kg/m ²)					
<25	349	3.16 (1.64 to 6.09)	I	2.66 (1.27 to 5.55)	4.03 (1.86 to 8.72)
≥ 25	130	24.64 (3.89 to 155.92)	I	2.46 (0.61 to 9.96)	7.67 (1.70 to 34.63)

ORs were adjusted for covariables as in Table 3 except the subgroup.

Bold type denotes a consistency between the two models.

* Controlled for continuous age.

However, the association of periodontitis (%) (moderate versus no/mild) was not in the same trend in some subgroups such as men, obese adults, ever smokers, and those without DM. For patients who had experienced an ischemic stroke, the association with periodontitis (+) was higher among younger adults and normotensives than for those who had experienced a hemorrhagic stroke (Table 5).

DISCUSSION

To our knowledge, this is the first evidence that periodontitis is independently associated with non-fatal ischemic and hemorrhagic strokes among a non-Western population. This association was controlled for various potential confounders, including sociodemographic characteristics, lifestyle factors, cardiovascular risk factors, and familial cardiovascular history. A major strength of our study is the selection

Table 5.

OR and 95% CI of Periodontitis (CAL ≥ 6 mm: yes versus no) for Ischemic and Hemorrhagic Stroke in Subgroups

Subgroup	Ischemic Stroke		Hemorrhagic Stroke	
	n	OR (95% CI)	n	OR (95% CI)
Age* (years)				
40 to 59	160	25.86 (5.77 to 116.79)	194	2.33 (0.54 to 10.00)
60 to 79	197	2.45 (1.06 to 5.67)	138	2.80 (0.81 to 9.74)
Hypertension				
Yes	153	4.93 (1.80 to 13.46)	149	1.79 (0.47 to 6.77)
No	204	8.33 (3.34 to 20.79)	183	2.97 (0.86 to 10.24)

ORs were adjusted for covariables as in Table 3 except the subgroup.

* Controlled for continuous age.

of valid cases and population controls: the stroke cases were recruited at the National Rehabilitation Center, the largest stroke center in Seoul, Korea. The age frequency-matched controls were recruited from the general population. Our choice of direct end-point measurement methods, which included CAL for

evaluating periodontitis and CT and MRI assessment of brain strokes, support the validity of our results. Using the two models for the main explanatory variable, one for the presence of the ailment (CAL ≥ 6 mm) and another for the percentage dose of the ailment (CAL ≥ 5 mm [%]), we interpreted the results in both quality and quantity.

Since the first small case-control study¹³ among middle-aged men in Finland provided positive evidence that oral health, including periodontitis, was associated with stroke, eight more studies followed. All three case-control studies¹⁴⁻¹⁶ showed positive associations. However, five cohort studies¹⁷⁻²¹ yielded controversial results, ranging from major positive associations^{17,19,21} to some non-significant associations.^{18,20} Four case-control studies¹³⁻¹⁶ used clinical periodontal examination information, whereas some cohort studies^{18,20,21} used self-reported periodontal information. The four European studies in Finland¹³ and Germany¹⁴⁻¹⁶ were case-control studies, whereas four American studies^{17,19-21} and one Canadian study¹⁸ were cohort studies. The association of periodontal disease with stroke was the primary focus in all case-control studies with various possible confounders; it was the secondary analysis using secondary data in all cohort studies. Our results based on a case-control study using clinical periodontal examination add evidence that periodontitis is associated with stroke in Korean adults after controlling for all possible potential confounders, including familial cardiovascular risk factors, which is consistent with the current positive evidence.^{14-17,19,21} To the best of our knowledge, this is the first study to adjust for personal income, cardiovascular risk factors, and familial cardiovascular risk factors simultaneously when exploring the association between periodontitis and stroke.

High income had a negative association with stroke because it might involve the influence of various types of preventive factors, such as physical activity and prophylactic medication. It was speculated that income-related behavioral factors should be included as residual confounders. After controlling for cardiovascular risk factors, stroke was strongly linked to periodontitis. In the final model, personal cardiovascular risk factors influenced the increase of the association of periodontitis to stroke, whereas familial cardiovascular risk factors did not; this result may come from collinearity between the two. Because familial risk factors represent hereditary and/or genetic traits, this should be meticulously examined in future studies.

Compared to the report by Beck et al.¹⁷ (relative risk of total stroke of 2.8), our results showed a very strong association between periodontitis and total stroke (OR of 4.0 for CAL ≥ 6 mm; OR of 4.3 for CAL ≥ 5 mm [%]). Our results were similar to those of Grau et al.¹⁵

who showed an OR of 4.3 for the association between ischemic stroke and periodontitis (severe versus no/mild). Moreover, our results had a dose-response effect, which is consistent with previous evidence.¹⁵ Our strength of association was higher than those of DM and smoking (OR of 2.5 for DM and 1.8 for smoking) but lower than that of hypertension (OR of 9.4).

Grau et al.¹⁵ reported that ischemic stroke was associated with periodontitis among males or those younger than 60 years. Desvarieux et al.²² reported similar subgroup trends for the association between the risk for atherosclerosis and periodontitis. Hence, we decided to perform subgroup analyses for males and age <60 years at the beginning of the study and recruited subjects accordingly. Joshipura et al.²¹ reported that associations were different between various types of subgroups including cardiovascular risk factors. We considered more specific evidence by subgroup analysis across six factors comprising age group, gender, smoking, hypertension, DM, and obesity. Our study showed that the links of periodontitis with stroke might be stronger for adults (<60 years) or men, although interaction terms were not statistically significant because of the insufficient sample size of the subgroups. Our results support the hypothesis that periodontitis is an independent risk factor for ischemic stroke in male adults or those younger than 60 years.^{15,19,21} The associations in our study are also higher among ever smokers and normotensives, which was supported by the results of Joshipura et al.²¹ A stronger association was also found for those without DM and obese adults, which differs from the previous study.²¹ For the models for periodontitis of CAL ≥ 5 mm (%), the association of periodontitis in the subgroups showed a linear trend for younger adults and normotensives. Gender differences, DM, and smoking influence should be considered more carefully for reconciling previous studies with the results of future studies.

A case-control study has basic limitations, i.e., lack of causality, possible selection bias for controls, and potential misclassification and/or information biases. The examiner could not be masked to case or control status, which could lead to a misclassification bias for periodontitis. It might distort the association positively. Another major limitation of this study is the possibility of the lack of validity of the information about the history of systemic diseases, such as hypertension, DM, and cardiac disease, because we assessed them from the interview only. The lack of information about confounders, such as physical activity, can be added to this limitation. Despite these limitations, our data are sufficient to fulfill the aims of this study. Future systematically designed prospective studies will reduce the above-mentioned limitations and clarify the causality between periodontitis

and stroke. Biologic evidence is also needed to elucidate the link between periodontal inflammation and stroke more clearly.

CONCLUSIONS

Overall, our results strongly support the hypothesis that periodontal inflammation is an independent risk factor for stroke. After controlling for various potential confounders, including familial cardiovascular risk factors, the association between periodontitis and stroke was very strong among younger adults and normotensives. Although our results cannot prove a causal relationship, these findings might have valuable implications for the prevention of stroke.

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REFERENCES

- Gorelick PB. Stroke prevention therapy beyond antithrombotics: Unifying mechanisms in ischemic stroke pathogenesis and implications for therapy: An invited review. *Stroke* 2002;33:862-875.
- Syrjänen J, Valtanen VV, Iivanainen M, Hovi T, Malkamäki M, Mäkelä PH. Association between cerebral infarction and increased serum bacterial antibody levels in young adults. *Acta Neurol Scand* 1986;73:273-278.
- Preshaw PM, Seymour RA, Heasman PA. Current concepts in periodontal pathogenesis. *Dent Update* 2004;31:570-572, 574-578.
- Kinane DF. Causation and pathogenesis of periodontal disease. *Periodontol* 2000 2001;25:8-20.
- Abdellatif HM, Burt BA. An epidemiological investigation into the relative importance of age and oral hygiene status as determinants of periodontitis. *J Dent Res* 1987;66:13-18.
- Tomar SL, Asma S. Smoking-attributable periodontitis in the United States; findings from NHANES III. National Health and Nutrition Examination Survey. *J Periodontol* 2000;71:743-751.
- Spiekerman CF, Hujoel PP, DeRouen TA. Bias induced by self-reported smoking on periodontitis-systemic disease associations. *J Dent Res* 2003;82:345-349.
- Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *J Periodontol* 2005;76:2075-2084.
- Kim HD, Paek DM, Koh DH, Paik DI. The impact of cardiovascular related diseases on periodontitis. *J Korean Acad Dent Health* 2006;30:46-55.
- Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol* 2001;72:1221-1227.
- Pussinen PJ, Alftan G, Rissanen H, Reunanen A, Asikainen S, Knekt P. Antibodies to periodontal pathogens and stroke risk. *Stroke* 2004;35:2020-2023.
- Elter JR, Offenbacher S, Toole JF, Beck JD. Relationship of periodontal disease and edentulism to stroke/TIA. *J Dent Res* 2003;82:998-1001.
- Syrjänen J, Peltola J, Valtanen V, Iivanainen M, Kaste M, Huttunen JK. Dental infections in association with cerebral infarction in young and middle-aged men. *J Intern Med* 1989;225:179-184.
- Grau AJ, Buggle F, Ziegler C, et al. Association between acute cerebrovascular ischemia and chronic and recurrent infection. *Stroke* 1997;28:1724-1729.
- Grau AJ, Becher H, Ziegler CM, et al. Periodontal disease as a risk factor for ischemic stroke. *Stroke* 2004;35:496-501.
- Dorfer CE, Becher H, Ziegler CM, et al. The association of gingivitis and periodontitis with ischemic stroke. *J Clin Periodontol* 2004;31:396-401.
- Beck JD, Garcia R, Heiss G, Vancos PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996;67:1123-1137.
- Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk* 1999;6:7-11.
- Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease: The first National Health and Nutrition Examination Survey and its follow-up study. *Arch Intern Med* 2000;160:2749-2755.
- Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J Am Coll Cardiol* 2001;37:445-450.
- Joshihara KJ, Hung HC, Rimm EB, Willett WC, Ascherio A. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke* 2003;34:47-52.
- Desvarieux M, Demmer RT, Rundek T, et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: The Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Stroke* 2003;34:2120-2125.

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