ORIGINAL ARTICLE

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Relationship between periodontal disease and stroke history in the geriatric population

- Using logistic regression model with 3-step adjustment considering effect of confounder -

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ABSTRACT

Confounder를 고려한 3단계의 logistic regression model을 통한 노인 인구에 있어서의 치주질환과 뇌경색 경험 유무와의 상관관계에 대한 연구

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1980 년대 후반기부터, 치주 질환과 뇌경색 (ischemic stroke)자료의 연관성을 모색하는 시도가 있어왔다. 이번 연구의 목적은 치주질환과 뇌경색 유무와의 어떤 관계가 있는지를 60세 이상의 노인을 대상으로 조사, 통계 분석 하였다. 자료는 미국의 총 국민 조사 격인 The Third National Health and Nutrition Examination Survey (NHANES III)를 이용 하였다. 이번 연구에서 unadjusted logistic model 통계법을 이용하여 치아 상실수와 뇌경색 경험이 통계학적으로 유의한 수치의 상관성이 있음을 알게 되었다. 또한 나이와 흡연유무를 고려, 조정한 후 multiple logistic model 통계법으로 잔존치아가 적을수록 더욱 뇌경색에 걸릴 확률이 높음을 보였다. 그러나 두 질병에 동시에 선택된 중요한 위험 인자 (risk factor)를 모두 고려, 조정 한 후에는 통계학적인 유의성을 찾지 못했다. 치은퇴축, 치주낭 깊이, 치석, 탐침시 출혈과 뇌경색 경험은 각각의 비교법에서 약간의 상관성을 보이나, 모든 통계법을 통해 일관된 결과를 얻을 수는 없었다.

Key word : 뇌경색 (ischemic stroke), 치주 질환 (periodontal disease), 노인

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INTRODUCTION

The mean age of the population is growing older ; with this aging comes the economic burden of caring for patients with age-related diseases. One of the most debilitating diseases of the elderly is cerebrovascular disease (CVD), or stroke. The World Health Organization's (1980) definition of stroke is : "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin"[1].

Another highly prevalent chronic disease of the elderly is periodontal disease. Based on the Third National Health and Nutrition Examination Survey (NHANES III), 53% of US adults, aged 30 to 90 years old, had 3 millimeters (mm) or more of attachment loss[2].

The connection between cardiovascular disease and periodontal disease has been examined, but results have been obscure[3]. For more than 10 years, this relationship has been the focus of many studies, with specific interest concentrating on the ability of dental infections to cause cardiovascular disease[4,5,6]. In a meta-analysis of nine such longitudinal studies, Janket et al., concluded that there was a small but significant increase in the risk of cardiovascular disease among persons who had periodontal disease at baseline[7].While most of these studies suggest that periodontal disease was more frequent in coronary heart disease patients or ischemic stroke subjects[8,9,10,11], this finding is not universal, since other studies could not detect a statistically significant association[12,13,14,15].

One of difficulty to find relationship between two diseases is that both disease share common important risk factors such as age and smoking, which could lead over adjusting as confounders in cross- sectional study[16,17].

Other studies have shown that subjects with periodontal disease have elevated levels of cardiovascular risk factors, such as C-reactive protein, fibrinogen, and cholesterol[18,19,20]. The relationship of periodontal disease to cardiovascular disease is further bolstered by several recent trials that have reported a decrease in systemic C-reactive protein (CRP) after periodontal treatment[21,22,23].

Despite all of these studies, the association between periodontal disease and stroke remains unclear, and requires additional research until a clear consensus is reached. Few studies have been performed on large populations, with the most notable studies utilizing data from the NHANES I Follow-up Study[9,13,15,24]. Since the information collected was from 1970 and was based on the Russell index with only visual examination and no periodontal probing, it may not accurately reflect the relationship of cumulative periodontal disease to stroke. In addition, no adjustment for C-reactive protein was available from NHANES I data. Hence, it is the aim of this study to use the more recent NHANES III study population to examine the association between cumulative periodontal disease and stroke history in the elderly.

METHODS

Study population : The purpose of this study is to investigate the relationship of periodontal disease to self-reported history of stroke (60 years of age and

older) with a special emphasis on the elderly. Data from the Third National Health and Nutrition Examination Survey (NHANES III), a large population-based cross-sectional survey of the United States, were utilized for this study.

The National Health and Nutrition Examination Survey (NHANES) is a periodic survey conducted by the National Center for Health Statistics (NCHS). The Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 through 1994. It was designed to provide national estimates of the health and nutritional status of the United States' civilian, non-institutionalized population between the ages of two months and over 90 years old. All adults 60 years of age and older who were examined and responded to the questionnaires as part of NHANES III are included in the study. 5,123 elderly adults were included in the study.

Clinical parameter : Several clinical variables were created for testing the relationship of periodontal disease to stroke history. Clinical attachment loss for each site of each tooth was used to obtain the percent of sites with at least 2 mm clinical attachment loss and the percent of sites with at least 3 mm clinical attachment loss. Probing depth for each site of each tooth was used to obtain the percent of sites with at least 2 mm probing depth and the percent of sites with at least 3 mm probing depth. Recession for each site of each tooth was used to obtain the percent of sites with at least 1 mm recession and the percent of sites with at least 2 mm recession. The percent of sites with bleeding was also tabulated.

Putative risk factors that were investigated for this study included age, gender, race/ethnicity, educational level, smoking status, alcohol intake, total folate, plasma fibrinogen, serum C-reactive protein, the ratio of total serum cholesterol to serum HDL cholesterol, history of diabetes, and history of hypertension.

Statistical analysis : Summary statistics were computed for continuous measures, and Mann-Whitney U tests were used to test for differences in continuous measures by stroke history. Multiple logistic regression analysis was used to test for an association between cumulative periodontal disease and stroke history. In all logistic regression modeling, the complex sample design of NHANES III was taken into account with adjustment for both *weighting* and *sample stratification*. All statistical analyses were weighted to account for the complex sampling design so that population-based statistics were obtained. The sample weights included in the NHANES III database take into account the differential probabilities of selection. Sample weighting also includes adjustments for non-coverage and non-response. With the large over-sampling of young children, the elderly, blacks, and Mexican-Americans in NHANES III, the use of sample weights is essential to conducting valid statistical analyses. Results obtained from unweighted statistical analyses are subject to misinterpretation. One of the purposes of weighting is to allow one to obtain estimates of statistics that would have been obtained if the sampling frame consisting of the entire United States had been surveyed, instead of over-sampling of minorities, the very young, and the very old.

In order to develop a multiple logistic regression model with adjustment for significant confounders, a baseline model was constructed. Demographic, social, clinical, and blood laboratory

values were considered for inclusion in the baseline model, if there was not a significant amount of missing data. Some blood laboratory values were not considered for this baseline model because over half of the data were missing.

A base multiple logistic regression model was fit by including all putative risk factors (in addition to age and smoking status) that were statistically significant at =0.05 level of significance.

To further investigate gender differences, logistic regression models for dental and periodontal parameters were refit with stratification by gender. However, we did not mention gender stratification in this particular article not to lose focus.

RESULTS

From Table 1, the mean number of teeth in the stroke group was 9.96 whereas an average of 13.6 teeth were present among non-stroke subjects ($p < 0.001$). The percent of sites with at least 1 mm of recession, the percent of sites with at least 2 mm of recession, the percent of sites with at least 2 mm attachment loss, and the percent of sites with at least 3 mm attachment loss were significantly greater in the stroke group compared to the non-stroke group.

When used logistic regression model, Each analysis were Performed 3 times as same manners repeatedly such as non-adjustment, adjustment with age and smoking only, adjustment with all important risk factors as followed. (Table2-1, Table2-2, Table2-3, Table3-1, Table3-2, Table3-3, Table4-1, Table4-2, Table4-3.)

Results from unadjusted logistic regression modeling are presented in Tables 2-1, 2-2, and 2-3. The number of teeth was significantly related with stroke history ($p < 0.001$) with increasing number of teeth associated with a decreased risk of having a history of stroke. People who were edentulous in one or both arches were significantly more likely to have a history of stroke compared to people who had teeth present in both arches (OR = 1.88 for edentulous in one arch ; OR = 1.77 for completely edentulous).

The results from Table 2-2 show that the percent of sites with at least 3 mm probing depth as a continuous variable did show a strong positive relationship with stroke history ($p = 0.005$). The continuous parameters for the percent of sites with calculus present and the percent of sites with subgingival calculus present showed statistically significant relationships with stroke history. Increased percent of sites with at least 1 mm of recession and increased percent of sites with at least 2 mm of recession, as continuous variables, showed a significantly increased likelihood of stroke history. When we tested the association of the continuous variable for percent of sites with bleeding present, we found a strong positive relationship with stroke history ($p = 0.002$).

From Table 2-3, the results showed that the percent of sites with at least 2 mm of attachment loss and percent of sites with at least 3 mm of attachment loss were significantly related to stroke history in unadjusted models ($p = 0.003$, $p = 0.001$ respectively) with increasing percentages of sites with clinical attachment loss

I. Descriptive Statistics by History of Stroke

Table 1. Summary Statistics of Dental Parameters by Stroke History

Parameter	n	Mean(Median)	SD	Range	p
Number of Teeth					
Stroke	305	9.96(7.72)	10.2	(0 to 31)	
No Stroke	4526	13.6(14.0)	11.1	(0 to 32)	<0.001
% of Sites with =1 mm of Recession					
Stroke	138	39.3(35.7)	33.0	(0.0 to 100)	
No Stroke	2654	31.4(25.0)	28.8	(0.0 to 100)	0.008
% of Sites with = 2 mm of Recession					
Stroke	138	27.1(16.7)	30.8	(0.0 to 100)	
No Stroke	2654	20.4(10.7)	25.5	(0.0 to 100)	0.009
% of Sites with =2 mm Probing Depth					
Stroke	138	40.2(37.5)	27.3	(0.0 to 100)	
No Stroke	2654	38.0(37.5)	24.5	(0.0 to 100)	0.484
% of Sites with =3 mm Probing Depth					
Stroke	138	14.1(4.73)	19.3	(0.0 to 100)	
No Stroke	2654	10.5(4.55)	14.9	(0.0 to 100)	0.475
% of Sites with =2 mm Attachment Loss					
Stroke	138	54.5(54.7)	32.9	(0.0 to 100)	
No Stroke	2654	46.5(44.4)	31.2	(0.0 to 100)	0.003
% of Sites with =3 mm Attachment Loss					
Stroke	138	34.6(25.0)	32.4	(0.0 to 100)	
No Stroke	2654	26.6(16.7)	28.6	(0.0 to 100)	0.004
% of Sites with Any Calculus					
Stroke	138	54.0(50.0)	35.3	(0.0 to 100)	
No Stroke	2654	43.1(36.4)	32.4	(0.0 to 100)	0.002
% of Sites with Subgingival Calculus					
Stroke	138	34.8(12.5)	39.0	(0.0 to 100)	
No Stroke	2654	25.6(10.0)	32.1	(0.0 to 100)	0.182
% of Sites with Bleeding					
Stroke	138	16.5(4.17)	25.4	(0.0 to 100)	
No Stroke	2654	11.6(3.85)	18.0	(0.0 to 100)	0.148

being associated with an increased risk of stroke history.

In Tables 3-1, 3-2, and 3-3, logistic regression models were constructed for dental variables with adjustment for age and current tobacco use. Having fewer teeth had a positive relationship with stroke history, regardless of whether number of teeth was analyzed as a continuous variable, a categorical variable, or as three levels of dentate status.

After adjustment for age and tobacco use, when the percent of sites with at least 3 mm probing depth was analyzed as a continuous variable did any relationship between the percent of sites with periodontal pockets show a statistically significant positive relationship with

II. Unadjusted Logistic Regression Models for Predicting Stroke History from Dental Parameters

Table 2-1. Unadjusted Odds Ratios of Stroke History for Number of Teeth and Dentate Status

Parameter	n	OR	95%CI	p
Number of Teeth (continuous)	5123	0.970	(0.96,0.98)	<0.001
Number of Teeth				
25 to 32 teeth	1062	1.00		
15 to 24 teeth	1373	1.38	(0.94,2.03)	
1 to 14 teeth	1121	2.30	(1.60,3.32)	
No teeth	1567	2.27	(1.61,3.21)	<0.001
Dentate Status				
Teeth present (both arches)	2845	1.00		
Edentulous in one arch	709	1.88	(1.38,2.56)	
Completely edentulous	1569	1.77	(1.38,2.27)	<0.001

Table 2-2. Unadjusted Odds Ratios of Stroke History for Probing Depth, Recession, Calculus, and Bleeding

Parameter	n	OR	95% CI	p
% of Sites with 2mm Probing Depth (continuous)	2954	1.004	(1.00,1.01)	0.286
% of Sites with 3mm Probing Depth (continuous)	2954	1.013	(1.00,1.02)	0.005
% of Sites with 1 mm of Recession (continuous)	2954	1.009	(1.00,1.01)	0.001
% of Sites with 2 mm of Recession (continuous)	2954	1.009	(1.00,1.01)	0.002
% of Sites with Any Calculus (continuous)	2966	1.010	(1.01,1.02)	<0.001
% of Sites with Subgingival Calculus (continuous)	2966	1.008	(1.00,1.01)	0.001
% of Sites with Bleeding (continuous)	2968	1.012	(1.00,1.02)	0.002

Table 2-3 : Unadjusted Odds Ratios of Stroke History for Attachment Loss

Parameter	n	OR	95%CI	p
% of Sites with 2 mm Attachment Loss (continuous)	2954	1.008	(1.00,1.01)	0.003
% of sites with 2 mm Attachment Loss				
Lower Half	1286	1.00		
Upper Half	1668	1.60	(1.14,2.24)	0.006
% of Sites with 3 mm Attachment Loss (continuous)	2954	1.009	(1.00,1.01)	0.001
% of Sites with 3 mm Attachment Loss				
Lower Half	1277	1.00		
Upper Half	1677	1.32	(0.95,1.84)	0.104

history of stroke (p=0.006).

The percent of sites with any calculus present and the percent of sites with subgingival calculus present were both significantly associated with stroke history in the logistic regression model adjusted for age and current tobacco use. Increased percent of sites with at least 1 mm of recession and increased percent of sites with at least 2 mm of recession showed a significantly increased likelihood of stroke history.

Table 3-3 shows the relationship for clinical attachment loss with adjustment for age and

III. Logistic Regression Models for Predicting Stroke History from Dental Parameters with Adjustment for Age and Current Tobacco Use

Table 3-1. Odds Ratios for Number of Teeth and Dentate Status with Adjustment for Age and Current Tobacco Use, n=4929

Parameter	n	OR	95%CI	p
Number of Teeth (continuous)	4929	0.979	(0.968,0.990)	<0.001
Number of Teeth				
25 to 32	1015	1.00		
15 to 24	1334	1.21	(0.82,1.79)	
1 to 14	1077	1.82	(1.25,2.65)	
No teeth	1503	1.72	(1.20,2.45)	0.002
Dentate Status				
Teeth present in both arches	2739	1.00		
Edentulous in one arch	685	1.60	(1.17,2.21)	
Completely edentulous	1505	1.45	(1.12,1.88)	0.003

Table 3-2. Odds Ratios for Probing Depth, Recession, Calculus, and Bleeding after Adjustment for Age and Current Tobacco Use

Parameter	n	OR	95% CI	p
% CIp% of Sites with 2mm Probing Depth (continuous)	2845	1.005	(0.998,1.011)	0.174
% of Sites with 3mm Probing Depth (continuous)	2845	1.013	(1.004,1.023)	0.006
% of Sites with 1 mm of Recession (continuous)	2845	1.006	(1.001,1.012)	0.024
% of Sites with 2 mm of Recession (continuous)	2845	1.007	(1.001,1.013)	0.029
% of Sites with Any Calculus (continuous)	2857	1.008	(1.003,1.013)	0.002
% of Sites with Subgingival Calculus (continuous)	2857	1.006	(1.002,1.011)	0.008
% of Sites with Bleeding (continuous)	2859	1.010	(1.003,1.018)	0.007

Table 3-3. Odds Ratios for Attachment Loss after Adjustment for Age and Current Tobacco Use

Parameter	n	OR	95%CI	p
% of Sites with 2 mm Attachment Loss (continuous)	2845	1.006	(1.001,1.012)	0.027
% of sites with 2 mm Attachment Loss				
Lower Half	1234	1.00		
Upper Half	1611	1.45	(1.02,2.06)	0.038
% of Sites with 3 mm Attachment Loss (continuous)	2845	1.007	(1.001,1.012)	0.014
% of Sites with 3 mm Attachment Loss				
Lower Half	1227	1.00		
Upper Half	1618	1.17	(0.83,1.65)	0.370

current tobacco use. When clinical attachment loss was examined as a continuous variable, the percent of sites with at least 2 mm clinical attachment loss, and the percent of sites with at least 3 mm clinical attachment loss showed significant positive relationships with stroke history.

After fitting the full model of significant factors associated with stroke without dental variables, we added each dental variable

IV. Logistic Regression Models for Predicting Stroke History from Dental Parameters with Adjustment for Significant Cardiovascular Risk Factors

Table 4-1. Odds Ratios for Number of Teeth and Dentate Status Individually (model includes age, gender, race/ethnicity, education, diabetic, hypertension, tobacco use, alcohol consumption, total cholesterol/ high-density lipoprotein cholesterol ratio, plasma fibrinogen, C-reactive protein, total folate)

Parameter	n	OR	95%CI	p
Number of Teeth (continuous)	4365	0.988	(0.98,1.00)	0.056
Number of Teeth				
25 to 32 teeth	932	1.00		
15 to 24 teeth	1185	1.12	(0.72,1.73)	
1 to 14 teeth	946	1.55	(1.01,2.37)	
No Teeth	1302	1.31	(0.86,1.99)	0.167
Dentate Status				
Teeth present (both arches)	2460	1.00		
Edentulous in one arch	601	1.53	(1.08,2.17)	
Completely edentulous	1304	1.18	(0.88,1.60)	0.057

Table 4-2. Odds Ratios for Probing Depth, Recession, Calculus, and Bleeding Parameters Individually (model includes age, gender, race/ethnicity, education, diabetic, hypertension, tobacco use, alcohol consumption, total cholesterol/ high-density lipoprotein cholesterol ratio, plasma fibrinogen, C-reactive protein, total folate)

Parameter	n	OR	95% CI	p
% of Sites with 2 mm Probing Depth (continuous)	2562	1.003	(0.996,1.011)	0.425
% of Sites with 3 mm Probing Depth (continuous)	2562	1.011	(1.001,1.022)	0.038
% of Sites with 1 mm of Recession (continuous)	2562	1.009	(1.002,1.015)	0.008
% of Sites with 2 mm of Recession (continuous)	2562	1.009	(1.002,1.016)	0.009
% of Sites with Any Calculus (continuous)	2571	1.007	(1.000,1.013)	0.035
% of Sites with Subgingival Calculus (continuous)	2571	1.003	(0.997,1.009)	0.297
% of Sites with Bleeding (continuous)	2573	1.009	(1.001,1.018)	0.025

Table 4-3. Odds Ratios for Attachment Loss Parameters Individually (model includes age, gender, race/ethnicity, education, diabetic, hypertension, tobacco use, alcohol consumption, total cholesterol/ high-density lipoprotein cholesterol ratio, plasma fibrinogen, C-reactive protein, total folate)

Parameter	n	OR	95%CI	p
% of Sites with 2 mm Attachment Loss (continuous)	2562	1.008	(1.001,1.014)	0.018
% of sites with 2 mm Attachment Loss				
Lower Half	1131	1.00		
Upper Half	1431	1.61	(1.08,2.40)	0.021
% of Sites with 3 mm Attachment Loss (continuous)	2562	1.008	(1.002,1.015)	0.011
% of Sites with 3 mm Attachment Loss				
Lower Half	1129	1.00		
Upper Half	1433	1.36	(0.92,2.02)	0.123

individually to test for the association of each dental parameter to history of stroke with adjustment for all significant confounders. Results for each dental parameter added individually to the multiple logistic regression model for stroke are presented in Tables 4-1, 4-2, and 4-3. When we adjusted for significant confounders, we obtained slightly different results from the models with adjustment for only age and current tobacco use or for unadjusted models. The number of teeth as a categorical variable was no longer associated with stroke history, although this parameter was strongly related to stroke history in both the unadjusted model and the model with adjustment for current tobacco use and age.

Table 4-2 presents the results of multiple logistic regression models with parameters for probing depth added individually to the baseline model with all significant confounders included. We found that the percentage of sites with 3 mm or more probing depth as a continuous variable was still significantly related with stroke history ($p=0.038$). The percentage of sites with any calculus was significantly associated with stroke history. The percentage of sites with at least 1 mm recession and the percentage of sites with at least 2 mm recession both had a positive significant association with stroke history when these variables were continuous. The percentage of sites with bleeding also had a statistically significant relationship with stroke history in the continuous model only.

When we analyzed the continuous parameters for percent of sites with at least 2 mm of attachment loss and percent of sites with at least 3 mm of attachment loss in the multivariate model with adjustment for significant confounders, we found that both parameters for attachment loss had a strong positive relationship with stroke history. We also analyzed both parameters for attachment loss as categorical parameters. The categorical variable for at least 2 mm loss of attachment that divided subjects in half, there was a statistically significant positive association to stroke history (Table 4-3).

DISCUSSION

In this study, we found a statistically significant relationship between the number of teeth and stroke history in the unadjusted logistic model and also in the multiple logistic model adjusted for age and tobacco use with fewer teeth associated with a greater likelihood of stroke history. However, when we adjusted our model for all significant risk factors, the association between number of teeth and stroke history was no longer statistically significant.

Joshipura et al.,[10] showed a similar significant association between number of teeth and ischemic stroke in a study of 44,116 health professional, although inaccurate measurement of exposure could lead to misclassification. In addition, the validity of data is limited when the study uses a proxy measurement[7]. For instance, Joshipura and Howell gave their cohorts surveys every 2-years and every year, respectively. They found that their survey answers underestimated the relative risks of periodontal disease by 29.7% based on proxy measurement evaluation[10,14]. Another measurement limitation occurs when trying to measure attitudes or perceptions about dental health because it is difficult to measure

an inherently non-quantifiable attitude.[29]

One reason for the difference in results obtained from the models fit with adjustment for tobacco use and age only and the models fit with adjustment for all significant confounders is that some of the significant confounders included in the full model may actually be in the causal pathway. Hence, over-adjusting for confounding may potentially be a problem in this study. This latter possibility might be applied to the inclusion of diabetes, serum glucose, and C-reactive protein. Although these confounders are independent risk factors for cardiovascular disease, regardless of periodontal status, untreated periodontitis has been shown to have a detrimental effect on the control of diabetes[25], serum glucose levels[16,26], and increased C-reactive protein levels[27,28].

These results are similar to the increased risk of incident ischemic stroke among adults with edentulousness and periodontitis reported by Wu, et al.[9] Interestingly, the subjects with periodontitis had a somewhat higher relative risk (2.11, 95% CI : 1.30-3.42) than did their edentulous subjects (relative risk : 1.41, 95% CI : 0.96-2.06). These results are quite similar to what we noted in the current study with partially edentulous subjects with extensive periodontal disease having a higher risk of stroke history than the completely edentulous subjects.

This study is also consistent with the association between periodontitis and stroke reported by Beck, et al.[8] In the study by Beck et al.,[8] they had 40 strokes as outcomes. However, among those strokes, the number of pure strokes included only 11 cases, which means that 29 of the strokes were mixed with coronary heart disease. It is not unusual for an individual with stroke to also have coronary heart disease. Because of this association, it is difficult to obtain a large enough sample of pure strokes to analyze this disease separately from coronary heart disease. Even with enough long-term follow-ups, the disease may not always occur in sufficient number, small sample sizes may not have enough power to detect the association. We cannot exclude the possibility that results were obtained just by chance. Also, a small number of outcomes can lead to lack of validity, since small numbers may make it difficult to control for multiple confounders. For that reason, a meta-analysis can be a good solution for the problem of insufficient numbers of subjects or outcomes[7].

Besides many strength of this study, there are several limitations.

First, many articles emphasized the importance of properly controlling for confounders. Because this is a cross-sectional analysis, any results obtained will depend on the method of categorization and the degree of adjustment for other confounders[29]. Not controlling for common risk factors that are confounders can lead us to observe an association between stroke and periodontal disease in the absence of a true casual association[10,29]. Janket et al.,[7] suggest in their meta-analysis that inadequate confounding adjustment could overestimate the relative risk by 12.9%. For example, although Syrjänen et al.,[4] found a positive relationship between dental disease and stroke, they did not control for confounders other than age and sex. It is possible that if they had adequately controlled for confounders, that they might not have been able

to detect an association. The common risk factors which are frequently considered to be confounders include older age, heavy smoking, heavy alcohol use, other poor health behaviors and habits, genetic association/predisposition, low socio-economic status, high stress, obesity, Western diet (high fat, high calorie), low physical activity, less access to health care, diabetes, hypertension, and poor nutrition (alcohol, vitamin C, sugar intake, etc)[10,29]. The impact of poor nutrition on disease development has become a point of interest in the last several years, and some studies suggest that nutrition should be addressed in multivariate analyses[29]. This component is important because periodontal disease can lead to loss of masticatory function, and physical disabilities resulting from stroke also can cause nutritional deficiencies. Also, the possibility exists that the person experiencing tooth loss may be suffering from nutritional deficiencies, and that these deficiencies might result in stroke[29]. While adequate adjustment for confounding is important, it is also important to avoid over-adjustment when controlling for confounders. For example, Hujoel et al,[14] did not find any association between periodontal disease and coronary heart disease, when they adjusted for 21 confounding factors in their analysis of 8,032 subjects. However, some of those common risks, such as systolic and diastolic blood pressure, and also race, education, poverty and income were correlated with each other, which might also explain the lack of a relationship. This may be why the results were different from those of Destefano and Janket et al,[7, 24] who used the same NHANES I population. Over-adjusting for confounding may potentially be a problem in this study. In particular, several authors have criticized the control of smoking since smoking is a variable considered to be one of the most important common risk factor for periodontal disease and stroke[15,29].

Second, one reason for these results might be the use of are stricted study group that only included subjects 60 years of age or older. Risk factors for systemic disease among the elderly have relatively different characteristics compared to younger people. An interesting result was that the meta-analysis study based on six longitudinal studies showed different results for the younger subjects than for the older subjects[7]. Subjects younger than 65 years old with periodontal disease had a relative risk of 1.44 for cardiovascular disease, whereas the relative risk for the whole population was only 1.19. Also in the study by Morrison et al., they found statistically significant results (RR=3.39) for subjects aged 35 to 69. However, in subjects aged 70 to 84, they did not find a positive relationship (RR=0.86, 95% CI=0.46-1.61) between periodontitis and fatal coronary heart disease[12]. That finding isinteresting since age is one of the most important risk determinants for both periodontal disease and cardiovascular disease.

For this older age group, leaving behind healthy survivors to participate in the study, the heavy smokers may have already died, i.e., a healthy survivor's effect, or subjects may have strong genetic characteristics that make smoking less of a risk factor. The findings for Hyman et al., also support this phenomenon since their study failed to find a significant association

between smoking and heart attack among older subjects[30].

Third, since the only measure of stroke for our study is the history of stroke and since NHANES III is a cross-sectional study without any follow-up, any temporal association between risk factors for stroke and stroke history is lost. periodontal conditions can change over time[31]. A baseline measurement of periodontal disease in long-term longitudinal studies may, in fact, be a misclassification of exposure status at the time of the stroke occurrence because periodontal disease status does not remain static over time[15,31]. The time between exposure and disease development can be long or short for cardiovascular disease, and it might be important to change the oral status over the follow-up period. One meta-analysis study evaluated studies that had at least 10 years of follow-up as one of the criteria for inclusion[7]. Since cardiovascular disease may take about 10 years to develop, measuring oral status changes at least greater than 10 years prior to study completion may be appropriate. A well-designed prospective case-control study is able to measure the disease and exposure conditions simultaneously, perhaps making them as good as a longitudinal study to address this question. A study, which measured periodontal disease status during a time frame close to when the stroke occurred, might be more representative than a measurement made a decade earlier than the stroke event. A periodontal measurement made at the time of the stroke is better than one measured after the stroke (as in a cross-sectional study), because it would be less likely to be impacted by any physical handicaps from the stroke which might affect dental health[4,5] Clearly, the lack of a temporal sequence restricts the inference that can be drawn from the results obtained, but the associations detected provide enough evidence of an association between periodontal disease and stroke to merit.

CONCLUSION

Based on the results of this study, there is evidence of an association between cumulative periodontal disease, based on periodontal disease parameter and history of stroke. However, further investigation of the subject via longitudinal studies so that we can understand the how the progression of periodontal disease may promote stroke and/or how stroke may inhibit proper oral hygiene leading to the progression of periodontal disease and loss of teeth.

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