Dental Prophylaxis and Periodontal Treatment Are Protective Factors to Ischemic Stroke

Ya-Ling Lee, DDS; Hsiao-Yun Hu, PhD; Nicole Huang, PhD; De-Kuang Hwang, MD; Pesus Chou, DrPH; Dachen Chu, MD, PhD

Background and Purpose—A correlation has been found between periodontal disease (PD) and stroke. This study was conducted to investigate whether dental prophylaxis and periodontal treatment reduce the incidence rate (IR) of ischemic stroke.

Methods—We identified 510762 PD cases and 208674 non-PD subjects from January 1, 2000, to December 31, 2010. The PD cases were divided into dental prophylaxis, intensive treatment, and no treatment groups. The stroke IRs were assessed among groups during follow-up. Cox regression analysis was used after adjustment for age, sex, and comorbidities to determine the relationship between periodontal treatment and incidence of ischemic stroke.

Results—The stroke IR of the non-PD subjects was 0.32%/year. In the PD group, subjects who received dental prophylaxis had the lowest stroke IR (0.14%/year); subjects with intensive treatment or tooth extraction had a higher stroke IR (0.39%/year); and subjects without PD treatment had the highest stroke IR (0.48%/year; P<0.001). After adjustment for confounders, the dental prophylaxis and intensive treatment groups had a significant lower hazard ratios for stroke than the non-PD group (hazard ratio=0.78 and 0.95; 95% confidence interval=0.75–0.81 and 0.91–0.99, respectively), whereas the PD without treatment group had a significant higher hazard ratio for stroke (1.15; 95% confidence interval=1.07–1.24), especially among the youngest (20–44) age group (hazard ratio=2.17; 95% confidence interval=1.64–2.87) after stratifying for age.

Conclusions—Maintaining periodontal health by receiving dental prophylaxis and PD treatment can help reduce the incidence of ischemic stroke. (Stroke. 2013;44:1026-1030.)

Key Words: dental prophylaxis ■ ischemic stroke ■ periodontal disease

The prevalence of periodontal disease (PD) is high but varies widely. Approximately ≥90% of the world population have mild to advanced PD.1 Recent studies have estimated that ≥50% of the American population ≥30 years of age have moderate to severe PD,2,3 and 10% to 15% of adults worldwide experience advanced PD with severe alveolar bone loss.4

PD is caused by specific bacterial biofilm, also known as dental plaque, that accumulates around the teeth, and dental calculus (calcified plaque). This plaque induces periodontal tissue inflammation and causes further destruction of the periodontal connective tissue and alveolar bone. In adults, PD is also a major cause of tooth loss.1

Chronic inflammation induces atherosclerosis and certain types of systemic disease, such as type 2 diabetes mellitus and cardiovascular and cerebrovascular disease, whereas PD is a prevalent chronic inflammatory disease.5–8 Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis that colonize in the periodontal pocket are the main disease-causing bacterial strains of PD. Previous studies have shown that A, actinomycetemcomitans, P, gingivalis, and other microbes are also present in atherosclerotic plaques.9–11 These pathogens induce macrophages to secrete cytokines that play important roles in atherothrombogenesis.12

Several observational studies have shown that poor periodontal health status is associated with an increased risk for stroke.13–17 The first National Health and Nutrition Examination Survey further showed that PD is one of the risk factors for nonhemorrhagic stroke.18 In their 12-year cohort study, Holmlund et al19 reported that people with ≤10 teeth had higher coronary heart disease or cardiovascular disease mortality rates than those who had >25 teeth remaining in their mouth. Previous meta-analysis studies have shown that PD and poor oral health increase the risk of cardiovascular disease and stroke.5,20,21

Other studies have suggested a significant association between poor periodontal condition, or lack of dentition, and the rise of C-reactive protein or fibrinogen.22–24 High-sensitivity C-reactive protein is an independent predictor of coronary heart disease/cardiovascular disease in intermediate-risk individuals.27–29

Received November 7, 2012; accepted January 7, 2013.

From the Department of Dentistry, Taipei City Hospital, Taipei, Taiwan (Y.-L.L.); Institute of Public Health and Community Medicine Research Center (Y.-L.L., H.-Y.H., D.-K.H., P.C., D.C.) and Institute of Hospital and Health Care Administration (N.H.), National Yang-Ming University, Taipei, Taiwan; Department of Neurosurgery (D.C.) and Department of Education and Research (H.-Y.H., N.H.), Taipei City Hospital, Taipei, Taiwan; and Department of Ophthalmology, Taipei Veterans General Hospital—Taoyuan Branch, Taoyuan, Taiwan (D.-K.H.).

Correspondence to Dachen Chu, MD, PhD, Superintendent, Taipei City Hospital, Zhongxing Branch No 145, Zheng Zhou Rd, Datong District, Taipei City, Taiwan. E-mail DAD57@tpech.gov.tw

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.000076

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PD is a preventable and treatable disease because poor oral hygiene is a major cause of PD. An increase in the self-reported tooth-brushing frequency decreases the concentrations of C-reactive protein and fibrinogen in the serum. Chen et al found that tooth scaling decreases the incidences of stroke and total cardiovascular events of people ≥50 years of age. However, previous research has not studied the influences of different treatments among different age status of PD on stroke.

This study conducts a retrospective cohort study based on the Taiwanese National Health Insurance (NHI) Research Database administrative data to estimate the incidence rate (IR) and hazard ratio (HR) for ischemic stroke among different treatments of PDs and age groups during a 10-year follow-up period.

Methods

Data Source
The NHI program in Taiwan is a compulsory and universal health insurance program that includes all inpatient and outpatient medical benefit claims. Up to 99% of the inhabitants of Taiwan are enrolled. The National Health Research Institute cooperates with the Bureau of NHI to establish an NHI research database. The National Health Research Institute guards the privacy and confidentiality of all beneficiaries and provides health insurance data to researchers who have obtained ethical approval. The Longitudinal Health Insurance Database contains all the original claim data of 10,000,000 beneficiaries, randomly sampled from the beneficiaries of the NHI Research Database in 2000. The sex and age distribution of the sampled subjects in the Longitudinal Health Insurance Database 2000 are similar to those of all beneficiaries. These data include details of medical orders, procedures, and medical diagnoses with codes based on the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD9-CM). The identification of all patients in the database for analysis.

Study Samples
This study conducts a retrospective cohort study retrieved from the Taiwanese NHI Research Database administrative data from January 1, 2000, to December 31, 2010. The study cohort included 723,024 beneficiaries who were followed up between 2000 and 2010 after excluding patients <20 years of age because PD occurs less commonly in children and adolescents. The index date for the study cohort is the date of the first ambulatory care visit between 2000 and 2010, which resulted in a diagnosis code for PD (ICD9-CM 523.0–523.5). Other excluded criteria were individuals who had stroke before being diagnosed with PD (n=2973) and unknown sex (n=615). A total of 719,436 subjects were included in the analysis, and the total person-years of follow-up were 5,985,121. The study cohort was divided into 3 different groups according to the different periodontal treatment they received: (1) PD patients who only received dental prophylaxis (n=343,944; person-years=2,801,625); (2) PD patients who received intensive periodontal treatments, such as subgingival curettage and root planning or periodontal flap operation or tooth extraction (n=121,552; person-years=784,344); and (3) PD patients who received no treatments (n=45,296; person-years=168,525). Individuals who were never diagnosed with PD during the study period were included as a control group (n=208,674; person-years=2,230,628).

Starting from the cohort entry date, the study subjects were followed until the occurrence of hospitalization with ischemic stroke (ICD-9-CM 433–434) or death, whichever came first, or at the end of the study (December 31, 2010) if no stroke or death.

The comorbidities of risk factors include hypertension (ICD-9-CM 401–405), diabetes mellitus (ICD-9-CM 250), atrial fibrillation (ICD-9-CM 437.3), subclinical atherosclerosis (ICD-9-CM 440.437.0), chronic kidney diseases (ICD-9-CM 580–589), and dyslipidemia (ICD-9-CM 272). To increase the validity of diagnoses in the administrative data set, we only included outpatients who received ≥3 diagnoses of the above comorbidities during the period between January 1, 2000, and December 31, 2010.

Results

Among the total of 719,436 subjects, 15,141 patients developed ischemic stroke between 2000 and 2010. The total person-years of follow-up were 5,985,121, and the IR of ischemic stroke was 0.25%/year (Table 1). The stroke IR increased as age increased (P<0.001). The stroke IR of people 20 to 40 years of age was only 0.03%/year, that of people 45 to 64 years of age was 0.36%/year, and that of people ≥65 years of age increased to 1.0%/year. Men had a higher stroke IR than women (0.29%/year versus 0.22%/year; P<0.001). There was also a significantly higher stroke IR among subjects with comorbidities.

| Table 1. Baseline Characteristics of the Study Subjects |
|-----------|-----------|-----------|-----------|-----------|-----------|
| Variables | n | Stroke, n | Person-years | IR (%/y) | P Value |
| Total     | 719,436 | 15,141 | 5,985,121 | 0.25 | <0.001 |
| Age at baseline, y | |
| 20–44     | 436,390 | 1059 | 3,621,982 | 0.03 | <0.001 |
| 45–64     | 186,525 | 5407 | 1,497,626 | 0.36 | <0.001 |
| ≥65       | 96,521  | 8675 | 865,513  | 1.00 | <0.001 |
| Sex       | |
| Women     | 351,797 | 6371 | 2,911,642 | 0.22 | <0.001 |
| Men       | 367,639 | 8770 | 3,073,480 | 0.29 | <0.001 |
| Comorbidity | |
| Hypertension | 173,723 | 10,814 | 1,380,932 | 0.78 | <0.001 |
| Diabetes mellitus | 81,260 | 5398 | 643,782  | 0.84 | <0.001 |
| Atrial fibrillation | 5966 | 746  | 48,008   | 1.55 | <0.001 |
| Atherosclerosis | 10,941 | 829  | 87,010   | 0.95 | <0.001 |
| Chronic kidney diseases | 29,495 | 1701 | 240,693  | 0.71 | <0.001 |
| Dyslipidemia | 113,782 | 4061 | 890,802  | 0.46 | <0.001 |
| Periodontal disease | <0.001 |
| No periodontal disease | 208,674 | 7223 | 2,230,628 | 0.32 | |
| Dental prophylaxis | 343,944 | 4023 | 2,801,625 | 0.14 | |
| Intensive treatment or extraction | 121,522 | 3081 | 784,344  | 0.39 | |
| PD without treatment | 45,296 | 814  | 168,525  | 0.48 | |

IR indicates incidence rate; and PD, periodontal disease.
such as hypertension, diabetes mellitus, and atrial fibrillation, with stroke IR values of 0.78, 0.84, and 1.55, respectively (P<0.001).

There were 208,674 subjects (29%) who never received PD diagnosis and periodontal treatment. Among them, 7,223 people developed ischemic stroke (stroke IR=0.32%/year). Of the remaining 510,762 subjects who were diagnosed with PD, 7,918 people developed ischemic stroke. Among the PD group, subjects who received dental prophylaxis had the lowest stroke IR (0.14%/year); subjects with intensive treatment or tooth extraction had a higher stroke IR (0.39%/year); and subjects without PD treatment had the highest stroke IR (0.48%/year) among all subjects (P<0.001).

When comparing stroke IRs after being stratified by age, sex, and comorbidity variables (Table 2), the lowest stroke IR of the PD population always appeared in the dental prophylaxis group, followed by intensive treatment or tooth extraction group, and the highest stroke IR appeared in PD without treatment group (P for trend test <0.001 or =0.006).

In Cox regression analysis (Table 3) after adjustment of age, sex, and comorbidity, the dental prophylaxis group and the intensive treatment group had a significantly lower HR for stroke than the non-PD group (HR=0.78 and 0.95; 95% CI=0.75–0.81 and 0.91–0.99, respectively). For the PD group without treatment, the HR was significantly higher than the non-PD group (1.15; 95% CI=1.07–1.24). When stratified by age, dental prophylaxis was associated with significantly lower risk of stroke among the 20 to 44 and 45 to 64 age groups (HR=0.74 and 0.68; 95% CI=0.64–0.86 and 0.64–0.73, respectively). However, intensive treatment or tooth extraction was associated with significantly higher risk of stroke for 20 to 44 years of age (HR=1.35; 95% CI=1.12–1.62) and significantly lower risk of stroke for 45 to 64 years of age (HR=0.89; 95% CI=0.83–0.96). Subjects with PD but without treatment had a higher risk of stroke among all age groups, especially that of the youngest group (HR=2.17, 1.19, and 1.13; 95% CI=1.64–2.87, 1.05–1.35, and 1.03–1.25, respectively).

**Discussion**

This is the first nationwide, population-based study to examine the strength of association between periodontal treatment and the incidence of ischemic stroke. Results show that PD is an important risk factor for ischemic stroke, and PD patients who received treatment have a lower risk of stroke, especially among young subjects.

PD was reported to be a significant risk factor for total cerebrovascular accident and nonhemorrhagic stroke after adjustment for known cerebrovascular accident risk factors by the first National Health and Nutrition Examination Survey cohort study, which compared the IRs of cerebrovascular accident between the PD and non-PD subjects based on the baseline records.18 The age-adjusted IRs were reported to be increased with poor periodontal status (non-PD<PD), especially in nonhemorrhagic stroke. PD and <25 teeth at baseline are also reported to be associated with increased risk of ischemic stroke by another 12-year follow-up study that documented 349 ischemic stroke cases from 41,380 men who were free of cardiovascular disease at baseline.19

Our study classified the PD subjects based on their treatment. The significant trend of stroke IR was found among different

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**Table 2. The Stroke Prevalence Among Study Subjects by Periodontal Disease Types**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Periodontal Disease n=208674</th>
<th>Dental Prophylaxis n=343944</th>
<th>Intensive Treatment or Extraction n=121522</th>
<th>PD Without Treatment n=45296</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, y</td>
<td>Stroke, IR n Person-y (%/y)</td>
<td>Stroke, IR n Person-y (%/y)</td>
<td>Stroke, IR n Person-y (%/y)</td>
<td>Stroke, IR n Person-y (%/y)</td>
</tr>
<tr>
<td>20–44</td>
<td>107559 368 1162955 0.03</td>
<td>246415 441 2025035 0.02</td>
<td>56602 190 350282 0.05</td>
<td>25814 60 83710 0.07</td>
</tr>
<tr>
<td>45–64</td>
<td>47935 2093 514908 0.41</td>
<td>77807 1728 621209 0.28</td>
<td>47247 1308 310285 0.42</td>
<td>13536 278 51223 0.54</td>
</tr>
<tr>
<td>≥65</td>
<td>53180 4762 552764 0.86</td>
<td>19722 1854 155381 1.19</td>
<td>17673 1583 123776 1.28</td>
<td>5946 476 33591 1.42</td>
</tr>
<tr>
<td>Sex</td>
<td>Women 88550 3185 942288 0.34</td>
<td>187276 1754 1542882 0.11</td>
<td>54484 1073 347350 0.31</td>
<td>21487 359 79122 0.45</td>
</tr>
<tr>
<td></td>
<td>Men 120124 4038 1288339 0.31</td>
<td>156668 2269 1258743 0.18</td>
<td>67038 2008 436994 0.46</td>
<td>23809 455 89403 0.51</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Hypertension 45102 4775 468625 1.02</td>
<td>71326 2996 564909 0.53</td>
<td>43615 2403 288543 0.83</td>
<td>13680 640 58855 1.09</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus 20118 2259 207925 1.09</td>
<td>32068 1492 255252 0.58</td>
<td>23071 1360 154131 0.88</td>
<td>6003 287 26475 1.08</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation 1849 289 18947 1.53</td>
<td>2115 237 16474 1.44</td>
<td>1559 169 10303 1.64</td>
<td>443 51 2284 2.23</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis 2715 308 28290 1.09</td>
<td>4258 267 34013 0.78</td>
<td>3116 207 20733 1.00</td>
<td>852 47 3974 1.18</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease 7953 698 83779 0.83</td>
<td>12022 473 97376 0.49</td>
<td>7283 415 49055 0.85</td>
<td>2237 115 10483 1.10</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia 19276 1325 206057 0.64</td>
<td>55879 1431 452902 0.32</td>
<td>30712 1004 200761 0.54</td>
<td>7915 221 31082 0.71</td>
</tr>
</tbody>
</table>

Follow-up time, y (mean±SD) 10.6±1.6 8.1±2.4 6.4±2.6 3.7±3.4

IR indicates incidence rate; and PD, periodontal disease.
PD groups (dental prophylaxis-intensive treatment-without treatment). Those who were diagnosed with PD but not treated had the greatest risk for ischemic stroke among all PD and non-PD groups. This finding suggests that PD must be treated to reduce the risk of stroke. The PD patients who needed intensive treatment or tooth extraction had more severe irreversible PD, and the stroke IRs were higher than those of dental prophylaxis group among all different age, sex, and comorbidity groups.

The PD patients who received only dental prophylaxis during the 10-year follow-up period had the lowest stroke IRs among all age and comorbidity groups and even lower than those of the non-PD group (except the 65+ age group). These patients might have mild periodontitis or relatively healthy periodontal tissue. The Taiwan NHI provides free dental checkups and prophylaxis twice a year to promote the prevention of PD. Therefore, those who received dental prophylaxis on a regular basis are likely to have healthier periodontal conditions and are less likely to have systemic chronic inflammatory reaction.

Chen et al also found that tooth scaling decreases the incidence of stroke, but their population was restricted in those ≥50 years of age. However, Grau et al reported that severe PD is a risk factor in younger (<60 years of age), but not older, subjects. In our study, the preventive effect of dental prophylaxis to stroke is found among all age groups and better among the younger population.

Our findings suggest that age is an important risk factor for stroke. The risk of stroke dramatically increases after 65 years of age. However, the HRs of the youngest subjects were the highest in the fully adjusted models among intensive treatment and without-treatment groups. This might be because the effect of aging superseded the influence of periodontal health condition on stroke. Therefore, young people should pay more attention to maintaining their oral hygiene and periodontal health to reduce the risk of stroke coming from the influence of PD.

The incidence of stroke in men was significantly higher than that of women in the total population and among the PD groups. A meta-analysis studying the sex disparities in stroke concluded that men had more atherothrombotic strokes and women were older than men at stroke onset with a mean difference of 5.2 years. The sex differences in the relationship among PD, tooth loss, and atherosclerosis were reported by Desvarieux et al. They concluded that tooth loss and PD were related to subclinical atherosclerosis in men but not women, and the influence of sex on carotid artery plaque prevalence was most evident in the age group <59 years. A case–control study reported that severe PD is a risk factor in men and not women. They checked the dental conditions of 303 patients within 7 days after acute ischemic stroke or transient ischemic attack. Subjects with severe PD had a 4.3× more risk of cerebral ischemia than subjects with mild PD or without PD. Our study shows that the HRs to stroke of male subjects at 20 to 44, 45 to 64 years, or >65 years of age were all higher than that of women. The sex disparity of the risk of PD to ischemic stroke decreased while age increased.

Several limitations must also be considered. First, the accuracy of diagnosis based on administrative data is an issue of concern, and a potential for misclassification of PD and stroke outcomes is inevitable. However, the Bureau of NHI routinely samples patient charts randomly to cross-check the quality of claims from all medical institutions, and bias from mis-coding or misclassification could be minimized. In addition,
when we included PD patients using the ICD-9 diagnosis codes, we also collected treatment codes for PD. When we collected ischemic stroke cases, we selected inpatient cases because of ischemic stroke. For other comorbidity cases, we selected those who had outpatient visits >3x. We strictly ruled out other patients to lower the nondifferential misclassification bias. Second, the database could not provide information for some other risk factors of stroke, such as body mass index, family history, and smoking, and some comorbidities, such as inflammatory diseases. Smoking is proven to be one of the important risk factors for PD and will influence the outcome of PD treatments. A clinical trial showing the effect of PD treatment (or prophylaxis) on the ischemic stroke outcome in individuals with PD is needed in the future.

The results of this study show that PD increases the incidence of ischemic stroke, especially among the younger population. Because PD can be prevented and treated as long as people improve their oral hygiene and attend regular dental checkups and prophylaxis, those who already have PD should seek treatment to alleviate tissue inflammation and thereby reduce the incidence of ischemic stroke.

Disclosures

None.

References

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Stroke. 2013;44:1026-1030; originally published online February 19, 2013;
doi: 10.1161/STROKEAHA.111.000076
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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