Journal of
PERIODONTAL RESEARCH

J Periodont Res 2010; 45: 223–228
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JOURNAL OF PERIODONTAL RESEARCH
doi:10.1111/j.1600-0765.2009.01220.x

Periodontitis as a risk factor for cerebrovascular accident: a case–control study in the Indian population

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Pradeep AR, Hadge P, Arjun Raju P, Shetty SR, Shareef K, Guruprasad CN. Periodontitis as a risk factor for cerebrovascular accident: a case–control study in the Indian population. J Periodont Res 2010; 45: 223–228. © 2009 John Wiley & Sons A/S

Background and Objective: Chronic infections have been reported to be risk factors for coronary heart disease and ischemic stroke. However, the association of coronary heart disease and ischemic stroke with periodontal disease, which is also a chronic inflammatory disease, needs to be evaluated. The present case–control study was designed to determine if an association exists between periodontal disease and cerebrovascular accident in the Indian population.

Material and Methods: This case–control study consisted of 200 subjects (100 cases and 100 controls) who were 33–68 years of age. Cases were examined within 5 d after their first acute ischemic attack. Clinical parameters recorded included plaque index, gingival index, probing pocket depth and clinical attachment loss. The medical questionnaire collected information on family history of stroke, dietary history, history of smoking and history of alcohol consumption. Cases were additionally scrutinized for diabetes, hypertension and total serum cholesterol level. The education level of patients was also considered.

Results: The mean plaque index, gingival index, probing pocket depth and clinical attachment loss values of subjects with cerebrovascular accident were significantly higher when compared with those of the control group ($p < 0.05$). In fully adjusted logistic regression analysis, a probing pocket depth of > 4.5 mm was found to be the most significant factor for stroke (odds ratio = 8.5; confidence interval = 1.1–68.2) followed by hypertension (odds ratio = 7.6; confidence interval = 3.3–17.1) and smoking (odds ratio = 3.1; confidence interval = 1.3–7.4).

Conclusion: The data from this study support the proposed link between periodontitis and cerebrovascular accident in the Indian population. However, further studies are necessary to verify and quantify the role of oral infections and genetic factors in the process of atherosclerosis.

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Key words: periodontitis; cerebrovascular disease; risk factor

Accepted for publication February 21, 2009

Periodontal disease is a multifactorial infectious disease influenced by several risk factors such as genetics, environment and the host immune system. Although microorganisms are implicated as the etiologic agent responsible for the inflammatory lesion, the products of inflammation play an important role in the loss of connective tissue as

well as in the loss of supportive alveolar bone.

Chronic infections have been reported as one of the risk factors for coronary heart disease (1) and ischemic stroke (2). The major contributing factor in the majority of cases of cardiovascular disease and cerebrovascular disease (stroke) is atherosclerosis. One of the outcomes of this disease process is the narrowing of the arteries resulting from the subendothelial deposition of cholesterol, cholesterol esters and calcium within the vessel walls. These cholesterol-rich plaques also contain a variety of cell types, including fibroblasts and immune cells (3). Rupture of the atherosclerotic plaques yield thrombi that travel distally to occlude arteries, resulting in myocardial infarction and stroke.

In one study it was noted that 44% of the atheromas contained DNA from at least one target periodontal pathogen (4). The interaction between bacterial lipopolysaccharide (LPS) and monocytes leads to the release of various cytokines, which is fundamental in the initiation and progression of periodontal destruction. Bacterial LPS can have a significant vascular effect and trigger the release of tumor necrosis factor-α, interleukin-1β and thromboxane-A2 from monocytes and macrophages. These cytokines can initiate platelet adhesion and aggregation and promote the formation of lipid-laden foam cells and the deposition of cholesterol within the tunica intima. Also, cytokines released from monocytes, together with platelet-derived growth factor, will increase the smooth muscle proliferation, leading to a thickening of the vessel wall. Such thickening will also predispose to atheroma formation (5).

Elevated levels of C-reactive protein (CRP) (> 2.1 mg/L) are associated with a higher incidence of acute thrombotic events, including stroke and myocardial infarction (6). Periodontitis elicits a mild acute-phase response with consistently elevated CRP levels compared to healthy controls (7). Chronically elevated CRP levels in patients with periodontitis exacerbate ongoing inflammatory processes in atherosclerotic lesions, thereby increasing the risk for cardiovascular and cerebrovascular events (8–11). Lipopolysaccharides that pass to the blood, alongside inflammatory mediators such as tumor necrosis factor or interleukin-1β, can induce secretion of acute-phase proteins, such as CRP, in the liver. These proteins can form deposits in damaged blood vessels, with the consequent activation of phagocytes and the release of nitrous oxide, contributing to the formation of atheromas (12). These atheromatous changes result in partial or complete arterial occlusion, which can cause acute ischemic syndromes such as sudden coronary death, acute myocardial infarction, or unstable angina in the coronary circulation, transient cerebral ischemic attacks, or stroke as a result of cerebral infarction in the brain circulation, or critical limb ischemia (13). There are two main types of stroke. The most common, an ischemic stroke, occurs when an artery in the brain is blocked, usually because of atherosclerosis. Alternatively, a hemorrhagic stroke can occur when a portion of the arterial wall weakens and bursts.

Recently, markers of acute inflammation and chronic infectious diseases were discussed to also increase the risk of stroke (2,14–22). Studies have shown that periodontitis could be an independent risk factor for cardiovascular disease and ischemic stroke (2,3,14,16,18,21,23,24,26). However, two studies did not show such an association (27,28). Evidence on the role of periodontal disease in stroke is still limited because of inadequate sample size, retrospective data analyses, or potential residual confounding. Despite these studies, insufficient evidence is available to justify periodontal intervention to prevent the onset or progression of atherosclerosis-induced diseases. To our knowledge, not a single study has been published on the relationship between periodontal disease and cerebrovascular disease or stroke in the Indian population.

Hence, this case–control study was carried out (i) to assess the periodontal status of patients suffering from cerebrovascular accident (CVA) or stroke and (ii) to find out the relationship between periodontal disease and cerebrovascular disease or stroke.

Material and methods

One-hundred patients who were diagnosed as suffering from acute cerebral ischemia and had been hospitalized for the same reason, and 100 age- and gender-matched controls were selected for the study from the Department of Neurology, Victoria Hospital and the National Institute of Mental Health and Neurosciences, Bangalore, India. This study was carried out from December 2005 to November 2006. Ethical approval for the study was obtained from the ethics committees of the respective institutions. The study procedures were explained to each subject, and written informed consent was obtained from those who agreed to participate voluntarily in this study. Case and control groups consisted of 56 men and 44 women ranging from 33 to 68 years of age.

The patients were diagnosed as suffering from acute cerebral ischemia from their medical records and having an acute ischemic lesion on brain imaging ($n = 76$) and/or a neurological deficit lasting for more than 24 h, or if they were suffering from transient ischemic attack ($n = 24$). Transient ischemic attack was defined as a neurological deficit of less than 24 h in duration without a new ischemic lesion. Cases were examined within 5 d after the first acute ischemic attack. Controls were persons admitted to the same department because they were suffering from neurological diseases, such as degenerative disc disease, myasthenia gravis, or Wilson's disease. In the sampling procedure, the controls were randomly selected each week to match the number of cases. Exclusion criteria were a history of previous attack of stroke (i.e. more than one attack), being completely edentulous, receipt of periodontal treatment in the previous 12 mo and being diagnosed as suffering from hemorrhagic stroke on neuroimaging. Among 131 consecutive patients, 100 who were eligible for the study were selected. Similarly, 100 age-matched

and gender-matched hospital controls were selected.

Medical health questionnaire

During interview, a standardized questionnaire pattern was used which included dietary history (vegetarian/nonvegetarian), a history of smoking (current smoker/ex-smoker/never-smoker), a history of alcohol consumption (i.e. patients taking alcoholic beverages never/occasional/regular) and being literate/illiterate (patients who had completed primary education were considered as literate). Individuals were also scrutinized for hypertension (systolic, > 140 mm of Hg; diastolic, > 90 mm of Hg), diabetes (random blood glucose level ≥ 126 mg/dL), total serum cholesterol level (SCL) (a SCL of ≥ 220 mg/dL was considered as a high SCL) and history of stroke from their medical records.

Dental examination

The oral examination was carried out by two calibrated examiners (ARP) and (PH) who were calibrated with respect to all the parameters examined. The calibration was performed approximately 4 wk before the start of the study in the Department of Periodontics, Government Dental College and Research Institute, Bangalore, India. Trained examiners for the study underwent calibration trials to determine inter-examiner and intra-examiner reliability both before the study and at intervals during the study. It was found that clinical attachment loss (CAL) measurements were in agreement within 2 mm for more than 95% of the time. Cases and controls were examined in a supine position with the help of a regular torch for illumination. The periodontal variables were recorded using a sterile mouth mirror and with a University of North Carolina periodontal probe (UNC 15; Hu-Friedy, Chicago, IL, USA). Measurements of probing pocket depth and CAL (the distance between the probed base of the pocket and the cemento–enamel junction) were performed in all teeth at four sites (mesiobuccal, midbuccal, distobuccal and lingual) and rounded up or down to the nearest millimeter. Plaque index (PI) was used for assessment of plaque in all teeth at four sites (29). Gingivitis was determined using the Loe & Silness gingival index (29). Individual mean values were calculated. Attachment levels were analyzed as a continuous variable and, after stratification, into the absence of periodontitis or mild periodontitis (defined as a mean CAL of < 3 mm) and in 1.5-mm steps (mean CAL: 3–4.5 and > 4.5 mm), with a mean CAL of > 4.5 mm defined as severe periodontitis (25). Severe gingivitis was defined as index values > 1.2. Dental plaque was graded according to the Silness & Löe Plaque Index (29). All of these parameters were recorded after the cerebrovascular event had occurred and after starting the emergency treatment.

Statistical analysis

The design, coding and debugging of the database and its statistical analysis were carried out using the SPSS-PC/Windows version 10.5 software package (SPSS Inc., Chicago, IL, USA).

Logistic regression analysis was used to analyze the association of periodontitis with cerebrovascular accident. In the fully adjusted model, the most likely risk factors for stroke were included to assess whether these risk factors could modify the association. All variables of interest were adjusted for age and gender.

Results

Demographic data and risk factors are shown in Table 1. The age and gender distribution in population controls was close to that in cases. Stroke cases exhibited a higher prevalence of hypertension, diabetes mellitus and smoking, and a higher SCL compared with controls, but the same proportion of drinkers as controls. In terms of family history of stroke and nonvegetarian diet, more stroke cases had a family history of stroke and a nonvegetarian diet. Literacy was also lower among stroke cases.

Compared with controls, the mean PI, gingival index (GI), probing pocket depth and CAL was higher in cases, indicating more severe periodontitis in patients with CVA (Table 1). After adjusting for age and gender, severe periodontitis, hypertension and current smoking were significantly associated with CVA ($p < 0.05$) (Table 2).

Cerebrovascular accident was strongly and significantly associated with severe periodontitis (mean probing pocket depth > 4.5 mm), which was associated with an 8.5 [confidence interval (CI) = 1.1–68.2] times higher odds ratio (OR) for CVA than a status without periodontitis (mean probing pocket depth < 3 mm). Hypertension and current smoking were found to have 7.6 (CI = 3.3–17.1) and 3.1 (CI = 1.3–7.4) times higher ORs than non-hypertension and nonsmoking, respectively (Table 2). Patients suffering from CVA had a higher CAL (> 4.5 mm) than controls, but this did not reach significance in a fully adjusted model (OR = 2.4; CI = 0.3–17.1).

Discussion

The present study was designed with the purpose of detecting whether an association exists between periodontitis and CVA in the Indian population. The study clearly showed that CVA subjects had worse periodontal status than the controls, and the means of characteristics for CVA or stroke subjects were significantly higher than those of the control group ($p < 0.05$). These results are in agreement with the results of previous studies (2,21,25), which stated a possible association between periodontal infection and stroke. These studies found that patients with cerebrovascular ischemia had significantly more severe periodontal infection, worse dental status and a greater number of periapical lesions than patients of the control group. A similar study showed that older patients with cerebrovascular ischaemia tended to have significantly worse dental status and had more severe periodontitis and periapical lesions than control subjects (35).

Several causal and noncausal pathways have been postulated to explain

Table 1. Demographic variables and risk factors

Variables	Cases (n = 100)	Controls (n = 100)	p-value
Age (years)	52.3 ± 8.1	51.7 ± 9.2	0.1506[a]
Gender			
Male	56	56	1[b]
Female	44	44	
Diabetes			
Yes	60	42	0.011*[b]
No	40	58	
Hypertension			
Yes	65	32	< 0.001*[b]
No	35	68	
SCL			
High	62	23	< 0.001*[b]
Normal	38	77	
Smoking			
Never	24	44	0.005*[b]
Ex-smoker	20	21	
Current	56	35	
Alcohol drinking			
Never	22	22	0.051[b]
Occasional	25	40	
Regular	53	38	
Family H/O stroke			
Yes	38	25	0.048*[b]
No	62	75	
Education			
Literate	76	89	0.016*[b]
Illiterate	24	11	
Diet			
Vegetarian	32	65	< 0.001*[b]
Nonvegetarian	68	35	
PI (Mean ± SD)	1.73 ± 0.45	1.48 ± 0.5	< 0.0001*[a]
GI (Mean ± SD)	1.23 ± 0.31	1.07 ± 0.38	0.002*[a]
PPD (Mean ± SD)	4.5 ± 1.16	3.65 ± 0.86	< 0.0001*[a]
CAL (Mean ± SD)	3.99 ± 1.21	3.18 ± 0.94	< 0.0001*[a]

*Statistically significant.
[a]Student's t-test.
[b]Chi-squared test.
CAL, clinical attachment loss; GI, gingival index; H/O, history of; PI, plaque index; PPD, probing pocket depth; SCL, serum cholesterol level; SD, standard deviation.

the observed association of periodontitis (or other chronic infections) with atherosclerosis and coronary heart disease (4,16,30). Causal pathways may involve direct and indirect effects of the periodontal infection, whereas genetic and other host factors that increase the susceptibility to both atherosclerosis/thrombosis and chronic periodontitis would be an alternative noncausal pathway (37). Chronic infections, including periodontitis, increase the risk for coronary vascular disease and stroke. Oral microorganisms, including periodontal pathogens, enter the bloodstream during transient bacteremias, where they play a role in the development and progression of atherosclerosis leading to CVA or stroke (4). Braunwald (30) suggested that certain infections, including periodontal disease, may play a significant role in the process of atherosclerosis. Beck *et al.* (16) hypothesized that subjects with a genetically determined strong monocytic response to bacterial antigen could be at high risk for developing both periodontal disease and atherosclerosis. Deshpande *et al.* suggested that organisms such as *Porphyromonas gingivalis*, *Bacteroides forsythus* (currently known as *Tannerella forsythia*) and *Actinobacillus actinomycetemcomitans* (currently known as *Aggregatibacter actinomycetemcomitans*) appear to be common in periodontitis atherosclerosis syndrome. These organisms interact with the neutrophil and monocyte T-cell axis to elicit an acute and chronic inflammatory response (34). These results provide indirect evidence for a causal role of periodontitis in the pathogenesis of atherosclerosis and coronary heart disease. However, the relative importance of such causal mechanisms compared with confounding by common pro-inflammatory susceptibility factors is uncertain (37).

Periodontal disease and CVA share common risk factors. Both conditions, like undesirable weeds, share a common soil. Several factors, including arterial hypertension, cardiac disease, hyperlipidemia, high fibrinogen concentration, diabetes mellitus, a high intake of alcohol and smoking, are associated with an increased risk of brain infarction (31). However, in our study we found that subjects with hypertension and current smoking were more prone to develop CVA compared with controls. It was found that in Japanese men there was a positive association between alcohol consumption and risk of hemorrhagic stroke, and a reduced risk of ischemic stroke, among light-to-moderate drinkers. The excess risk among heavy drinkers was confined primarily to hemorrhagic stroke, particularly intraparenchymal hemorrhage (36). Hillbom *et al.* (32) suggested, from their study, that alcohol consumption, arterial hypertension and diabetes were significant risk factors for CVA, while smoking was not. In the present study it was noted that hypertension and smoking were significant risk factors for CVA, while alcohol consumption was not. This could have been because it was difficult to classify the subjects on the basis of the quantity of alcohol consumed and so regular drinkers were not divided into mild and moderate alcohol consumers.

The higher OR for periodontitis indicates that the occurrence of CVA is higher in periodontitis subjects. This is in accordance with the study conducted by Grau *et al.*, in which periodontitis patients had a 2.6 (OR 2.6) times greater risk of the occurrence of CVA. Similarly, in a report by Losche

Table 2. Age-adjusted and gender-adjusted analysis of maximum likelihood risk factors (variables)

Parameter	Category	Cases	Controls	Odds ratio (95% CI)
Diabetes	No	40	58	1
	Yes	60	42	1.1 (0.5–2.3)
Hypertension	No	35	68	1
	Yes	65	32	7.6 (3.3–17.1)*
Education level	Literate	76	89	1
	Illiterate	24	11	0.8 (0.3–2.3)
Alcohol	Never	22	22	1
	Occasional	25	40	0.8 (0.3–2.1)
	Regular	53	38	1.1 (0.4–2.9)
Smoking	Never	24	44	
	Ex	20	21	1.4 (0.5–4.0)
	Current	56	35	3.1 (1.3–7.4)*
PI	≤ 1	7	24	1
	> 1 to ≤ 1.5	30	32	0.8 (0.1–5.5)
	> 1.5 to ≤ 2	34	28	2 (0.2–19.0)
	> 2	29	16	2.1 (0.2–22.5)
GI	≤ 0.4	2	2	1
	> 0.4 to ≤ 0.8	7	30	0.1 (0.1–2.1)
	> 0.8 to ≤ 1.2	39	27	0.5 (0.02–13.4)
	> 1.2	52	41	0.1 (0.00–2.8)
PPD	≤ 3.0	10	25	1
	> 3.0 to ≤ 4.5	44	59	1.2 (0.3–4.8)
	> 4.5	46	16	8.5 (1.1–68.2)*
CAL	≤ 3.0	22	47	1
	> 3.0 to ≤ 4.5	45	41	1.5 (0.5–4.8)
	> 4.5	33	12	2.4 (0.3–17.1)

*Statistically significant.
CAL, clinical attachment loss; CI, confidence interval; GI, gingival index; PI, plaque index; PPD, probing pocket depth.

et al., an association between CVA and PI was assessed. In that study, the OR for PI was 1.81 (33). Wu *et al*. found that the relative risk for incident nonhemorrhagic stroke was 2.11 for periodontitis (95% CI = 1.30–3.42). Their results also showed that increased relative risks for total CVA and nonhemorrhagic stroke were associated with periodontitis.

From their study, Dorfer *et al*. reported that patients suffering from cerebral ischemia had higher CAL than population controls ($p < 0.001$). After adjustment for age, gender, number of teeth, vascular risk factors and diseases, childhood and adult socioeconomic conditions and lifestyle factors, patients with a mean CAL of > 6 mm had a 7.4 times (95% CI = 1.55–15.3) higher risk, patients with a gingival index of > 1.2 had a 18.3 times (95% CI = 5.84–57.26) higher risk and patients with radiographic bone loss had a 3.6 times (95% CI = 1.58–8.28) higher risk of cerebral ischemia than subjects without periodontitis or gingivitis, respectively (24). Compared with previous studies, our study showed a very strong association between periodontitis and CVA (an OR of 8.5 for a mean probing pocket depth of > 4.5 mm). Although the probing pocket depth and CAL are correlated (data not shown), in a fully adjusted model CAL was unable to reach a level of significance to have an association with stroke. Another reason could be that because CVA patients are bedridden they were not able to maintain oral hygiene. This might lead to higher gingival inflammation and mild gingival enlargement, which caused a higher level of probing pocket depth to be recorded compared with CAL.

We had to restrict our study to patients with transient ischemic attack and mild to moderately severe stroke. Therefore, the results cannot be extrapolated to severe and fatal stroke or hemorrhagic stroke. Although a blinded observer method is preferred for clinical examinations, the fact that the stroke patients and controls were in different sections of the department made this impractical, potentially leading to an ascertainment bias. Residual confounding by factors not adjusted for in the multivariate analysis (e.g. physical activity) may be a further limitation. Also, as mentioned earlier, stroke patients usually receive anticoagulant drug treatment, which can increase the degree of gingival bleeding. In future we are planning to carry out a similar study including other risk factors such as waist : hip ratio, socio-economic status, and patients' lifestyle.

In the present study the effect of periodontal status was assessed by PI, GI, probing pocket depth and CAL. Gingival bleeding is an indicator of gingival inflammation. As mentioned above, stroke patients usually receive anticoagulant drug treatment, which can increase the degree of gingival bleeding. However, periodontitis should not be affected by the aforementioned bias because of the longer period required for the destruction of periodontal support. In conclusion, it is highly unlikely that these possible biases could affect our finding of a strong and significant association between periodontitis and being a case. The mean PI, GI, probing pocket depth and CAL values of cases were significantly higher when compared with the control group ($p < 0.05$) and thus it clearly shows that periodontitis may be a potential risk factor for stroke.

To our knowledge, the present case–control study represents the first research on periodontal health and CVA in the Indian population and has the largest study sample, after that studied by Dorfer *et al*. (24), among the case–control studies reported in the international literature. The data from this study supports the proposed link between periodontitis and CVA. Similarly to other risk factors, periodontitis may also be one of the risk factors for CVA. As there is a safe treatment for periodontitis, better control of periodontal disease may contribute to the decline of CVA. However, further studies are necessary to verify and

quantify the role of oral infections and genetic factors in the process of atherosclerosis.

Acknowledgements

The authors wish to thank all the staff members, postgraduate students and PhD students of the National Institute of Mental Health and Neurosciences, Bangalore, India, and also all the staff members and postgraduate students of the Department of Neurology, Victoria Hospital, Bangalore, India, for their help during the completion of our study. All authors want to express special appreciation to all participants of this study and their relatives.

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