Acta Odontologica Scandinavica. 2014; 72: 687–693

informa
healthcare

ORIGINAL ARTICLE

Association between periodontal disease and non-fatal ischemic stroke: a case-control study

ARNAUD LAFON[1,2,3], STÉPHANE TALA[4], VICTORIN AHOSSI[3], DANIEL PERRIN[3], MAURICE GIROUD[5] & YANNICK BÉJOT[5]

[1]*University of Champagne-Ardenne*, Reims Cedex, France, [2]*Functional Unit Oral Surgery, Division of Dentistry, University Hospital of Reims, Maison Blanche Hospital, Reims Cedex, France,* [3]*University Hospital of Dijon, Dental Service, General Hospital, Dijon, France,* [4]*Lorraine University, Medical School, Nancy, France, and* [5]*Dijon Stroke Registry, Medical School, University of Burgundy, Department of Neurology, University Hospital of Dijon, Dijon, France*

Abstract

Objective. This study aimed to investigate the association between clinical and radiological markers of periodontal disease and ischemic stroke and to assess the potential influence of inflammatory response on the observed associations. ***Methods.*** A prospective case-control study including a series of 48 cases with a minor ischemic stroke and 47 controls was conducted at the University Hospital of Dijon. Vascular risk factors, clinical dental examination (plaque index, gingival index, percentage of pockets >5 mm, percentage of bleeding on probing (BOP) sites), dental panoramic (bone loss) and biological parameters (CRP, total cholesterol, HDL, LDL, fasting glucose) were collected. Conditional regression analyses were performed to identify factors associated with ischemic stroke. ***Results.*** The prevalence of hypertension, high CRP and glucose levels and overall odontological variables was higher in stroke patients. In multivariable analyses, hypertension (OR = 12.56; 95% CI = 2.29–69.96, $p = 0.004$), CRP levels >5 mg/L (OR = 18.54; 95% CI = 2.01–171.17, $p = 0.010$), BOP (OR = 1.049; 95% CI = 1.012–1.88, $p = 0.009$) and bone loss >20% (OR = 1.053; 95% CI = 1.017–1.091, $p = 0.004$) were associated with ischemic stroke. Among stroke patients, there was a non-significant trend towards higher CRP levels in patients with bone loss >20% compared with those with bone loss <20% (8.1 ± 1.27 mg/L vs 3.12 ± 3.14 mg/L, $p = 0.25$), whereas other biological parameters were very similar between the two groups. ***Conclusion.*** This case-control study demonstrates that periodontal disease, especially markers such as BOP and bone loss, is independently associated with ischemic stroke.

Key Words: *stroke, ischemic, risk factor, oral inflammation, periodontitis, bone loss*

Introduction

Periodontal disease and atherosclerosis are both common inflammatory diseases that affect up to 90% of the general population [1]. Epidemiological studies have pointed out the fact that periodontitis may be associated with atherosclerosis, making it a recently-described potential risk factor of cardiovascular diseases [2–4]. Similarly, results from recent case-control [5,6], cohort [2,3], longitudinal and cross-sectional studies [4,7] have established a well-documented link between periodontitis and the occurrence of ischemic stroke. However, the exact pathophysiological mechanisms explaining this association remain unknown. Since inflammation promotes the occurrence and recurrence of atherosclerotic diseases [8], it has been suggested that the inflammatory response observed in patients with periodontitis may contribute to the increased risk of ischemic stroke. Inflammation may involve the lipopolysaccharides (LPS) present in the membranes of Gram-negative bacteria, such as *Aggregatibacter actinomcetemcomitans* and *Porphyromonas gingivalis*, leading to bacteremia [9,10], and subsequently an increase in the systemic inflammatory response as suggested by the observed increase in blood levels of C-reactive protein (CRP), interleukins (IL-1beta, IL-6) or TNF-alpha [11,12].

In this case-control study, we aimed to investigate the association between both clinical and radiological markers of periodontal disease and ischemic stroke and

Correspondence: Arnaud Lafon, Department of Odontology, University Hospital of Dijon, General Hospital, 3 rue Faubourg Raines, 21000 Dijon, France. Tel: +33 (0)3 80 29 37 53. Fax: +33 (0)3 80 29 36 72. E-mail: lafon.arn@gmail.com

(Received 3 October 2013; accepted 21 January 2014)

ISSN 0001-6357 print/ISSN 1502-3850 online
DOI: 10.3109/00016357.2014.898089

to assess the potential influence of the inflammatory response on the observed associations.

Methods

Study population

Cases were prospectively recruited among patients with a first-ever ischemic stroke who were admitted to the stroke unit of the University Hospital of Dijon, France, a tertiary center for management of stroke patients, between March 2008 and September 2012. Ischemic stroke was defined according to the World Health Organization criteria as 'the rapid development of localized or global signs of brain dysfunction with symptoms lasting more than 24 h without any other apparent causes except those of vascular origin' (ICD 10: I63.0-9). The ischemic nature was systematically confirmed by brain imaging and all diagnoses were validated by a neurologist specialized in the stroke field. To be eligible, participants had to have suffered a minor stroke (defined as a NIHSS score <5) [13] associated with large artery atherosclerosis (defined as the presence of an atheromatous plaque resulting in a significant stenosis of a large artery supplying the territory involved) and to be independent 1 month after the event (modified Rankin Scale score 0–2) [14] so as to be able to undergo the dental examination. In patients with associated atrial fibrillation, the large artery atherosclerosis mechanism was considered only if watershed infarcts were found on brain imaging.

Controls were recruited from the department of Odontology of the University Hospital of Dijon among patients referred for oral surgery. Those with a history of stroke were excluded. They had no acute infections that required treatment with antibiotics. To be eligible, both cases and controls had to be aged 18–80 years old and to have at least one premolar or one molar in their mouth and a minimum of 12 teeth. This threshold was chosen to make the evaluation of periodontal disease reliable. The exclusion criteria were a history of oral cavity cancer, recent (<8 days) tooth extraction or scaling, recent cancer (<5 years), treatment with immunosuppressant therapy, an infectious syndrome or systemic or organ inflammation not related to periodontal disease, the use of antibiotics in the 15 days prior to inclusion, treatment with corticosteroids or non-steroidal anti-inflammatory drugs, dementia or psychiatric illness.

A total of 122 participants (64 cases and 58 controls) were screened. After the exclusion of 11 controls and 16 patients with ischemic stroke because they did not come to the inclusion visit, we finally included 48 cases and 47 controls.

Ethics

This study was approved by the local ethics committee (Comité de Protection des Personnes, CPP). Cases and control participants gave their written consent to participate in this study.

Data collected

For both cases and control subjects, the following vascular risk factors were collected: arterial hypertension (high blood pressure noted in a patient's medical history or patients under anti-hypertensive treatment), diabetes mellitus (glucose level ≥7.8 mmol/l reported in the medical record or patients under insulin or oral hypoglycemic agents), hypercholesterolemia (total cholesterol level ≥5.7 mmol/L reported in the medical history or patients treated with lipid-lowering therapy), atrial fibrillation, smoking, alcohol consumption, coronary heart disease, body mass index (BMI) and familial history of cardiovascular disease (stroke and myocardial infarction). Educational level was assessed (0–4 years, 4–8 years and >8 years), as was regular physical activity.

Dental examination

The periodontium and teeth were examined at inclusion for controls and 1 month after the ischemic stroke for cases. Data were collected by two dentists (A.L. and V.A.) and reported on a case report form. Concerning the clinical dental data, the degree of oral inflammation was assessed by the plaque index (PI), the Löe and Silness gingival index (GI) [15], the percentage of pockets >5 mm and the percentage of bleeding on probing sites. The number of teeth (T), decayed (D), missing (M) and filled (F) were identified (DMFT index). A dental panoramic was performed to quantify bone loss in the area of the most affected molar or premolar. Bone loss was measured in millimeters, around the root under the cemento-enamel junction using a radiographic grid.

Biological data

Biological laboratory tests of all participants in the study were performed by the laboratory of the University Hospital of Dijon using their routine technique. The samples were taken at admission for stroke cases (all within the first 8 h of symptoms) and at inclusion for controls. The levels of C-reactive protein, total cholesterol, triglycerides, lipoproteins (HDL, LDL) and fasting plasma glucose were collected.

Statistical analysis

Continuous variables were expressed as a mean ± SD and categorical variables as frequencies. Proportions and mean values of baseline characteristics were compared using the Chi-Square Test and *T*-test, respectively. Conditional regression analyses were

performed to identify factors associated with ischemic stroke. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Firstly, adjustment was made on age and sex. Secondly, multivariable analyses were performed. After testing the robustness of different models, the following characteristics were entered into the final model: BOP, periodontal pocket >5 mm, radiological bone loss, CRP > 5 mg/L, missing teeth, DMFT > 20, gingival index, plaque index, age, gender, school education level, tobacco consumption, alcohol consumption, physical activity, diabetes, hypercholesterolemia, hypertension, coronary heart disease and a BMI > 25. All covariates were kept in the final multivariate models. The 2-tailed significance level was set at $p < 0.05$. All analyses were performed with SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Table I presents the baseline characteristics of study participants. Demographic variables and risk factors in the two groups were similar except for a higher proportion of patient with hypertension in ischemic stroke patients (50% vs 17%, $p = 0.014$). In contrast, major differences were observed for odontological variables. The percentage of pockets greater than 5 mm, the bleeding on probing (BOP) index, the mean GI, the mean PI and the mean DMFT index score were all higher in cases than in the control group. Mean bone loss around the most affected molar or premolar was also greater in cases. Concerning biological parameters, both fasting plasma glucose and CRP levels were higher in stroke patients than in controls (Table II).

In multivariable analyses, arterial hypertension (OR = 12.56; 95% CI = 2.29–69.96, $p = 0.004$) and CRP levels >5 mg/L (OR = 18.54; 95% CI = 2.01–171.17, $p = 0.010$) were associated with ischemic stroke (Table III). Concerning odontological variables, although an association was found for each variable in gender- and age-adjusted analyses, only BOP (OR = 1.049; 95% CI = 1.012–1.88, $p = 0.009$) and bone loss (OR = 1.053; 95% CI = 1.017–1.091, $p = 0.004$) remained significantly associated with ischemic stroke in multivariable models.

To explore the association between bone loss and ischemic stroke, we compared biological variables according to bone loss in ischemic stroke patients. As a result, we found a non-significant trend towards higher CRP levels in patients with bone loss >20% than in those with bone loss <20% (8.1 ± 1.27 mg/L vs 3.12 ± 3.14 mg/L, $p = 0.25$), whereas other biological parameters were very similar between groups (Table IV). Similarly, controls with bone loss greater than 20% had higher levels of CRP than did controls with no or mild bone loss (4.7 ± 7.3 mg/L vs 1.7 ± 1.5 mg/L, $p < 0.001$).

Discussion

This case-control study demonstrated that periodontal disease, especially markers such as BOP and bone loss, was independently associated with ischemic stroke. Our study was justified by the fact that the quality and characteristics of the previous works on this topic varied greatly, especially with regard to the way periodontitis was evaluated, leading to heterogeneity in their results. For example, in a study that included both non-fatal ischemic and hemorrhagic stroke, no association was found between periodontitis, evaluated using a simple questionnaire, and stroke [16]. In contrast, in a high-quality study that explored the relationship between ischemic stroke and periodontal bone loss, a strong positive association was noted (RR = 3.52; 95% CI = 1.59, 7.81) [3].

In this series of 95 participants, although the associations we found were of a low magnitude, these findings confirm those from previous studies that focused on this topic [2,3,5,6,17–21]. We observed that bone loss was the main odontological factor associated with ischemic stroke in individuals with no documented infection except oral inflammation. This result is in agreement with the study of Dörfer et al. [22], which demonstrated an increased risk of ischemic stroke in people with bone loss greater than 5.5 mm. The originality of our study was the presence of a laboratory test that made it possible to identify the potential impact of bone loss on CRP levels and lipid profile. The gingival index was significantly higher among stroke patients. This finding contrasts with previous works [4,7], which found no such association. The higher gingival index in stroke patients than in the control group could be explained by the introduction of anti-platelet therapy in the days following stroke onset. This treatment could have artificially increased bleeding on probing and the gingival index values. In our study, the increase in the gingival index was logically associated with an increase in the plaque index. Of note, since we only included patients with a minor stroke, a deficit in dental hygiene related to post-stroke motor impairment cannot explain this finding. On the contrary, it certainly reflects the pre-stroke dental status of patients.

Our results also demonstrated that CRP levels were greater in stroke patients than in the control group. It has been established that high CRP levels may increase the risk of ischemic stroke and acute ischemic stroke may also be accompanied by an increase in CRP levels [23,24], but in a delayed manner [25]. In addition, it could be assumed that the high CRP levels observed in stroke patients could be related to a rise in inflammatory mediators stimulated by

Table I. Baseline characteristics of study participants.

Variables	Ischemic stroke patients (n = 48)	Controls (n = 47)	p-value
Demographic variables and risk factors			
Age (mean ± SD)	60.2 ± 11.8	56.1 ± 8.8	0.06
Men (n, [%])	26 (54)	21 (44)	0.47
Duration of education (n, [%])			
0–4 years	16 (33)	22 (46)	
4–8 years	24 (50)	18 (38)	
>8 years	8 (16)	7 (14)	0.39
Tobacco consumption (n, [%])			
Non-smoker	17 (35)	18 (38)	
Smoker	19 (39)	10 (21)	
Former smoker	12 (25)	19 (40)	0.11
Physical activity (n, [%])	19 (40)	27 (57)	0.14
Alcohol consumption (n, [%])			
No	18 (38)	27 (57)	
Yes	30 (62.5)	20 (42)	0.81
Arterial hypertension (n, [%])	24 (50)	8 (17)	0.014
Coronary heart disease (n, [%])	6 (12.5)	1 (2)	0.12
Atrial fibrillation (n, [%])	10 (20)	0 (0)	0.006
Peripheral artery disease (n, [%])	3 (6)	1 (2)	0.62
BMI > 25 (n, [%])	32 (66)	26 (55)	0.35
Diabetes (n, [%])	9 (18)	2 (4)	0.058
Hereditary cardiovascular disease (n, [%])	20 (41)	25 (53)	0.35
Odontological variables			
% of Pockets >5 mm (n, [%])			
0–5%	19 (42)	30 (65)	
>5%	26 (57)	16 (34)	0.04
Bleeding on probing (n, [%])			
Present	39 (88)	31 (67)	
Not present	5 (1)	15 (32)	0.003
Bone loss			
0–19% (n, [%])	28 (58)	38 (81)	
>20% (n, [%])	20 (41)	9 (19)	0.003
Mean bone loss (mean ± SD)	18.1 ± 9	13.7 ± 6	0.007
Dental mortality			
Low, 0–14 (n, [%])	28 (58)	38 (80)	
High, >14 (n, [%])	20 (41)	20 (41)	0.03
Mean ± SD	13.7 ± 10.4	8.6 ± 6.5	0.005
DMFT			
0–19 (n, [%])	22 (45)	37 (78)	
>20 (n, [%])	26 (54)	10 (21)	0.002
Mean ± SD	18.1 ± 9.2	13.7 ± 6.4	0.007
Periapical infection (n, [%])	27 (57)	23 (48)	0.5
Gingival Index (mean ± SD)	2.68 ± 0.94	2.17 ± 1.14	0.002
Plaque Index (mean ± SD)	2.63 ± 1.01	2.12 ± 1.27	0.003

AL, Attachment Loss; BMI, Body Mass Index; DMFT, Decayed Missing Filled Teeth.

Table II. Biological data of study participants.

Variables	Ischemic stroke patients (n = 48)	Controls (n = 47)	p-value
CRP mg/L (n, [%])			
<5	30 (62)	40 (76)	
>5	18 (38)	6 (13)	0.01
Mean (± SD) CRP mg/L	6.9 ± 10.8	3.2 ± 5	0.04
Cholesterol mmol/L (mean ± SD)	5.34 ± 1.2	5.15 ± 1.29	0.47
Triglycerides mmol/L (mean ± SD)	1.59 ± 0.69	1.37 ± 0.78	0.18
LDL mmol/L (mean ± SD)	3.2 ± 0.9	3.07 ± 1.1	0.29
HDL mmol/L (mean ± SD)	1.47 ± 0.49	1.50 ± 0.63	0.55
Fasting plasma glucose mmol/L (mean ± SD)	6.15 ± 1.79	5.47 ± 1.14	0.003

periodontogenic bacteria [26]. Therefore, CRP levels could represent the link between oral inflammation and the occurrence of ischemic strokes. Consistently with this hypothesis, it has been shown that treating periodontitis may reduce the level of CRP [27] and the occurrence of ischemic stroke [28]. The finding in our study that CRP levels were higher in ischemic stroke patients with bone loss >20% than in those with bone loss <20% strongly supports this hypothesis, even though differences did not reach the significance level because of the small sample size. Of note, other studies showed that bone disease is associated with an increase in CRP levels [29,30]. In addition, the fact that CRP levels were higher in both controls and cases with periodontal disease reinforces this hypothesis.

Although triglyceride levels were higher and HDL cholesterol levels lower in patients with periodontitis [31], we failed to demonstrate any significant association between bone loss and lipid profile in our stroke patients. It has been suggested that *Aggregatibacter actinomcetemcomitans* may decrease the HDL level, which would increase the risk of developing atherosclerosis [32]. This supports the hypothesis according to which the presence of a biological pro-inflammatory and pro-atherosclerotic profile may be observed in patients with severe periodontitis, illustrating the role of oral inflammation in atherogenesis [33,34]. Again, our study may have lacked sufficient power to detect such differences.

Table III. Factors associated with adjusted ischemic strokes (dental and CRP data).

Variables	OR (95% CI) Gender and age adjusted	p-value	OR (95% CI) Multivariable analyses	p-value
BOP	3.77 (1.23–11.52)	0.005	1.05 (1.01–1.09)	0.009
Site > 5	2.57 (1.1–6)	0.005	0.99 (0.92–1.08)	0.95
Bone loss	5.61 (2.1–15)	< 0.001	1.05 (1.02–1.09)	0.004
Dental mortality	3.02 (1.2–7.6)	0.050	0.99 (0.87–1.12)	0.89
DMFT > 20	4.37 (1.78–10.7)	0.010	2.13 (0.31–14.5)	0.44
Age	1.57 (0.45–5.22)	0.5	0.96 (0.89–1.04)	0.33
Gender	0.52 (0.12–1.02)	0.7	0.29 (0.06–1.45)	0.13
Hypercholesterolemia	2.07 (0.92–4.64)	0.05	4.12 (0.85–19.9)	0.08
Arterial hypertension	4.81 (1.8–12.5)	< 0.001	12.56 (2.29–69.96)	0.004
Coronary heart disease	0.15 (0.02–1.3)	0.05	0.67 (0.17–2.66)	0.57
Tobacco	0.88 (0.38–2)	0.09	0.99 (0.94 –1.04)	0.64
Alcohol	2.25 (0.99–5.12)	0.01	3.61 (0.9–14.44)	0.07
BMI > 25	1.62 (0.71–3.7)	0.02	1.31 (0.35–4.91)	0.69
Physical activity	1.54 (0.65–3.43)		0.44 (0.10–1.95)	0.28
Diabetes	5.12 (1.06–25)	0.005	0.97 (0.06–16.72)	0.98
CRP	5.63 (2.01 –15.7)	0.05	18.54 (2.01–171.17)	0.01
Occupation	1.83 (0.75–4.45)	0.2	1.30 (0.9–4.12)	0.33

OR, Odds Ratios; BOP, Bleeding on Probing; CRP, C-reactive protein; DMFT, Decayed Missing Filled Teeth; Site > 5, pockets greater than 5 mm; BMI, Body Mass Index.

Table IV. Biological variables according to bone loss in ischemic stroke patients.

Variables	Bone loss <20% (n = 7)	Bone loss >20% (n = 41)	p-value
CRP mg/L (mean ± SD)	3.12 ± 3.14	8.10 ± 1.27	0.25
Total cholesterol mmol/L (mean ± SD)	5.74 ± 0.86	5.28 ± 1.52	0.39
Triglycerides mmol/L (mean ± SD)	1.30 ± 0.27	1.64 ± 0.75	0.36
HDL cholesterol mmol/L (mean ± SD)	1.40 ± 0.26	1.45 ± 0.25	0.83
LDL cholesterol mmol/L (mean ± SD)	3.45 ± 0.43	3.26 ± 0.93	0.65
Fasting plasma glucose mmol/L (mean ± SD)	6.01 ± 0.71	6.20 ± 3.75	0.8

Several limitations of our study must be acknowledged. As described above, the relatively small sample size limited our conclusions on the association between both CRP levels and lipid profile, and periodontitis. Control patients were recruited from the oral surgery clinic, which may explain that they tended to be younger than stroke patients. Moreover, the risk of selecting patients whose oral health status is worse than that of the general population was certainly not negligible. The fact that, contrary to the results of previous works [11,19,20], tooth loss was not a significant risk factor for ischemic stroke in our study illustrates this limitation. This could be explained by a greater number of missing teeth in patients recruited from an oral surgery unit, who could be considered at a terminal inflammatory state [1].

To conclude, periodontal disease, assessed both clinically and radiologically, may increase the risk of ischemic stroke via an inflammatory reaction. So as to harmonize the definition of periodontal diseases in future studies, it would be interesting to develop more reliable and valid indicators.

Acknowledgments

This work was supported by a grant from the French Society of Oral Surgery. We thank the team of the Dentistry and Neurology Unit of the University Hospital of Dijon.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366:1809–20.

[2] 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: 2749–55.

[3] Jimenez M, Krall EA, Garcia RI, Vokonas PS, Dietrich T. Periodontitis and incidence of cerebrovascular disease in men. Ann Neurol 2009;66:505–12.

[4] Pow EHN, Leung KCM, Wong MCM, Li LSW, McMillan AS. A longitudinal study of the oral health condition of elderly stroke survivors on hospital discharge into the community. Int Dent J 2005;55:319–24.

[5] Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, et al. Periodontal disease as a risk factor for ischemic stroke. Stroke 2004;35:496–501.

[6] 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 Periodontal Res 2010;45:223–8.

[7] Lee H-J, Garcia RI, Janket S-J, Jones JA, Mascarenhas AK, Scott TE, et al. The association between cumulative periodontal disease and stroke history in older adults. J Periodontol 2006;77:1744–54.

[8] Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circ J 2010; 74:213–20.

[9] Saito A, Inagaki S, Kimizuka R, Okuda K, Hosaka Y, Nakagawa T, et al. Fusobacterium nucleatum enhances invasion of human gingival epithelial and aortic endothelial cells by Porphyromonas gingivalis. FEMS Immunol Med Microbiol 2008;54:349–55.

[10] Nebel D, Arvidsson J, Lillqvist J, Holm A, Nilsson BO. Differential effects of LPS from Escherichia coli and Porphyromonas gingivalis on IL-6 production in human periodontal ligament cells. Acta Odontol Scand 2013;71:892–8.

[11] Mattuella LG, Campagnaro MB, Vargas AE, Xavier LL, Opperman RV, Chies JA, et al. Plasma cytokines levels in aggressive and chronic periodontitis. Acta Odontol Scand 2013;71:683–8.

[12] Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005;76:2106–15.

[13] Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–70.

[14] Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke 1988;19:1497–500.

[15] Loe H, Silness J. Periodontal disease in pregnancy. Prevalence and severity. Acta Odontol Scand 1963;21:533–51.

[16] 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;37:445–50.

[17] Sim S-J, Kim H-D, Moon J-Y, Zavras AI, Zdanowicz J, Jang S-J, et al. Periodontitis and the risk for non-fatal stroke in Korean adults. J Periodontol 2008;79:1652–8.

[18] Joshipura KJ, Hung H-C, Rimm EB, Willett WC, Ascherio A. Periodontal disease, tooth loss, and incidence of ischemic stroke. Stroke 2003;34:47–52.

[19] Abnet CC, Qiao Y-L, Dawsey SM, Dong Z-W, Taylor PR, Mark SD. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. Int J Epidemiol 2005;34:467–74.

[20] Heitmann BL, Gamborg M. Remaining teeth, cardiovascular morbidity and death among adult Danes. Prev Med 2008;47: 156–60.

[21] Holmlund A, Holm G, Lind L. Number of teeth as a predictor of cardiovascular mortality in a cohort of 7,674 subjects followed for 12 years. J Periodontol 2010;81:870–6.

[22] Dörfer CE, Becher H, Ziegler CM, Kaiser C, Lutz R, Jörss D, et al. The association of gingivitis and periodontitis with ischemic stroke. J Clin Periodontol 2004;31:396–401.

[23] Muir KW, Tyrrell P, Sattar N, Warburton E. Inflammation and ischaemic stroke. Curr Opin Neurol 2007;20:334–42.

[24] Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012;367: 1310–20.

[25] Winbeck K, Poppert H, Etgen T, Conrad B, Sander D. Prognostic relevance of early serial C-reactive protein measurements after first ischemic stroke. Stroke 2002;33: 2459–64.

[26] Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J Periodontol 2013;84:S51–69.

[27] D'Aiuto F, Nibali L, Parkar M, Suvan J, Tonetti MS. Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. J Dent Res 2005;84:269–73.

[28] Lee H-J, Garcia RI, Janket S-J, Jones JA, Mascarenhas AK, Scott TE, et al. The association between cumulative periodontal disease and stroke history in older adults. J Periodontol 2006;77:1744–54.

[29] Romagna C, Dufour L, Troisgros O, Lorgis L, Richard C, Buffet P, et al. Periodontal disease: a new factor associated with the presence of multiple complex coronary lesions. J Clin Periodontol 2012;39:38–44.

[30] Yakob M, Meurman JH, Jogestrand T, Nowak J, Söder P-Ö, Söder B. C-reactive protein in relation to early atherosclerosis and periodontitis. Clin Oral Investig 2012;16:259–65.

[31] Monteiro AM, Jardini MAN, Alves S, Giampaoli V, Aubin ECQ, Figueiredo Neto AM, et al. Cardiovascular disease parameters in periodontitis. J Periodontol 2009;80: 378–88.

[32] Pussinen PJ, Jauhiainen M, Vilkuna-Rautiainen T, Sundvall J, Vesanen M, Mattila K, et al. Periodontitis decreases the antiatherogenic potency of high density lipoprotein. J Lipid Res 2004;45:139–47.

[33] Ross R. Atherosclerosis is an inflammatory disease. Am Heart J 1999;138:S419–20.

[34] Hosomi N, Aoki S, Matsuo K, Deguchi K, Masugata H, Murao K, et al. Association of serum anti-periodontal pathogen antibody with ischemic stroke. Cerebrovasc Dis 2012; 34:385–92.