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The association of gingivitis and periodontitis with ischemic stroke

Christof E. Dörfer[1], Heiko Becher[2], Christoph M. Ziegler[3], Claudia Kaiser[1], Rainer Lutz[1], Daniela Jörß[1], Christoph Lichy[4], Florian Buggle[4], Stefan Bültmann[4], Michael Preusch[4] and Armin J. Grau[4]

[1]Policlinic for Conservative Dentistry and Periodontology, University of Heidelberg Dental School; [2]Department of Tropical Hygiene and Public Health, University of Heidelberg; [3]Clinic and Policlinic for Maxillofacial Surgery, University of Heidelberg Dental School; [4]Department of Neurology, University of Heidelberg, Germany

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Abstract

Objectives: The aim of this study was to assess the associations of different periodontal parameters with cerebral ischemia.

Methods: In a case–control study, 303 consecutive patients with ischemic stroke or transient ischemic attack, and 300 representative population controls received a complete clinical and radiographic dental examination. Patients were examined on average 3 days after ischemia. The individual mean clinical attachment loss measured at four sites per tooth was used as indicator variable for periodontitis.

Results: Patients had higher clinical attachment loss than population ($p < 0.001$). After adjustment for age, gender, number of teeth, vascular risk factors and diseases, childhood and adult socioeconomic conditions and lifestyle factors, a mean clinical attachment loss >6 mm had a 7.4 times (95% confidence interval 1.55–15.3) a gingival index >1.2 a 18.3 times (5.84–57.26) and a radiographic bone loss a 3.6 times (1.58–8.28) higher risk of cerebral ischemia than subjects without periodontitis or gingivitis, respectively.

Conclusion: Periodontitis is an independent risk factor for cerebral ischemia and acute exacerbation of inflammatory processes in the periodontium might be a trigger for the event of cerebral ischemia.

Key words: acute inflammation; case–control study; chronic inflammation; gingivitis; infection; ischemic stroke; periodontitis

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Cerebrovascular diseases are among the most prevalent causes of death and disablement in industrialized countries. The expression stroke summarizes sudden central nervous deficits of different but always vascular etiologies. These deficits either result from intracerebral bleeding which account for 10–15% of all strokes, or from ischemia.

The established stroke risk factors do not fully account for the risk of stroke. Recently, markers of acute inflammation and chronic infectious diseases were discussed to increase the risk of stroke as well (Syrjänen et al. 1986, 1989, Beck et al. 1996, Grau et al. 1997, 1998b, Beck & Offenbacher 1998, Danesh 1999, Fagerberg et al. 1999, Wu et al. 2000a, Heuschmann et al. 2001). It was, therefore, concluded from retrospective analyses of two longitudinal cohort studies (Beck et al. 1996, Wu et al. 2000b) and two smaller case–control studies (Syrjänen et al. 1989, Grau et al. 1997) that periodontitis could be an independent risk factor for cardiovascular disease and ischemic stroke. In the case of cardiovascular disease, these associations, however, were doubted and explained by inadequate corrections for confounding variables such as smoking (Armitage 2000, Hujoel et al. 2000, 2001a, b, 2002). In the case of stroke, no such criticism was published except the results of studies in which the participants were not dentally examined but asked for the presence of periodontitis only (Howell et al. 2001, Joshipura et al. 2001).

However, periodontitis is difficult to define and although it appears to result in a chronic progression, mostly, it is characterized by active stages with the loss of attachment and stages of disease stagnation as it results from a complex interplay between chronic bacterial infection and the local and systemic inflammatory host response (Newcomb 1973, Page & Beck 1997, Paquette et al. 1999, Salvi et al. 2000, Noack et al. 2001). The clinical and radiographical parameters to evaluate the degree of periodontal destruction give different information on the activity of disease. Whereas radiographs represent most the bone loss over the years and are almost not modified by acute changes of the inflammatory status, the clinical attachment level (CAL) is influenced by acute inflammation because of the depth of invasion of the periodontal probe into the bottom of the periodontal pocket, which is correlated to the edema of the periodontal connective tissues. Gingival bleeding, finally, is related to the acute inflammatory situation only and gives no information on the long-term changes of the disease.

The existing studies provide limited evidence, of which the periodontal

parameters would describe best an association between inflammations of the periodontal tissues and ischemic stroke, as they neither have the size nor the depth of data acquisition to sufficiently consider for possible confounding. Even more, none of the larger studies have studied the periodontal situation at the time of the ischemic event. The aim of this case–control study was, therefore, (I) to investigate whether periodontitis and gingivitis are independently associated with acute ischemic stroke or transient ischemic attack (TIA) and (II) whether the more acute or the more long-term mechanisms of periodontal inflammatory processes contribute to the risk of ischemic stroke.

Materials and Methods

In a case–control study, 303 patients hospitalized for acute cerebral ischemia and 300 population controls admitted for non-vascular and non-inflammatory neurological diseases were examined for the presence of periodontitis. The control group was matched to patients for age and gender distribution and time of examination. Subjects aged between 18 and 75 years who were residents of the city of Heidelberg or the neighboring county and only native German speakers were included. Exclusion criteria for patients and controls were pregnancy, previous professional radiation exposure, inability to give informed consent or to cooperate in the dental examination within 1 week after ischemia or admission, and any known condition in which a prophylactic antibiotic treatment before dental examination is required.

Patients with acute cerebral ischemia had ischemic stroke ($n = 208$) defined as an acute ischemic lesion on brain imaging and/or a neurological deficit lasting more than 24 h or TIA ($n = 95$) defined as a neurological deficit of less than 24 h without a new ischemic lesion. A cerebral hemorrhage was excluded by neuroimaging in all patients. Among 497 consecutive patients admitted for acute cerebral ischemia, 367 were eligible for the study and 303 (82.8%) agreed to participate. Patients were examined as soon as possible (3.3 ± 2.2 days, mean $\pm$ standard deviation) after ischemia.

Population controls were selected randomly from the population registry of the study area frequency matched by age and sex. They were examined and interviewed parallel to patient recruitment. Controls were contacted first by mail and thereafter by telephone if available. We offered a reimbursement of transport costs, a small financial incentive and individual medical and dental advise to potential controls. Among 497 controls contacted, 435 were eligible for the study among which 300 (69.0%) participated. All participating individuals gave informed consent to study participation and separately for radiography. The study protocol was approved by the local ethics committee.

Interview and dental examination

All individuals were interviewed by trained interviewers using a standardized questionnaire that focused on previous diseases, vascular risk factors, including smoking, drinking habits and nutrition, social history, previous and present medication, and a detailed assessment of dental care. A history of vascular risk factors or diseases was acknowledged if a physician had made the respective diagnosis prior to stroke or examination. Smoking and drinking habits during whole lifetime and current nutrition habits were assessed in great detail as reported previously (Becher et al. 1991, Mandell et al. 1992). A positive family history of stroke was diagnosed if a first-degree relative had suffered from stroke. Social history included the highest degree of school and professional education, present or last profession and for childhood socioeconomic conditions parents' profession and age at which current warm water was available (Mandell et al. 1992). To assess the individual dental care we asked for the frequency, the day times related to meals and the duration of daily tooth brushing, the frequency of dentist visits and previous dental treatments.

All individuals were examined in a standardized way in a dental unit using illumination by a standard dental light, compressed air and a mouth mirror. Almost all dental examinations were performed by one specially trained dentist (C. K.), few ($n = 80$) were examined by one substitute (R. L.) who was calibrated with respect to all parameters examined. For obvious reasons, the dentist could not be blinded for the patient's status. However, analyses of radiographs were done in a blinded way (all by R. L.) and the dentist was not aware of radiographic results when examining the patient.

We registered the number of teeth in each individual. For assessment of periodontitis, the CAL (distance between the probed base of the pocket and the cemento-enamel junction) was selected as the main variable. Measurements were made to the nearest mm using a North Carolina periodontal probe (Carranza 1990) and performed at four sites in each tooth (buccal, mesio-lingual, lingual and disto-lingual). Mean values were individually calculated. Attachment levels were analyzed as continuous variable and after stratification into normal values ($\leqslant 3$ mm) and steps of 1.5 mm. Gingivitis was determined by the Löe and Silness gingival index (Löe et al. 1965). Oral hygiene was assessed by the Sillness and Löe plaque index (Löe et al. 1965). Plaque and gingivitis were scored at four sites per tooth (buccal, mesio-lingual, lingual and disto-lingual) and individually averaged. Panoramic radiographs were taken in 261 (86%) stroke patients and 285 (95%) population controls. Radiographic bone loss was measured as the distance from the cemento-enamel to the most apical extension of the bony defect at two sites per tooth (mesial and distal) and expressed as absolute values (mm) and relative to the overall root length (%) (data not shown). Mean values were individually calculated.

Statistical analysis

All data were entered twice into a data bank to minimize data input errors. Dichotomous variables are presented as percentages and continuous variables are presented as mean and standard deviation (SD) or as median and quartiles as appropriate. Logistic regression analysis was used to analyze the association of the investigated parameters with cerebral ischemia. All variables of interest were first analyzed in a univariate model with adjustment for age, gender, and numbers of teeth in dental parameters. Variables were entered into the multivariate model if they were significant in univariate analysis ($p < 0.05$) or if they were generally accepted risk factors for cerebral ischemia. Individuals with no teeth left, for which dental parameters could not be measured, were assigned to the respective baseline categories and an additional binary variable ''no teeth'' was included in the model for adjustment. Odds ratios and 95% confidence intervals are given for all factors and refer to

the comparison between stroke patients and the control group. The software package SAS (SAS Inc., Heidelberg) was used for the analyses.

Results

Demographic data and risk factors are shown in Table 1. The age and sex distribution in population controls was close to that in cases. According to the results from dental examinations patients with cerebral ichaemia had significantly less teeth and less filled teeth than controls. Also, complete edentolousness was more common in patients than in controls (Table 2).

Compared with controls the mean CAL, the mean radiographic bone loss and the gingival index were higher in patients, indicating more severe periodontitis in patients with cerebral ischemia. After adjustment for age, gender and number of teeth, severe periodontitis (mean CAL >6 mm) was associated with four times higher odds ratio for cerebral ischemia than a status without periodontitis (mean CAL $\leqslant 3$ mm). After adjustment for the same variables, a radiographic bone loss >5.5 mm was associated with a three times higher odds than a bone loss of $\leqslant 2.5$ mm and a gingival index of >1.2 resulted in a 15-fold odds compared with a gingival index $\leqslant 0.4$ mm (Table 3). Gingivitis was not associated with the time period between cerebral ischemia and dental examination ($R = 0.037$; NS).

We furthermore adjusted for all those risk factors that were significantly more common in patients than either of the control groups in univariate analysis (Table 1). In this multivariate model, the role of periodontitis was not modified as compared with univariate analyses, neither with respect to CAL (Table 4) nor gingival index (Table 5) and radiographic bone loss (Table 6). Arterial hypertension, diabetes mellitus, previous stroke, smoking, high lifetime alcohol consumption, atrial fibrillation, family history of stroke, and low childhood socioeconomic conditions (father's profession) were also independently associated with the risk of cerebral ischemia.

Table 1. Demographic variables and risk factors

Variable	Patients with cerebral ischemia ($n = 303$)	Population controls ($n = 300$)	p-value
Age (years)	59.7 ± 11.2	59.3 ± 8.0	NS
Sex			NS
male	208 (68.7)	213 (71.0)	
female	95 (31.4)	87 (29.0)	
Hypertension	172 (56.8)	102 (34.0)	<0.001
Smoking			<0.001
never	98 (32.3)	150 (50.0)	
ex-smoker*	95 (31.4)	87 (29.0)	
current	110 (36.3)	63 (21.0)	
packyears†	28.9 ± 23.3	27.9 ± 25.1	NS
Diabetes mellitus	71 (23.4)	21 (7.0)	<0.001
Hyperlipidemia	109 (36.0)	90 (30.0)	NS
Previous stroke / transient ischemic attack	86 (28.4)	10 (3.3)	<0.001
Coronary heart disease‡	46 (15.2)	19 (6.3)	0.002
Peripheral arterial disease	34 (11.2)	8 (2.7)	<0.001
Atrial fibrillation	21 (6.9)	4 (1.3)	0.007
Alcohol drinking§			0.002
no or low	110 (36.3)	90 (30.0)	
moderate	171 (56.4)	202 (67.3)	
heavy	22 (7.3)	8 (2.7)	
Body mass index¶	26.9 ± 4.1	26.7 ± 3.8	NS
Positive family history of stroke‖	110 (36.3)	88 (29.3)	0.02
School education ⩽ 10 years	89 (29.4)	118 (39.3)	0.003
Vocational training			0.17
none	41 (13.5)	29 (9.7)	
apprenticeship	214 (70.6)	214 (71.3)	
academic	44 (14.5)	56 (18.7)	
Current or last profession			0.003
housewife/-man	17 (5.6)	12 (4.0)	
untrained	21 (6.9)	5 (1.7)	
blue collar	116 (38.3)	109 (36.3)	
white collar	112 (37.0)	122 (40.7)	
academic	30 (9.9)	44 (14.7)	
Father's profession			0.008
untrained	7 (2.3)	2 (0.7)	
blue collar	215 (71.0)	188 (62.7)	
white collar	52 (17.2)	72 (24.0)	
academic	13 (4.3)	27 (9.0)	
Mother's profession			NS
housewife	221 (72.9)	208 (69.3)	
untrained	6 (2.0)	15 (5.0)	
blue collar	41 (13.5)	37 (12.3)	
white collar	24 (7.9)	32 (10.7)	
academic	1 (0.3)	4 (1.3)	
Fixed hot water <age 20			NS
yes	107 (35.3)	104 (34.7)	
no	151 (49.8)	175 (58.3)	

Values represent numbers (percentages) or mean values ± standard deviation as appropriate. Percentages do not always add up to 100% due to missing values. Intake of nutritional factors (meat, sugar, vitamin C, vitamin E, β-carotene) was not different between groups and data are not shown. p-values are based on univariate logistic regression analysis stratified for sex and age.

*Non-smoker for at least 2 years.

†Mean ± standard deviation among smokers and ex-smokers.

‡Coronary heart disease: angina pectoris, myocardial infarction and/or cardiac bypass surgery.

§Alcohol drinking: no or low: 0–251 pure alcohol/lifetime; moderate: 25–10001 pure alcohol/lifetime; heavy: >10001 pure alcohol/lifetime.

¶Body mass index: weight (kg)/(height (m))^2, mean ± standard deviation.

‖First-degree relative with stroke.

NS, not significant.

Discussion

In this study, periodontal inflammation was associated with cerebral ischemia independent of other risk factors, socioeconomic variables and lifestyle factors with increasing odds from radiological assessment over clinical attachment measurements to gingivitis assessment. Blinded radiological assessment confirmed the clinical analyses.

This is the largest case–control study investigating the association between infectious dental disease and cerebral ischemia. Case–control studies in prin-

Table 2. General dental variables

Variable	Patients with cerebral ischemia ($n = 303$)	Population controls ($n = 300$)	p-value
Number of teeth*	15.14 ± 9.43	19.19 ± 8.30	<0.001
Decayed teeth	1.0 ± 1.57	0.74 ± 1.35	0.061
Filled teeth	9.67 ± 5.41	11.87 ± 5.28	<0.001
DMFT index†	22.10 ± 5.71	20.73 ± 5.72	0.088
Gingival index‡	0.97 ± 0.35	0.68 ± 0.37	<0.001
Plaque index§	1.68 ± 0.60	1.55 ± 0.51	0.0012
Radiological bone loss			
(%)	24.13 ± 12.85	20.17 ± 8.47	<0.001
(mm)	3.82 ± 1.97	3.28 ± 1.53	<0.001
Probing pocket depth (mm)	4.04 ± 0.97	3.72 ± 0.81	<0.001
Clinical attachment loss (mm)	4.30 ± 1.33	3.87 ± 1.18	<0.001

Data include only subjects with at least one tooth except for ''number of teeth'' and ''DMFT index''. Values represent mean values ± standard deviations. p-values are based on univariate logistic regression analysis stratified for sex and age.

*Including wisdom teeth.

†DMFT-index: number of decayed, missing and filled teeth (Klein 1946),

‡Gingival index: intra-individual mean from four sites per tooth of degrees 0 (normal gingiva), 1 (mild inflammation: slight change in color, slight edema, no bleeding on palpation), 2 (moderate inflammation: redness, edema, and glazing, bleeding on palpation) and 3 (severe inflammation: marked redness and edema, ulcerations, tendency to spontaneous bleeding) (Löe et al. 1965).

§Plaque index: intra-individual mean from four sites per tooth of degrees 0 (no plaque in the gingival area), 1 (a film of plaque adhering to the free gingival margin and adjacent area of the tooth), 2 (moderate plaque accumulation of soft deposits within the gingival pocket and on the gingival margin and/or adjacent tooth surface) and 3 (abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface) (Löe et al. 1965).

Table 3. Frequencies and odds ratios for dental variables

Variable	Patients with cerebral ischemia	Population controls	Odds ratio (95% CI)
Number of teeth			
all present	12 (4.0)	25 (8.3)	1.0
1–19 teeth lost	194 (64.0)	224 (74.7)	1.94 (0.9–4.0)
20–27 teeth lost	49 (16.2)	34 (11.3)	2.79 (1.2–6.5)
no teeth left	48 (15.8)	17 (5.7)	3.77 (1.6–8.9)
Radiological bone loss			
⩽2.5 mm	64 (26.1)	92 (34.6)	1.0
>2.5–4.0 mm	92 (37.6)	122 (45.9)	1.54 (0.8–2.0)
>4.0–5.5 mm	51(20.8)	37 (13.9)	2.22 (1.3–3.9)
>5.5 mm	38 (15.5)	15 (5.6)	3.37 (1.6–6.9)
Clinical attachment loss			
⩽3.0 mm	39 (15.2)	61 (21.6)	1.0
>3–⩽4.5 mm	118 (46.1)	164 (58.2)	1.87 (0.9–3.9)
>4.5–⩽6 mm	66 (25.8)	39 (13.8)	3.00 (1.4–6.6)
>6 mm	33 (12.9)	18 (6.4)	4.07 (1.7–10.0)
Gingival index			
⩽0.4	22 (8.6)	74 (26.2)	1.0
>0.4–0.8	48 (18.8)	99 (35.0)	1.70 (0.6–1.6)
>0.8–1.2	137 (53.7)	99 (35.0)	4.89 (1.6–3.8)
>1.2	48 (18.8)	11 (3.9)	15.48 (3.0–31.2)
Plaque index			
⩽1	37 (14.5)	43 (15.2)	1.0
>1–⩽1.5	60 (23.5)	94 (33.2)	0.96 (0.6–1.6)
>1.5–⩽2	91 (35.7)	88 (31.1)	1.60 (1.0–2.7)
>2	67 (26.3)	58 (20.5)	2.13 (1.2–3.7)

Percentages do not always add up to 100% due to missing values. Odds ratios are based on univariate logistic regression analysis, stratified for sex and age.

ciple have some limitations. Because of their design the periodontal status was evaluated retrospectively after cerebral ischemia had occurred or, in the case of the controls, a certain age was reached. Therefore, our study is characterized by all the limitations inherent to such a design including the risk of a selection bias towards controls with higher health awareness. Nevertheless, the participation rate in our control groups was comparably good, thus minimizing this risk.

On the other hand, the case–control design is the only design to evaluate a possible association between short-term and swiftly moving entities, e.g. gingivitis and acute incidents such as stroke. In addition to this, there are several strengths in our study including a meticulous evaluation of the dental status that was much more detailed than in previous cohort studies. Our hospital serves as the main health-care center for stroke in the area and most stroke patients under the age of 75 years are admitted to our wards. Therefore, our patient group is representative for stroke patients in the age segment studied. As suggested recently (Hujoel et al. 2000, 2001a, Howell et al. 2001, Joshipura et al. 2001), the role of periodontitis as a risk factor may be explained by residual confounding, mainly by smoking. In our study, smoking was extensively evaluated and periodontitis remained independently associated with stroke after adjustment for smoking among other factors.

Our study was limited to patients with TIA and mild-to-moderately severe stroke and results cannot be automatically transferred to severe stroke. For obvious reasons, our dentist could not be blinded for the patients' status and this could have led to an ascertainment bias in dental evaluation. However, the radiological assessment was blinded and showed results that confirmed the clinical periodontal examination, a fact that strengthens our results.

Periodontitis is a disease that can newly develop, regress or progress over time. Therefore, retrospective analyses as in our study have some advantages over prospective studies evaluating their patients only once at baseline (Beck et al. 1996, Wu et al. 2000a). It could be a matter of concern whether periodontal findings are partly a sequel rather than a precursor of cerebral ischemia. However, the temporal sequence of a possible association is out of doubt as bone loss and attachment loss require long periods to develop (Kinane 2001). Furthermore, the increased risk associated with periodontitis was independent of previous stroke and also present in patients with first-ever stroke.

Whereas the temporal sequence is quite clear in the case of periodontitis, it

Table 4. Odds ratios for clinical attachment loss and other risk factors based on a multiple logistic regression model

Variable	Odds ratio	95% confidence interval	*p*-value
Clinical attachment level*			
⩽3 mm	1.00		
>3–⩽4.5 mm	1.64	0.73–4.39	0.230
>4.5–⩽6 mm	4.82	1.13–8.13	0.028
>6 mm	7.38	1.55–15.03	0.007
Hypertension	1.81	1.24–2.60	0.002
Diabetes mellitus	2.25	1.35–3.80	0.002
Smoking†	1.48	1.10–2.00	0.001
Ex-smoker‡	0.69	0.44–1.07	0.098
High lifetime alcohol consumption§	3.16	1.26–7.92	0.014
Atrial fibrillation	7.13	2.42–21.00	<0.001
Coronary heart disease and/or peripheral arterial disease	1.47	0.87–2.50	0.150
Previous stroke and/or transient ischemic attack	9.87	5.23–18.60	<0.001
Family history of stroke	1.58	1.08–2.33	0.020
School education ⩾10 years	1.25	0.79–2.00	0.340
Current or last profession¶	0.86	0.70–1.07	0.180
Father's profession¶	0.68	0.49–0.95	0.020

Odds ratios are stratified for sex and age.
*Individuals without teeth in baseline category.
†Variable entered as continuous covariable, log-transformed [log(packyears +1)]; odds ratio for 10 packyears versus 0.
‡Definition: non-smoker for at least 2 years.
§Lifetime consumption of >10001 pure alcohol; 10001 pure alcohol approximately correspond to 1.51 beer per day over 40 years.
¶Score 0 (low)–4 (high): 0 = housewife/houseman, 1 = untrained, 2 = blue collar, 3 = white collar, 4 = academic; the odds ratio given relates to a difference of one.

Table 5. Odds ratios for the gingival index based on the same multiple logistic regression model as in Table 4

Variable	Odds ratio	95% confidence interval	*p*-value
Gingivitis*			
⩽0.4	1.00		
>0.4–⩽0.8	1.98	0.95–4.13	NS
>0.8–⩽1.2	5.72	2.79–11.76	<0.001
>1.2	18.29	5.84–57.26	<0.001

Odds ratios are stratified for sex and age.
*Individuals without teeth in baseline category.

Table 6. Odds ratios for the radiographic bone loss based on the same multiple logistic regression model as in Table 4

Variable	Odds ratio	95% confidence interval	*p*-value
Radiographic bone loss*			
⩽2.5 mm	1.00		
>2.5–⩽4.0 mm	1.18	0.70–1.99	NS
>4.0–⩽5.5 mm	1.98	1.02–3.85	0.010
>5.5 mm	3.62	1.58–8.28	0.001

Odds ratios are stratified for sex and age.
*Individuals without teeth in baseline category.

is not so clear in the case of gingivitis. Gingivitis can develop within days and, therefore, could be partly a sequel of poor health care after stroke. However, we examined our patients as rapidly after cerebral ischemia as possible and found no correlation between gingivitis and time elapsed after ischemia. This supports the hypothesis that gingivitis preceded cerebral ischemia. Gingivitis was not a significant risk factor for stroke in a recent cohort study (Wu et al. 2000a), a finding that is not surprising given the discontinuous presence and variable strength of gingivitis over time. When assessed at the time of ischemia, gingivitis was strongly and independently associated with cerebral ischemia according to our results. As shown recently, acute infection, mainly respiratory infection, is a trigger factor for ischemic stroke (Grau et al. 1998a, b, Syrjänen et al. 1988). Severe gingivitis could be another important trigger event for stroke, although our findings require confirmation by further studies. Taking this into account, the higher odds between clinical attachment loss and stroke compared with the radiographic assessment of bone loss could partially be explained by active pockets influencing the measurements because of the depth of invasion of the periodontal probe into the bottom of the periodontal pocket.

Several pathophysiological mechanisms could link periodontitis and stroke. Triggered by apparently innocuous procedures such as tooth brushing and chewing, periodontal bacteria and endotoxin can enter the systemic circulation primarily in the case of acute gingival inflammation (Lockhart 2000). Periodontal pathogens were detected in carotid plaques and may contribute to atherogenesis by damage to the endothelial lineage and stimulation of inflammatory processes in large arteries (Chiu 1999, Haraszthy et al. 2000). Periodontal bacteria can stimulate thrombogenesis by induction of platelet aggregation and increased clotting factors (Kweider et al. 1993, Herzberg & Meyer 1996, Sharma et al. 2000).

In conclusion, our study indicates that periodontitis and gingivitis are independently associated with the risk of cerebral ischemia. There seem to be several mechanisms linking both, acute and chronic aspects of periodontal inflammations to cerebral ischemia. Among all periodontal parameters, gingival bleeding seems to give the highest association to stroke.

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References

Armitage, G. C. (2000) Periodontal infections and cardiovascular disease – how strong is the association? *Oral Diseases* **6**, 335–350.

Becher, H., Jockel, K. H., Timm, J., Wichmann, H. E. & Drescher, K. (1991) Smoking cessation and nonsmoking intervals: effect of different smoking patterns on lung cancer risk. *Cancer Causes Control* **2**, 381–387.

Beck, J., Garcia, R., Heiss, G., Vokonas, P. S. & Offenbacher, S. (1996) Periodontal disease and cardiovascular disease. *Journal of Periodontology* **67**, 1123–1137.

Beck, J. D. & Offenbacher, S. (1998) Oral health and systemic disease: periodontitis and cardiovascular disease. *Journal of Dental Education* **62**, 859–870.

Carranza, F. A. (1990) Clinical Diagnosis. In: *Glickman's clinical periodontology*, ed. Carranza, F. A., 7th edition, pp. 476–501. Philadelphia: WB Saunders.

Chiu, B. (1999) Multiple infections in carotid atherosclerotic plaques. *American Heart Journal* **138**, S534–S536.

Danesh, J. (1999) Coronary heart disease, *Helicobacter pylori*, dental disease, *Chlamydia pneumoniae*, and cytomegalovirus: meta-analyses of prospective studies. *American Heart Journal* **138**, S434–S437.

Fagerberg, B., Gnarpe, J., Gnarpe, H., Agewall, S. & Wikstrand, J. (1999) *Chlamydia pneumoniae* but not cytomegalovirus antibodies are associated with future risk of stroke and cardiovascular disease: a prospective study in middle-aged to elderly men with treated hypertension. *Stroke* **30**, 299–305.

Grau, A. J., Buggle, F., Becher, H., Zimmermann, E., Spiel, M., Fent, T., Maiwald, M., Werle, E., Zorn, M., Hengel, H. & Hacke, W. (1998a) Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: clinical and biochemical studies. *Neurology* **50**, 196–203.

Grau, A. J., Buggle, F., Ziegler, C., Schwarz, W., Meuser, J., Tasman, A.-J., Bühler, A., Benesch, C., Becher, H. & Hacke, W. (1997) Association between acute cerebrovascular ischemia and chronic and recurrent infection. *Stroke* **28**, 1724–1729.

Grau, A. J., Eckstein, H. H., Schafer, B., Schnabel, P. A., Brandt, T. & Hacke, W. (1998b) Stroke from internal carotid artery occlusion during mumps infection. *Journal of Neurological Science* **155**, 215–217.

Haraszthy, V. I., Zambon, J. J., Trevisan, M., Zeid, M. & Genco, R. J. (2000) Identification of periodontal pathogens in atheromatous plaques. *Journal of Periodontology* **71**, 1554–1560.

Herzberg, M. C. & Meyer, M. W. (1996) Effects of oral flora on platelets: possible consequences in cardiovascular disease. *Journal of Periodontology* **67**, 1138–1142.

Heuschmann, P. U., Neureiter, D., Gesslein, M., Craiovan, B., Maass, M., Faller, G., Beck, G., Neundoerfer, B. & Kolominsky-Rabas, P. L. (2001) Association between infection with *Helicobacter pylori* and *Chlamydia pneumoniae* and risk of ischemic stroke subtypes: results from a population-based case–control study. *Stroke* **32**, 2253–2258.

Howell, T. H., Ridker, P. M., Ajani, U. A., Hennekens, C. H. & Christen, W. G. (2001) Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *Journal of American College of Cardiologists* **37**, 445–450.

Hujoel, P. P., Drangsholt, M., Spiekerman, C. & DeRouen, T. A. (2000) Periodontal disease and coronary heart disease risk. *Journal of American Medical Association* **284**, 1406–1410.

Hujoel, P. P., Drangsholt, M., Spiekerman, C. & Derouen, T. A. (2001a) Examining the link between coronary heart disease and the elimination of chronic dental infections. *Journal of American Dental Association* **132**, 883–889.

Hujoel, P. P., Drangsholt, M., Spiekerman, C. & DeRouen, T. A. (2002) Pre-existing cardiovascular disease and periodontitis: a follow-up study. *Journal of Dental Research* **81**, 186–191.

Hujoel, P. P., Drangsholt, M. T., Spiekerman, C. & DeRouen, T. A. (2001b) Periodontal disease and risk of coronary heart disease. *Journal of American Medical Association* **285**, 40–41.

Joshipura, K., Hung, H. C., Ascherio, A., Rimm, E. & Willet, W. (2001) Periodontal disease and incidence of ischemic stroke: a preliminary analysis. Paper presented at the The Periodontal–Systemic Connection: A State of the Art Symposium, Bethesda, USA.

Klein, H. (1946) The family and dental disease. IV. Dental disease (DMF) experience in parents and offspring. *Journal of American Medical Association* **33**, 735–737.

Kinane, D. F. (2001) Causation and pathogenesis of periodontal disease. *Periodontology 2000* **25**, 8–20.

Kweider, M., Lowe, G. D., Murray, G. D., Kinane, D. F. & McGowan, D. A. (1993) Dental disease, fibrinogen and white cell count; links with myocardial infarction? *Scottish Medical Journal* **38**, 73–74.

Lockhart, P. B. (2000) The risk for endocarditis in dental practice. *Periodontology* **23**, 127–135.

Löe, H., Theilade, E. & Jensen, S. B. (1965) Experimental gingivitis in man. *Journal of Periodontology* **36**, 177–187.

Mandell, R. L., Dirienzo, J., Kent, R., Joshipura, K. & Haber, J. (1992) Microbiology of healthy and diseased periodontal sites in poorly controlled insulin dependent diabetics. *Journal of Periodontology* **63**, 274–279.

Newcomb, G. M. (1973) Host factors in the aetiology of periodontal disease. *Australian Dental Journal* **18**, 207–211.

Noack, B., Genco, R. J., Trevisan, M., Grossi, S., Zambon, J. J. & De Nardin, E. (2001) Periodontal infections contribute to elevated systemic C-reactive protein level. *Journal of Periodontology* **72**, 1221–1227.

Page, R. C. & Beck, J. D. (1997) Risk assessment for periodontal diseases. *International Dental Journal* **47**, 61–87.

Paquette, D. W., Madianos, P., Offenbacher, S., Beck, J. D. & Williams, R. C. (1999) The concept of ''risk'' and the emerging discipline of periodontal medicine. *Journal of Contemporary Dental Practice* **1**, 1–8.

Salvi, G. E., Lawrence, H. P., Offenbacher, S. & Beck, J. D. (2000) Influence of risk factors on the pathogenesis of periodontitis. *Periodontology* **14**, 173–201.

Sharma, A., Novak, E. K., Sojar, H. T., Swank, R. T., Kuramitsu, H. K. & Genco, R. J. (2000) Porphyromonas gingivalis platelet aggregation activity: outer membrane vesicles are potent activators of murine platelets. *Oral Microbiology and Immunology* **15**, 393–396.

Syrjänen, J., Peltola, J., Valtonen, V., Iivanainen, M., Kaste, M. & Huttunen, J. K. (1989) Dental infections in association with cerebral infarction in young and middle-aged men. *Journal of Internal Medicine* **225**, 179–184.

Syrjänen, J., Valtonen, V. V., Iivanainen, M., Hovi, T., Malkamäki, M. & Mäkelä, P. H. (1986) Association between cerebral infarction and increase serum bacterial antibody levels in young adults. *Acta Neurologica Scandinavica* **73**, 273–278.

Syrjänen, J., Valtonen, V. V., Iivanainen, M., Kaste, M. & Huttunen, J. K. (1988) Preceding infection as an important risk factor for ischaemic brain infarction in young and middle aged patients. *British Medical Journal* **296**, 1156–1160.

Wu, T., Trevisan, M., Genco, R. J., Dorn, J. P., Falkner, K. L. & Sempos, C. T. (2000a) Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Archives of Internal Medicine* **160**, 2749–2755.

Wu, T., Trevisan, M., Genco, R. J., Falkner, K. L., Dorn, J. P. & Sempos, C. T. (2000b) Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *American Journal of Epidemiology* **151**, 273–282.

Address
Christof Dörfer
Poliklinik für Zahnerhaltungskunde
School of Dental Medicine
University of Heidelberg Dental School Im Neuenheimer Feld 400
69120 Heidelberg
Germany
Fax: +49 6221 563738
E-mail: christof_doerfer@med.uni-heidelberg.de