Periodontal Disease and Risk of Cerebral Ischemic Stroke
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Summary
Objectives: In this study we investigated the association of periodontal disease including periodontitis and gingivitis - classified as inflammatory periodontal disease- with cerebral ischemia.

Methods: In a case-control study, 100 patients with acute ischemic stroke; 50 healthy hospital staff and 50 hospitalized patients without previous history of stroke as controls received complete periodontal examinations within 3.2 and 2.9 days after admission respectively. The individual mean Clinical Attachment Level (CAL) measured at 4 sites of each tooth served as the main indicator for periodontitis.

Results: Patients had higher loss of attachment than controls (P=0.048), whereas gingivitis was not associated with the risk of cerebral ischemia (P=0.35). The more severe periodontitis (CAL≥6 mm) was detected among men in patients with cerebral ischemia (P=0.012).

Conclusions: This study indicates that periodontitis, a treatable condition, is an independent risk factor for cerebral ischemia, especially in men.

Key words: Inflammation, gingivitis, periodontitis, risk factors, ischemic stroke

Periodontal Hastalıık ve Serebral İskemik İnme Riski

Özet
Amaç: Bu çalışmada yangısal periodontal hastalık olarak sınıflandırılan periodontit ve gingiviti de kapsayan periodontal hastalıkla birlikte görülen serebral iskemiyi araştırdık.

Yöntemler: Olgu-kontrol çalışması olarak iskemik inme geçiren 100 hasta, daha önceleri inme öyküsü olmayan 50 yatan hasta ve kontrol olarak 50 sağlıklı hastane çalışanı yatıştırların sırasıyla ortalamada 3.2 ve 2.9 gün içersinde tam periodontal muayeneden geçirildiler. Periodontit olarak temel gösterge alınan dört bölgesi ve her kişi için ortalamalar Klinik Tununma Seviyesi (KTS) ölçülü.

Sonuçlar: Hastalar kontollere göre yüksek oranda tutunma kaybı gösteriken (p=0.048), gingivitin varlığı serebral iskemi riski ile bir birliktelik göstermedi (p=0.35). Serebral iskemi gösteren erkeklerde daha ağır periodontit (KTS≥6 mm) saplandı (p=0.012).

Yargı: Bu çalışma, tedavi edilebilir bir durum olan periododontitin özellikle erkeklerde serebral iskemide bağımsız bir risk faktörü olduğunu gösterdi.

Anahtar Kelimeler: Yangı, gingivit, periodontit, risk faktörleri, iskemik inme
INTRODUCTION

No current issue in periodontal research is more visible or controversial than the relationship between periodontal disease and systemic disease\(^{\text{(2)}}\). Cerebrovascular diseases are among the most prevalent causes of death and disablement\(^{\text{(5)}}\). Periodontal disease is another highly prevalent disease of adults. Periodontal diseases are recognized as infectious processes that require bacterial presence and a host response and are further affected and modified by other local, environmental and genetic factors. Association of periodontal infection with organ systems like cardiovascular system, endocrine system, reproductive system and respiratory system makes periodontal infection a complex multiphase disease\(^{\text{(27)}}\).

Based on the third National Health and Nutrition Examination Survey (NHANES III), 53% of United States adults had at least one tooth with \(\geq 3\) mm periodontal attachment loss, with an average of 19.1% of teeth with \(\geq 3\) mm periodontal attachment loss per adult\(^{\text{(19)}}\).

Established risk factors for stroke do not fully account for the risk of stroke\(^{\text{(5)}}\). Markers of acute inflammation and chronic infectious disease are recently discussed to increase the risk of ischemic stroke and cardiovascular disease\(^{\text{(5,18-20,31)}}\). Though, no single infection is likely a major independent predictor\(^{\text{(6)}}\). In order to lower this burden it is essential to identify risk factors and respective preventive strategies besides the established stroke risk factors (e.g. hypertension, diabetes, hypercholesterolemia, atrial fibrillation) both acute and chronic infectious diseases have emerged as risk factors for stroke. Mainly acute respiratory tract infection but also urinary tract infections independently increase the risk of ischemic stroke. Such additional risk was shown to be highest for infection within 3 days before ischemia and the risk steadily declines with increasing time intervals between infection and stroke\(^{\text{(24)}}\). Since the late 1980s, several studies have been conducted to investigate the relationship between periodontal disease and ischemic stroke, with specific interest concentrating on the ability of periodontal disease to cause cardiovascular disease\(^{\text{(19)}}\). In a meta-analysis of nine longitudinal studies, Janket et al concluded that there was a small but significant increase in the risk of cardiovascular disease among patients with periodontal disease at baseline\(^{\text{(14,19,27,28)}}\). However, other studies could not detect a statistically significant association\(^{\text{(13,22)}}\).

Potential mechanisms for the relationship of periodontal-cardiovascular disease have been provided in many studies, which have identified common oral pathogens within atherosclerotic lesions\(^{\text{(10,11,19,31)}}\). The role of inflammatory factors in the etiopathogenesis of destructive changes in periodontal structure is unquestionable\(^{\text{(23,31)}}\). Recent data suggest that periodontitis (periodontal inflammatory disease with loss of attachment) may have more subtle but broad effects on the metabolism and properties of lipoproteins that may be reversed by periodontal treatment\(^{\text{(20)}}\). Other studies have identified elevated levels of cardiovascular risk factors such as C-reactive protein (CRP), fibrinogen and cholesterol in subjects with periodontal disease\(^{\text{(19,20)}}\). Several recent trials have reported a decrease in CRP after periodontal treatment\(^{\text{(3,4)}}\).

Tiejian et al in a cohort study in 2000 examined the association of the periodontal disease and the risk of cerebrovascular disease\(^{\text{(20)}}\). Joshipura et al in 2003 assessed the incidence of ischemic stroke in patients with periodontal disease and tooth loss by mailed validated questionnaires\(^{\text{(16)}}\). Khader et al in 2004, performed a meta-analysis and concluded that periodontal disease increases the risk of coronary heart and Cerebrovascular disease\(^{\text{(19)}}\). Grau et al and Dorfer et al in 2004 performed two case
control studies and evaluated the association of periodontal disease with ischemic stroke. Jimenez et al performed a study in USA population to identify associations between periodontitis and incidence of cerebrovascular disease in 2009. Pradeep et al in a case control study evaluated the relationship between periodontitis and ischemic stroke in Indian population in 2010.

However, periodontitis is difficult to define and although it appears to result in a chronic process, 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 systemic inflammatory host responses, that untreated will lead to loss of teeth.

In some of the previous studies, participants were not dentally examined to determine the presence of the periodontal disease. However, parameters of periodontal examination would evaluate best the periodontal condition of the patients. Furthermore, most of the studies have not evaluated the periodontal situation at the time of ischemic event. Dorfer et al and Grue et al have considered these parameters in their studies.

Due to several confounding factors and methodological difficulties, the true nature of the association between periodontal disease and ischemic stroke has proved difficult to elucidate. These deficits highlight the necessities of studies with accurate periodontal evaluation of the stroke patients.

The objectives of this case-control study were as follows:

- To investigate whether periodontal disease are independently associated with the ischemic stroke
- To study whether more severe periodontal inflammatory processes contribute to the risk of ischemic stroke

**MATERIAL AND METHODS**

In a case-control study, 100 patients hospitalized for cerebral ischemia and 50 population controls admitted in general surgery ward of Imam Hospital, Tabriz, Iran, and 50 population controls selected among the same hospital's staff were examined for the presence of periodontal disease.

Inclusion criteria for both case and controls were as follows:

15 years of age and older of both genders (as the hospital's criteria for admission of the patients)

Presence of acute cerebral ischemia demonstrated by brain imaging methods in case group and no history of stroke in controls without any consideration of periodontal disease

Less than 7 days of admission for hospitalized subjects (to prevent periodontal inflammation due to poor oral hygiene)

Subject's ability of cooperation for taking part in study

Written informed consent of the subjects

The controls were matched to patients for age and gender distribution and time of examination and were selected only when no history of stroke was reported. However, subjects with risk factors for stroke were not excluded. The periodontal condition of subjects was not considered in selection.

Exclusion criteria for subjects were:

- Cerebral hemorrhage diagnosed by neural imaging
- Pregnancy
- Inability to give informed consent or to cooperate in the dental examination
- Hospitalized subjects with more than 7 days passed after admission
- Edentulous patients
- Subjects with TIA
All patients were randomly selected among subjects matching our inclusion criteria through their charts using the website: www.randomizer.com

For non-hospitalized control groups, 500 volunteer hospital staff filled the study's questionnaire, from which 189 subjects matched the inclusion criteria. 50 subjects were randomly selected through the website above.

Data collection was performed by clinical examination, interview and questionnaire. The study protocol was approved by the local ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran.

**Interview and dental examination:**

All individuals were interviewed by one trained dentist using a standardized questionnaire that focused on individuals name, gender, profession, date of admission if hospitalized, previous disease, vascular risk factors including Diabetes Mellitus, hypertension, heart valve disease, atrial fibrillation, peripheral arterial disease, obesity (based on BMI), previous stroke/ ischemic attack, smoking, a positive family history of stroke, and a detailed assessment of periodontal condition.

All examinations were performed while subjects lying on the hospital bed using the same illumination for all subjects (blue light), with a mouth mirror and a periodontal probe (after isolation with cotton roles) by a specially trained dentist for all subjects. For obvious reasons, the dentist could not be blinded for the patient's status.

For assessment of periodontitis, Clinical Attachment Level (CAL) was considered as the main variable which is the distance between the probed base of the pocket and the Cemento-Enamel Junction (CEJ).

Probing was performed in four sites of each available tooth: Distofacial papilla, Facial gingival margin, Mesiofacial papilla and Lingual gingival margin. Mean values were individually calculated. Attachment levels were analyzed as continuous variables. Gingivitis (initial stage of periodontal inflammation without any loss of attachment) was determined by the Loe and Silness gingival index\(^{(2)}\) by probing the teeth at four sites. Scoring criteria for Gingival index of Loe and Silness are as follows\(^{(2)}\):

G0: Normal gingival without inflammation

G1: Mild inflammation, Slight change in color and texture. No bleeding on probing

G2: Moderate inflammation. Shinny redness, edema and bleeding on very slight and light probing

G3: Severe inflammation, marked shiny redness, edema, ulceration, and spontaneous bleeding on very slight and light probing. All data were subjected to statistical analysis by Chie Square test, cross tabs and Fisher's test by SPSS software.

**RESULTS**

A total of 200 patients were examined in this study with the mean age of 54.2 ± 12.15 for case group, 52.6 ± 14.28 for non-hospitalized controls and 53.1 ± 12.61 for hospitalized controls.

The case group included 52 (52%) males and 47 (47%) females, while in both control groups 23 males (46%) and 27 females (54%) were included.\(^{(2)}\) The mean time of examination after admission was 3.2 days for stroke patients and 2.9 days for hospitalized controls. Risk factors for cerebral ischemia are shown in Table 2.
Table 1 Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Case group</th>
<th>Non-Hospitalized controls</th>
<th>Hospitalized controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>54.2± 12.15</td>
<td>52.6± 14.28</td>
<td>53.1± 12.61</td>
</tr>
<tr>
<td>Male</td>
<td>52 (52%)</td>
<td>23 (46%)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (48%)</td>
<td>27 (54%)</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (100%)</td>
<td>50 (100%)</td>
<td>50(100%)</td>
</tr>
</tbody>
</table>

Table 2 Risk factors for ischemic stroke

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Case group</th>
<th>Non-Hospitalized controls</th>
<th>Hospitalized controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension n(%)</td>
<td>61 (61%)</td>
<td>15 (30%)</td>
<td>23 (46%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Smoking n(%)</td>
<td>17 (17%)</td>
<td>10 (20%)</td>
<td>13 (26%)</td>
<td>0.430</td>
</tr>
<tr>
<td>Diabetes Mellitus n(%)</td>
<td>17 (17%)</td>
<td>12 (24%)</td>
<td>12 (24%)</td>
<td>0.472</td>
</tr>
<tr>
<td>Peripheral Cardiovascular Disease n(%)</td>
<td>9 (9%)</td>
<td>7 (14%)</td>
<td>6 (12%)</td>
<td>0.632</td>
</tr>
<tr>
<td>Obesity n(%)</td>
<td>18 (18%)</td>
<td>10 (20%)</td>
<td>15 (30%)</td>
<td>0.231</td>
</tr>
<tr>
<td>Atrial Fibrillation n(%)</td>
<td>9 (9%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td>0.816</td>
</tr>
<tr>
<td>Familial history of ischemic stroke#</td>
<td>27 (27%)</td>
<td>11 (22%)</td>
<td>5 (10%)</td>
<td>0.049*</td>
</tr>
</tbody>
</table>

# First-degree relative with stroke
According to the results (Table 2), among cerebral ischemia risk factors, hypertension and positive family of stroke were statistically significant in case group comparing to controls; this was not observed for other risk factors of ischemic attack, which may be related to lower sample sizes for other risk factors. However, the close distribution of risk factors in case and control groups, might be considered desirable in association of the study's aim in matching subjects. Age and sex distribution in controls was close to that in cases as well.

According to the results (Table 3) 84% (84 subjects) of patients with cerebral ischemia indicated periodontitis while 16% (16 subjects) indicated gingivitis as the clinical diagnosis of periodontal disease. 80% in hospitalized controls (40 subjects) indicated periodontitis, and 20% indicated gingivitis (10 subjects); However, in non-hospitalized controls, 2.1% (1 subject) had normal gingival (no periodontal disease), 70.2% (33 subjects) indicated periodontitis and 27.7% (13 subjects) had gingivitis.

Compared with controls, the mean CAL, was significantly higher in case group, indicating more severe periodontitis and advanced stage of periodontal disease in patients with cerebral ischemia (Table 4). However, this was not true for gingivitis.

No significant difference was observed among controls considering the sex; However, it is interesting to note that more severe periodontitis (CAL ≥ 6 mm) was higher among males in patients with cerebral ischemia (p=0.012)  

We furthermore evaluated the association of the presence of periodontal disease with the risk factors of ischemic stroke and no significant association was observed.

### Table 3: Frequency of periodontal disease

| P-value | Normal gingival
<table>
<thead>
<tr>
<th>Group</th>
<th>Non-Hospitalized Controls(2)</th>
<th>Hospitalized Controls(3)</th>
<th>Between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal gingival</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>16 (16%)</td>
<td>13 (26%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>84 (84%)</td>
<td>36 (72%)</td>
<td>40 (80%)</td>
</tr>
</tbody>
</table>
Table 4: Severity of periodontitis

<table>
<thead>
<tr>
<th></th>
<th>Case group (1)</th>
<th>Non-Hospitalized Controls(2)</th>
<th>Hospitalized Controls(3)</th>
<th>Between groups P-value</th>
<th>p-value (1)_ (2)</th>
<th>p-value (1)_ (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CAL</td>
<td>2.98±1.97</td>
<td>2.14±1.98</td>
<td>2.48 ±2.11</td>
<td>0.048*</td>
<td>0.016*</td>
<td>0.017*</td>
</tr>
</tbody>
</table>

DISCUSSION

In this study, the more severe forms of periodontitis (the inflammatory periodontal disease with attachment loss) were associated with cerebral ischemia independent of other risk factors; especially in men. However, gingivitis—the initial stages of periodontal inflammation without any loss of attachment—was not significantly associated with the risk of ischemic stroke.

Several epidemiological studies have suggested associations between cerebral ischemia and periodontitis (5,8,18,19,22). The periodontal status was evaluated retrospectively after cerebral ischemia had occurred in most of the previous investigations using radiographs, self report questionnaires without any clinical examination at the time of the stroke, which is considered a limitation in their study's design (1,14,19,22,25). Few studies have examined the periodontal status in the stroke time (5,9).

However, it is extremely important to evaluate the periodontal status at the critical period of acute incidence of the ischemic stroke. In this study, patient's clinical examination to evaluate the periodontal status was performed within 7 days of the stroke, or admission to the hospital in controls to prevent gingivitis occurred due to the poor oral hygiene of the hospitalized patients. On the other hand, the case-control design is the only design to evaluate a possible association between short-term and swiftly moving entities like periodontal disease and acute incidences such as ischemic stroke. This method was previously utilized by Grau et al and Dorfer et al's studies (5,9). Another advantage of our study is that our hospital serves as the main health care center for stroke in the area.

Our results are in accordance with Grua et al and Dorfer et al's studies. In Grua et al's study, periodontitis was indicated as an independent risk factor for cerebral ischemia, especially in men and young subjects. However, gingivitis was also independently associated with the risk of cerebral ischemia. This study has utilized Loe and Silness gingival index for evaluation of periodontal condition, as is used in this study. In our study, more severe periodontitis was also considered higher in men comparing to women (p=0.012). In Dorfer's study, periodontal inflammation was independently associated with the risk of cerebral ischemia. The data from Pradeep et al in a case control study in India support the proposed link between periodontitis and cerebrovascular accident in the Indian population (26). Jimenez et al in a current study in USA revealed an association between history of periodontitis -but not current periodontal inflammation- and incidence of cerebrovascular disease in men, independent of established cardiovascular risk factors, particularly among men aged <65 years. However, in this study presence of a history of stroke was evaluated not the current periodontal status at the stroke time (15).

It is important to note that the majority of the subjects in our study, indicated periodontitis and only a few subjects had gingivitis, which was presented in the results. This may be associated with the great prevalence of periodontal disease and
limited general oral hygiene in our country. In contrast with Grua and Dorfer's studies, gingivitis was not significantly higher in patients with cerebral ischemia in this study. However, this conflict might be related to limited subjects indicating gingivitis in this study, due to the great prevalence of more advanced stages of periodontal disease in the country. It is of high importance to remember that the gingival inflammation-marked by bleeding on probing, shiny redness of the gingiva, edema, and sometimes ulceration which are diagnosed as gingivitis when no attachment loss is observed-is also present when periodontitis is the case of diagnosis. Hence, it can be concluded that, the more severe form of gingival inflammation is associated with the risk of stroke in this study.

Our study was limited to patients with mild to moderately-severe stroke and the more severe ischemic attacks which have led to death or in patients who could not cooperate in periodontal examination because of their complicated systemic conditions, the results cannot be transferred. Moreover, edentulous patients were not included in the study. For obvious reasons, the examining dentist could not be blinded for the subject's status.

Several pathophysiological mechanisms could link periodontitis and stroke. Periodontal bacteria and endotoxins can enter the systemic circulation by tooth brushing or chewing in case of periodontal disease. Periodontal pathogens have been detected in carotid plaque and may contribute to atherogenesis by damage to the endothelial lineage and stimulation of inflammatory process in large arteries\(^5\). Furthermore, periodontal bacteria can stimulate thrombogenesis by induction of platelet aggregation and increasing clotting factors\(^5\). Chronic infections, presently discussed as stroke risk factors mainly include periodontitis and infections with Helicobacter pylori (Hp) and Chlamydia pneumoniae (Cp). Although most respective studies identified these infectious diseases as independent stroke risk factors interventional trials have not been performed so far and causality is not proven, yet. There is preliminary evidence that the number of pathogens to which a subject had been exposed to rather than single pathogens are associated with the risk of stroke or other cardiovascular diseases\(^24\).

Although the strength of the reported associations is modest, the consistency of the data across diverse populations and a variety of exposure and outcome variables suggests that the findings are not spurious or attributable only to the effects of confounders. Analysis of limited data from interventional studies suggests that periodontal treatment generally results in favorable effects on subclinical markers of atherosclerosis, although such analysis also indicates considerable heterogeneity in responses. Experimental mechanistic in vitro and in vivo studies have established the plausibility of a link between periodontal infections and atherogenesis, and have identified biological pathways by which these effects may be mediated. However, the utilized models are mostly mono-infections of host cells by a limited number of 'model' periodontal pathogens, and therefore may not adequately portray human periodontitis as a polymicrobial, biofilm-mediated disease. Future research must identify in vivo pathways in humans that may (i) lead to periodontitis-induced atherogenesis, or (ii) result in treatment-induced reduction of atherosclerosis risk. Data from these studies will be essential for determining whether periodontal interventions have a role in the primary or secondary prevention of atherosclerosis\(^17\).

It is interesting to note that in a current study in UK it was supposed that the treatment of periodontal disease although may reduce cardiovascular risk in the longer term and concluded that Invasive dental treatment may be associated with a transient increase in the risk for vascular
events. However, whether such acute inflammatory effects translate into a short-lived increased risk for vascular events is yet not known. This highlights the importance of prevention of periodontal disease by appropriate oral hygiene\(^{21}\).

In conclusion, our study indicates that periodontal inflammatory disease is associated with the risk of cerebral ischemic stroke. Consequently, to help break potentially confounded associations, larger controlled studies are required to better identify association between periodontal disease and cerebral ischemic stroke.

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