



# Relationship between Moderate-Severe Periodontitis and Ischemic Stroke

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## ABSTRACT

This paper aims to make a preliminary discussion on the relationship between periodontitis, serum inflammatory factors and ischemic stroke based on measurements of the first two diseases. A case-control study operates between patients with ischemic stroke (experimental group) and healthy cases (control group) in comparison to the incidence of periodontitis, serum hyper-sensitivity C-reactive protein, interleukin and tumor necrosis factor. The results reveal that the experimental group presents higher than the control group in all these areas, and the differences in these regards are statistically significant. In the end, it is concluded that periodontitis and serum inflammatory factors are correlated to ischemic stroke. Hyper-sensitivity C-reactive protein, interleukin and tumor necrosis factor may serve as the serological indicators for testing the periodontitis and ischemic stroke in clinical practices.

**Key Words:** Periodontitis, Ischemic Stroke, Relationship

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## Introduction

Periodontitis is mainly the chronic inflammation of the periodontal support tissues caused by local factors. It is quite common among people aged over 35 years. If gingivitis is not treated in time, inflammation may progress from gingiva to the pericementum, alveolar bone, and cementum in deep sites, thus developing into periodontitis as one of the most common oral diseases. The early symptoms are not obvious, and the patients often present secondary gingival bleeding or halitosis, similar to the gingivitis (Loos *et al.*, 2000). During the examination, the swelling of the orbital edge, gingival papilla and attached gingiva is seen with soft cementum in crimson or in maroon; gingiva is easy to bleed when probing. With the further diffusion of inflammation, the following symptoms may occur: 1. Formation of periodontal pockets. Due to the diffusion of inflammation, the pericementum, is impaired, the alveolar bone is

gradually absorbed, the gingiva separates from the root such that the gingival sulcus deepens just as a periodontal pocket. Probes can measure the depth of the pocket. 2. Periodontitis overflows pus. There are ulcers on the wall of the periodontal pocket and inflammatory granulation tissue forms. There are residuals of purulent secretions in the pocket so that the pus can be seen when tapping gingiva (Yamazaki *et al.*, 2005). 3. Loose teeth. As the periodontal tissue is damaged, especially when the alveolar bone resorption aggravates, the supporting tooth strength is insufficient, so that teeth loosening and displacement and other phenomena occur. At this time the patients often feel occlusal weakness, dull pain, bleeding gums and bad breath. Periodontal abscess can be formed when the body immunity reduces and the drainage of seepage in periodontal pockets is poor, which is a common concomitant symptom of deep

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periodontal pockets at the late stage of periodontitis. At this time, the gums show ovoid protrusions, reddened and swollen, and bright on the surface; the loosening of the teeth worsens and there is percussion pain; the patients are accompanied by local acute throbbing pain, while they present fever, general malaise, submandibular lymph nodes, tenderness and other symptoms. The persistence of the periodontitis often with bad breath will eventually lead to the loss of teeth and affect the intake of nutrients, which poses a serious threat to human health.

Ischemic stroke refers to the general term for brain tissue necrosis due to stenosis or occlusion of the blood feeding artery (carotid artery and vertebral artery) in the brain and blood shortage to the brain. There are four types of cerebral ischemia: Transient Ischemic Attack (TIA); Reversible Ischemic Neurologic Deficit (RIND); Stroke in Progression (SIE); Complete Stroke (CS). There is no cerebral infarction in TIA, but any in different degrees in RIND, SIE and CS (Fichtlscherer *et al.*, 2000). Concurrently, a great number of basal and clinical studies have found that periodontitis may be closely associated with the occurrence and development of systemic diseases such as diabetes and cardiovascular and cerebrovascular diseases. Evidence suggests that periodontitis is a key risk factor that may cause systemic diseases such as cardiovascular and cerebrovascular diseases, while stroke is one of the most dangerous cardiovascular and cerebrovascular diseases. However, domestic and foreign studies on the relationship between the periodontitis, serum inflammatory factors and ischemic stroke are still in their infancy. There are few studies available, but most feature a small sample size of individual studies, many impact factors, and biased results. A professional merger analysis may draw a conclusion with higher credibility (Wilmore, 1991). On this basis, this study carries out a systematic and comprehensive electronic retrieval and manual search to acquire and systematically analyze the research data about the relationship between periodontitis and stroke, in order to explore this mysterious field. The serum high-sensitivity C-reactive protein, interleukin and the tumor necrosis factor are detected for a preliminary discussion on the relationship between the incidences of ischemic stroke and periodontitis and serum inflammatory factors so as to provide a theoretical basis for the

prevention and treatment of stroke and drive the further development of relevant fields.

## Methods

In accordance with the diagnostic code of WHO ischemic stroke, 23 cases of ischemic stroke patients, who are hospitalized in the Neurology Department of this hospital, 42 males and 56 females, at an average age of (278±10), are chosen. Exclusion criteria: progressive liver disease; severe infection at other sites; immune diseases; infectious diseases; kidney failure; diabetes; tumors. Additionally, 23 healthy cases (excluding those with a history of stroke) in the physical examination center of this hospital are chosen as the control group, 28 males and 32 females at an average age of (62±3).

Check the periodontal disease for relevant index and the missing teeth, respectively. Relevant indexes include: simplified oral hygiene (OHI-S), sulcus bleeding index (SBI), periodontal probing depth (PD), and adhesion level (AD). For all of these, fixed representative teeth 11, 16, 26, 36, 31, 46 are taken. All subjects should be examined by the one doctor. Specimen disposal: vacuum acquisition, fasting blood of patients in the morning (stroke group should have sampling done within 6 hours after morbidity), 4000r/min \* 8min centrifugation, serum separation, sealed at -20°C for inspection (no repeated freeze-and-thaw), generally examined within 4 months (Pickett *et al.*, 2010).

hs-CRP is examined by immunoturbidimetric assay with special protein instrument and supporting reagents and calibrators, mixed evenly and directly examined on the machine after rewarming of specimen. Interleukin and tumor necrosis factor use enzyme-linked immunosorbent assay (ELISA). MK2 enzyme-linked analyzer reads the value at 450nm, and automatically plots a curve to obtain the serum sample concentration. Color ultrasonography measures whether there is the formation of carotid atherosclerotic plaques and how carotid artery stenosis develops in each patient and recorded them.

Data is expressed as  $\bar{x} \pm s$ . The t-test is used for the intergroup comparison, and the  $\chi^2$  test for comparison of the rates. Calculate odds ratio (OR), 95% confidence interval (CI) and P value by one-way analysis of variance.



### Results and discussion

The incidence of periodontitis among experimental group reaches 63.4% (64/101) and 28.7% (29/101) among the control group. The difference has statistically significance ( $\chi^2=23.931, P<0.05$ ).

The results from test on the indexes of periodontal disease: there is a significant difference found in the oral health index (OHI-S), sulcus bleeding index (SBI), periodontal probing depth (PD), and loss of attachment level (AL) between the stroke group and the control group, as shown in Table 1. The number of missing teeth are (14.05±9.23) in the stroke group and (3.57±3.43) in the control group, there is a significant difference ( $u=8.25, P<0.01$ ). The rate of severe agomphiasis ( $\geq 10$ ) is 66.7% in the stroke group and 6.7% in the control group. There is a significant difference between the two groups ( $\chi^2=46.51, P<0.01$ ). According to one-way analysis of variance, the severe agomphiasis is strongly associated with ischemic stroke (Slade *et al.*, 1975).

**Table 1.** Comparison of periodontal disease indicators between stroke group and control group

Groups	n	OHI-S	SBI	PD (mm)	AL (mm)
Brain stroke group	60	1.89 ±0.65	2.88 ±0.60	3.71 ±1.49	3.10 ±2.26
Control group	60	1.09 ±0.21	2.37 ±0.32	2.58 ±0.37	0.16 ±0.39

Results from the test on serum inflammatory markers: There are significant differences in serum high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL-1 $\beta$ ) between the stroke group and the control group; while in serum tumor necrosis factor (TNF- $\alpha$ ), a statistical analysis shows that there is no significant difference between the two groups (Table 2).

**Table 2.** Comparison of serum inflammatory markers detected between stroke group and control group

Groups	n	hs-CRP	IL-1 $\beta$	TNF- $\alpha$
Brain stroke group	60	8.11±6.18	15.92±13.65	26.49±15.26
Control group	60	2.96±1.93	5.19±2.82	27.39±10.45

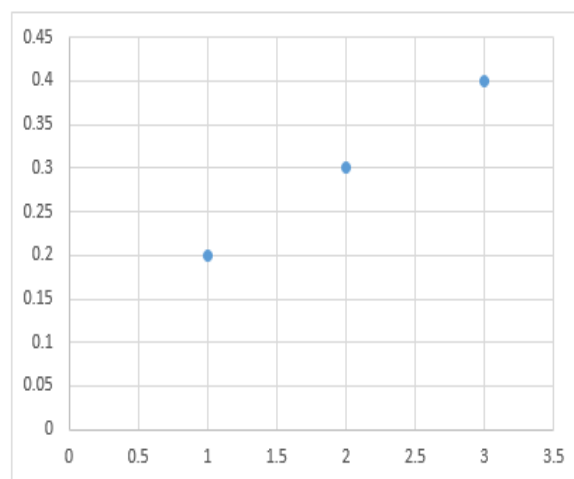
Results from test on carotid B-ultrasound: that the positive rate of carotid atherosclerosis plaque is 70.0% (42 cases) in the stroke group and 18.3% (cases) in the control group. There is a significant difference between the two groups ( $X^2 = 32.48, P<0.01$ ). The rate of severe agomphiasis ( $\geq 10$ ) is 58.9% in the cases who present positive carotid atherosclerotic plaque and 20.3% in the cases who present negative carotid atherosclerotic

plaque. There is a significant difference between the two groups, as shown in Table 3. According to the one-way analysis of variance, severe agomphiasis rate may be associated with carotid atherosclerosis in patients with periodontitis (OR=5.61, 95%).

The incidences of periodontitis in the two groups are studied. The funnel plot included in the study shows that the distribution of the studies is not completely symmetrical, but the difference between them is not significant. It is suggested that there is a little bias among the studies, possibly caused by different ages of patients ultimately included in the study, as shown in Fig. 1 (Sawecka *et al.*, 2003). The heterogeneity test is further conducted, the results are  $\chi^2=31.06, df=9, P=0.000, I^2=71\%>50\%$ , which indicates that there is heterogeneity among the groups.

**Table 3.** Comparison of carotid atherosclerotic plaque and tooth loss

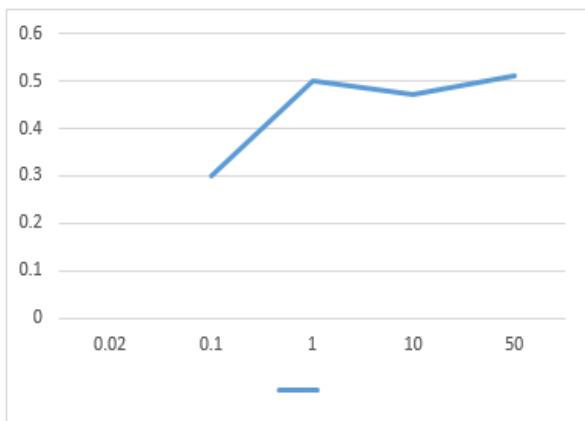
Groups	n	Severe tooth loss	X <sup>2</sup>	P
Positive group	51	30 (58.9%)	18.75	<0.01
Negative group	69	14 (20.3%)		



**Figure 1.** META analysis of patients with periodontitis

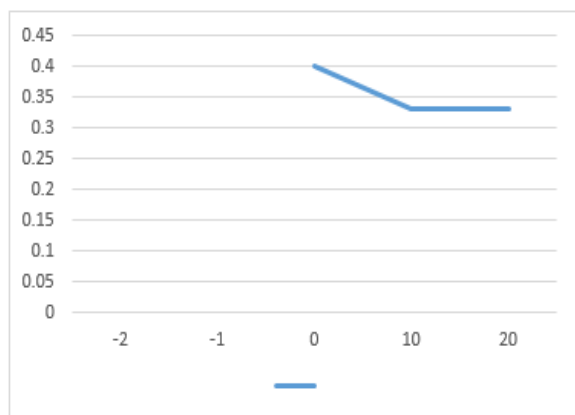
Clinical attachment loss: the CAL data is studied with the heterogeneity test results  $\chi^2=66.57, P<0.001<0.10, I^2=95\%>50\%$ . Use the random effect model for Meta analysis. The results from combined analysis show that the OR value is 1.25 and 95% CI is (0.50, 2.00), which implies that the periodontal CAL is significantly higher in stroke patients than in the control group. This difference has statistically significance ( $Z=3.27, P=0.001$ ). It is suggested that the incidence of stroke is closely associated with the severity of periodontitis, see Fig. 2.





**Figure 2.** Loss of clinical attachment

Plaque Index: the plaque index of the study subjects is tested. After the heterogeneity test,  $X^2=66.57$ ,  $P<0.001<0.10$ ,  $I^2=90\%>50\%$ . A random effect model runs for Meta analysis. The combined analysis shows that the OR value is 0.32, and 95% CI is (0.11, 0.54), which suggests that the oral hygiene of patients with stroke is worse than that of the control group ( $Z=2.92$ ,  $P=0.004$ ). It is therefore confirmed that the onset of stroke is closely associated with the situation of oral hygiene, as shown in Fig. 3.



**Figure 3.** Distribution of plaque index

### Conclusions

Stroke is a disturbance of cerebrovascular circulation that suddenly occurs and poses severe threaten to the health of middle-aged and elderly people over 50. It has extremely high disability rate and lethality. At present, as the onset age tends to younger people, the incidence is also increasing. According to statistics, there are more than 1.5 million new cases of stroke each year in the country. In clinical practices, stroke includes ischemic and hemorrhagic types. Atherosclerosis is the most common pathogen of ischemic stroke.

In recent years, the intensive study of the pathogenesis of atherosclerosis has found that inflammation is an important factor in the development of atherosclerosis.

Periodontitis is a chronic inflammation process in which periodontal pathogens temporarily invade the blood by ways of brushing teeth, chewing, and periodontal treatment, thus causing bacteremia and inducing body immunity responses (Wilmore, 1991). A large number of epidemiological and clinical studies have discovered that periodontitis as a risk factor is associated with ischemic stroke. However, due to differences in experimental design and study means, many scholars still hold different opinions on the exact relationship between ischemic stroke and periodontitis, for example, it is so far unclear whether periodontitis is an independent risk factor that induces ischemic stroke. The results of this study reveal that the incidence of periodontitis in the experimental group of ischemic stroke is 63.4% (64/101), significantly higher than the 28.7% in the control group (29/101). The difference is statistically significant ( $P<0.05$ ) and coincides with the relevant literature. This study has found that hs-CRP, IL-1 $\beta$ , and TNF- $\alpha$  in the ischemic stroke group are significantly higher than those in the control group ( $P<0.05$ ) with a statistical significance, which suggests that ischemic stroke may be associated with hs-CRP, IL-1 $\beta$ , TNF- $\alpha$ . The results in this study also show that the level of serum inflammatory factors has a positively correlation with the incidence of periodontitis in the experimental group. It is also suggested that increases of serum hs-CRP, IL-1 $\beta$  and TNF- $\alpha$  may be an important pathophysiological basis for the development and progression of ischemic stroke. As above, the incidence of periodontitis in patients with ischemic stroke is significantly higher than that in the control group. The chronic inflammation process of periodontal disease can change the levels of hs-CRP, IL-1 $\beta$  and TNF- $\alpha$ , and promote the morbidity and development of ischemic stroke. Since the periodontitis and ischemic stroke are diseases subjected to multi-factors, the relationship between ischemic stroke and periodontitis still needs to be further studied.

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