The Relationship Between Severity of Periodontitis with the Degree of Atherosclerosis in Ischemic Stroke Patients

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ABSTRACT

Background: Periodontal diseases affect up to 80% of the global population. Periodontitis is a long-term inflammatory disease that affects the soft and hard tissues around the teeth. It may also play a role in the pathogenesis of atheroma formation and is associated with cerebrovascular disease. The Carotid Intima Media Thickness (CIMT) is a good marker for detecting early and progressive atherosclerosis. Several hypotheses link chronic infectious diseases, including periodontal tissue disease, to the atherosclerosis process and are risk factors for stroke.

Objective: To determine the relationship between the severity of periodontitis and the degree of atherosclerosis in ischemic stroke.

Methods: This is an analytic observational study with a case-control approach. Subjects were ischemic stroke patients with inclusion criteria. Analyzed the severity of periodontitis with Miller’s Mobility Index (MMI), the degree of progression of atherosclerosis assessed by measuring the CIMT using an ultrasound device or B mode to detect the presence and progression of atherosclerosis.

Results: 54 subjects with a mean age were 63.43 ± 7.19 years, and the dominant sex was male. There was a significant relationship between severity of periodontitis (P: 0.011, OR: 3.425, CI 95% 1.332-8.807) and type of profile lipid triglyceride (P: 0.027, OR: 6.840, CI 95% 1.242-37.676) to Carotid intima media thickness.

Conclusion: There is an association between the severity of periodontitis and the degree of atherosclerosis. Severe periodontitis is related to the increases of CIMT, which is a marker of atherosclerosis, a risk factor for stroke.

Keywords:
Ischemic stroke, Atherosclerosis, Periodontitis, Miller’s Mobility Index, Carotid Intima Media Thickness

1. Introduction

Stroke is cerebrovascular with a background of atherosclerosis, the second cause of death and disability worldwide; stroke deaths accounted for 11.8% of total deaths worldwide. Prevalence in 2015 was 24.9 million, and the incidence in 2010, there were an estimated 11.6 million events of incident ischemic stroke. Basic health research of the Indonesia Ministry of Health, the incidence of stroke increased from 7% in 2013 to 11% in 2018 and showed a continuous increase in incidence, disability, nor death. The incidence of ischemic stroke is 80-85% of all strokes. Risk factors for cerebrovascular disease include smoking, diabetes mellitus, obesity, hypercholesterolemia, and hypertension. Currently, there is an increasing number of studies about the effects of oral health and atherosclerosis, which are then associated with cerebrovascular disease. Several studies have shown an association between chronic infectious diseases, including periodontal tissue disease, and risk factors for stroke. Sen Sauvik et al. show that periodontal disease is an independent risk factor for incident ischemic stroke. It is highly prevalent among adults worldwide and is an important public health problem, where important risk factors profiles in the United States show male sex, current cigarette smoking, and diabetes mellitus are important risk factors for periodontal disease.

Periodontitis is associated with an increase in systemic inflammation markers, and the contribution of periodontitis to ischemic stroke risk may be indirectly mediate by inflammatory mechanisms.
Chronic periodontal infection contributes to systemic inflammation characterized by the elevation of acute-phase proteins, including inflammatory cytokines such as IL-6, coagulation factors such as fibrinogen, and CRP 8. The mechanism periodontitis as a chronic infection promotes atherosclerosis, by resulting in subendothelial deposition of cholesterol, cholesterol esters, and calcium within the vessel walls can form the unstable atherosclerotic plaques that are prone to rupture have a thin fibrous cap, a large lipid core, few smooth muscle cells, and are rich in macrophages. Rupture of the atherosclerotic plaques releases debris and thrombi that may travel distally, resulting in distal embolization and stroke.9 Atherosclerotic expresses inflammatory markers such as C-Reactive Protein (CRP) and can provoke arterial wall thickening, which can be evaluated using Doppler ultrasound. The hypothesis was that periodontitis would relate to increasing IMT because periodontal pathogens colonizing atherosclerotic plaques can be observed throughout the circulatory system.9,10

Atherosclerosis is a chronic progressive inflammatory disease that often begins early in life with impairment of endothelial function, which leads to the formation of lesions in large and medium elastic and muscular arteries related with a multifactorial cause. It is caused by the accumulation of fat in the intima lining of the blood walls, infiltration of mononuclear cells or monocytes, and proliferation of vascular smooth muscle cells (VSMC). The disease process is dynamic and is associated with remodelling of the arterial wall, with the appearance of fatty streaks, which are precursor abnormalities of the atheromatous plaques that normally appear at more advanced ages.8,10,15

Atherosclerotic plaques can progress to significant stenosis after many years of silent development. In the final stages, they can become unstable and progress to rupture, exposing the sub endothelial layer, which contains lipids, collagen, and elastin, and the possibility of thrombus formation, which tends to be the final acute event in the majority of cases of obstructive AD.10,16

Risk factors for cerebrovascular disease include smoking, diabetes mellitus, obesity, hypercholesterolemia, and hypertension. There is currently increasing attention to research on the effects of oral health and atherosclerosis associated with cerebrovascular disease. Currently, there is an increasing number of developments regarding the effects of oral health and atherosclerosis, which in turn are associated with cerebrovascular disease, where several studies have shown an association between chronic infectious diseases, including periodontitis, as a risk factor for stroke.10,20

**Literature Review**

Periodontal disease is a chronic inflammation that results from the activity of altered oral microbiome leading to altered immune reaction, destruction of tissues supporting the teeth, and oral bone loss. Inflammatory reactions lead to the destruction of the gingiva and connective tissues, and, in particular, alveolar bone loss, if left untreated, it ultimately leads to tooth loss. The most common definition which used two criteria was the CDC/AAP working group, published in 2007 for moderate and severe used Clinical attachment level /CAL ≥ 4mm and PD ≥ 5mm in at least two proximal sites (not on the same tooth) for severe chronic periodontitis and CAL≥ 6mm in at least two interproximal sites (not on the same tooth) and PD ≥ 5mm in at least one site for severe chronic periodontitis. Definition for mild periodontitis in 2012, which was CAL≥ 3mm and PD ≥ 4mm in at least two interproximal sites (not on the same tooth) or one site with PD ≥ 5mm. Miller's mobility index (MMI) is the most widely accepted method for routine clinical examinations of tooth mobility; It was defined as severe periodontitis, the AUC value for MMI was 0.72. It may provide valuable information for diagnosing moderate and severe periodontitis when CAL is not obtainable during routine practice.10,11,12

Periodontitis is associated with an increased risk for cerebrovascular diseases through systemic inflammation as the most important etiopathogenetic link, and the potential biology underlying includes indirect and direct mechanisms. It is associated with both local and systemic inflammation, similarly associated with increased systemic inflammatory markers, including CRP, tumor necrosis factor-alfa, IL-1, IL-6, and IL-8, and cellular activation involving cellular adhesion molecules toll-like receptors, matrix metalloproteinase, and nuclear factor-kB activation. CRP predicts future vascular events, including MI, stroke, peripheral arterial disease, and sudden cardiac death.8

Indirect mechanism when the mediators are inflammatory cytokines produced by the gingival cells as the host response to bacterial insult, and higher levels of host-originated enzymes, cytokines, proteases, and Abs can be measured in saliva periodontitis patients compared with periodontally healthy controls. Matrix metalloproteinase (MMP)-8 or collagenase-2 is a catalytically complement endoprotease that can decisively process extracellular matrix components and non-matrix bioactive substrates, causing tissue destruction and modulation of immune responses in saliva and other oral fluids is regarded as a good biomarker of periodontitis, and in serum of systemic inflammation, myeloperoxidase
(MPO), by producing hypochloric acid can oxidatively activate latent MMP-8. IL-1b can regulate the expression of MMP-8, MPO, and tissue inhibitor of matrix metalloproteinase (TIMP)-1 by inflammatory and resident cells. 

Direct Mechanisms by the bacteremia and vascular infection by periodontal pathogens, where oral microbes and their products can gain systemic access via the circulatory system. In Adults harbor more than a billion bacteria in their mouths, although the flora varies in different oral regions, the area of greatest potential relevance to atherosclerosis is the periodontal pocket, from there, periodontal organisms circulate in the blood-stream either within phagocytic cells or extracellularly and subsequently are deposited in an atheromatous plaque.

Finally, periodontitis causes an increase in the systemic inflammatory response, which has been implicated in atherosclerosis and cerebrovascular diseases, resulting from a complex interplay between chronic bacterial infection and the inflammatory host response, leading to irreversible destruction of tooth-supporting tissues, with tooth loss as a common endpoint.

The resulting interplay between endothelium, monocytes, and platelets might be proatherogenic, contributing indirectly to atherogenesis or adverse cerebrovascular outcomes related to atheromatous plaque rupture in subjects with periodontitis. The inflammatory process is part of the pathophysiology of atherosclerosis and includes the initial process to development and finally to the final phase in the form of inflammatory changes that occur when arteries can only identify arterial stenosis if the lumen area is reduced by at least 40–50%.

The marker for atherosclerosis is the thickness of the intima-media tunica (IMT) of the carotid arteries, an early sign of atherosclerosis, and a general reflection of atherosclerosis, including intracranial atherosclerosis. IMT is a surrogate marker for atherosclerosis burden as well as cardiovascular disease risk assessment. FDA has approved IMT as a surrogate marker of atherosclerotic disease for application in clinical trials; however, the addition of IMT assessment to prevention guidelines is still under discussion. Carotid Intima Media Thickness (CIMT) is defined as the area of tissue starting at the luminal-intimal interface and the media-adventitia interface of CCA, as the double-line pattern visualized by B-mode vascular ultrasound formed by two parallel echogenic lines representing a junction of the vessel lumen. Colour Doppler ultrasonography is a safe, non-invasive, and cost-effective measure of heterogeneity that can aid in detecting the morphological changes that occur when arteries can only identify arterial stenosis if the lumen area is reduced by at least 40–50%.

The common carotid IMT >0.8 mm and an internal carotid IMT >0.9 mm increases vascular disturbance. For every 0.2 mm increase in the common carotid BMI, an increase in disease risk is 27%, and for every 0.55 mm increase in internal carotid IMT, there is a 30% increase in risk with age. The common carotid increases by an average of 0.04–0.05 mm per year. The diagnosis of carotid artery occlusion is based on the detection of a thrombus filling the lumen, absence of motion of the artery wall, and an accurate visualized flow signal. Assessment of carotid IMT and plaque is also used to predict ischemic cerebrovascular events.

The association between periodontal disease and increased CIMT has been described only in the middle-aged to the elderly population with chronic/adult periodontitis. Research is currently being conducted to study the relationship between severe periodontitis and subclinical atherosclerosis in systemically healthy young individuals in the age range of 20–40 years. Several studies have revealed a relationship between periodontitis and the thickness of the tunica intima. Lingeshwaran et al. examined the degree of periodontitis that was then evaluated by bilateral CIMT ultrasound at the carotid artery level; there was an association of severe periodontitis with subclinical atherosclerosis.

2. Methods

This is Neurological research at Dr. Kariadi Hospital from February 2020 to completion, an
analytic observational study with a case-control approach.

In this study, the subjects were 54 patients with acute ischemic stroke admitted to Dr. Kariadi Hospital, Semarang, who were included in the inclusion criteria. The dependent variable is the severity of periodontitis, and the independent variable is the degree of arteriosclerosis. Subjects were assessed for the degree of periodontitis using Miller's Mobility Index (MMI), and the degree of atherosclerosis was measured by assessing the thickness of the intima through Color Doppler ultrasonography.

The tooth is held between the metallic handles of two instruments and moved in the buccolingual or buccopalatal direction. The moved distance is visually estimated by the person conducting the examination. Mobility is then classified into Grades 0-3 (0 = no periodontitis, 1 = mild, 2 = moderate, 3 = severe). Although special devices such as periodontometer can be used to obtain quantitative measurements of tooth mobility, the operation of such devices is complicated and time-consuming.11

Carotid Intima Media Thickness (CIMT) measured by Color Doppler ultrasonography ‘B-mode’, patient in a supine position, and the point of measurement was taken 1 cm proximal to the carotid bulb at the site of maximum thickness, avoiding the plaque area. The ultrasound machine used had a sensitivity range of 0.1 mm; that is, each division was equivalent to 0.1 mm. 15, 21, 22

Bivariate analysis was done to determine the correlation between variables. Data on a numerical scale was tested for the Shapiro-Wilk normality. The association hypothesis test between the severity of periodontitis and CIMT normal data distribution was carried out by the Chi-square test.

### Results

The demographic characteristics of research subjects are statistically descriptive.

#### Table 1. Characteristics of research subjects

| Variable          | F   | %   | Mean ± SD | Median (min-max) |
|-------------------|-----|-----|-----------|------------------|
| **Gender**        |     |     |           |                  |
| Male              | 33  | 61,1|           |                  |
| Women             | 21  | 38,9|           |                  |
| **Age**           |     |     | 63,43 ± 7,19 | 64 (38 – 77)     |
| **Education**     |     |     |           |                  |
| Elementary        | 19  | 35,2|           |                  |
| Junior High       | 11  | 20,4|           |                  |
| Senior High       | 14  | 25,9|           |                  |
| **Blood pressure**|     |     |           |                  |
| HT St I           | 11  | 20,4|           |                  |
| HT St II          | 43  | 79,6|           |                  |
| **BMI**           |     |     | 24,15 ± 2,63 | 24,22 (19,5 – 29,1) |
| Normal            | 28  | 51,9|           |                  |
| Overweight        | 24  | 44,4|           |                  |
| Obesity           | 2   | 3,7 |           |                  |
| **HbA1c**         |     |     | 6,76 ± 1,23 | 7,6 (4 – 9,1)    |
| **DM type II**    | 30  | 55,6|           |                  |
| Not               | 24  | 44,4|           |                  |
| **Total Cholesterol** |   |    | 158,31 ± 74,07 | 135,5 (77 – 299) |
| Low               | 39  | 72,2|           |                  |
| High              | 15  | 27,8|           |                  |
| **Triglyceride**  |     |     | 127,43 ± 88,59 | 96 (13 – 416)    |
| Low               | 42  | 77,8|           |                  |
| High              | 12  | 22,2|           |                  |
| **HDL Cholesterol** | |    | 50,02 ± 21,89 | 52,5 (12 – 97)   |
| Low               | 19  | 35,2|           |                  |
| High              | 35  | 64,8|           |                  |
| **LDL Cholesterol** | |    | 131,83 ± 80,19 | 95 (26 – 276)    |
| Low               | 37  | 68,5|           |                  |
| High              | 17  | 31,5|           |                  |
| **Uric Acid**     |     |     | 5,45 ± 5,25 (2,9 – 13,4) | 5,25 (2,9 – 13,4) |
| Low               | 45  | 83,3|           |                  |
| High              | 9   | 16,7|           |                  |
| **Infarct Area**  |     |     |           |                  |
| Lakunar           | 23  | 42,6|           |                  |
| Teritori          | 31  | 57,4|           |                  |
| **NIHSS**         |     |     | 7,72 ± 3,63 | 8 (3 – 18)       |
| Mild              | 17  | 31,5|           |                  |
| Moderate          | 37  | 68,5|           |                  |
| **MMI**           |     |     |           |                  |
| Mild              | 10  | 18,5|           |                  |
| Moderate          | 16  | 29,6|           |                  |
| Severe            | 28  | 51,9|           |                  |
| **CIMT**          |     |     | 0,74 ± 0,19 | 0,78 (0,37 – 1,16) |
| < 0,8 mm          | 32  | 59,3|           |                  |
| > 0,8 mm          | 22  | 40,7|           |                  |
Table 1 shows there were 54 research subjects who entered the inclusion criteria, 33 (61.1%) were male, 43 (79.6%) were female. Clinically, periodontitis severity consists of 3 degrees, mild defined as the MMI was 1, moderate was two, and severe if MMI was 3. The degree of atherosclerosis was measured by CIMT, which increases if the thickness >0.8 mm, and clinically caused risk factors for cerebrovascular diseases, including ischemic stroke.

Table 2 shows the different risk factors of stroke-related to the severity of periodontitis and CIMT.

Based on the above results, there is a different risk factor of stroke (age, gender, HT, BMI, DM type II, Profile lipid, uric acid) related to clinical feature (NIHSS and infarction area) based on the severity of periodontitis and CIMT.

Table 3 shows a relationship between severity of periodontitis and type of profile lipid triglyceride to CIMT.
Based on the above results, there is a significant relationship between severity of periodontitis (P : 0.011, OR : 3.425, CI 95% 1.332-8.807) and type of profil lipid trygliceride (P : 0.027, OR : 6.840, CI 95% 1.242-37.676) to CIMT.

4. Discussion

The aim of the study is to determine the relationship between the severity of periodontitis and the degree of atherosclerosis in ischemic stroke patients. The independent variable in this study was the severity of periodontitis associated with carotid tunica intima thickness as a marker of atherosclerosis and related to cerebrovascular diseases, including stroke.

In our study, the mean Carotid Intima Media Thickness (CIMT) was 0.74 ± 0.19. Raised CIMT (>0.8mm) was found in 32 (59.3%), 11 (20.37% of all subjects) were male with severe periodontitis and CIMT > 0.8 with a mean age 62.3 ± 8.6 (P 0.834). We found 13 subjects with a history of hypertension (24.07; P: 0.643) and 13 subjects with type II diabetes (24.07%, P: 0.17). No history of alcohol, and history of smoking were 5 subjects, where 4 subjects had severe periodontitis (CIMT < 0.8 = 1, CIMT > 0.8 = 3, with P: 0.417). Subjects with st II had the highest degree of severe periodontitis with CIMT > 0.8, and there are 14 subjects (25.9% P: 0.786).

This is in accordance with the research of Savena Yogehs et al.; a case-control study was performed on 163 diagnosed cases of first-time ischemic stroke with increasing age along with the history of hypertension and right CIMT (OR >7), presence of plaque (OR 6.3) and daily smoking (OR 5.1) are also significant risk factors. CIMT is significantly related to the daily alcohol and smoking intake and the presence of plaques.21

The risk factor, especially diabetes, social status, and smoking, are common to the onset of ischaemic stroke and periodontitis. These factors need to be considered as confounding factors in the calculation of adjusted RR or HR values. In Jimenez et al., the HR values slightly decreased after adjustment (smoking index, cholesterol, hypertension, diabetes) but were still significant. The crude HR was 3.98 (1.83–8.63), and the adjusted HR was 3.52 (1.59–7.81). This indicates that periodontitis can be considered an independent risk factor for stroke. Previous studies have clearly shown that smoking increases the risk of both periodontitis and ischaemic stroke. In this field, it can be noticed that in Joshipura et al., the multivariate-adjusted HR value was higher for patients who were regular smokers at baseline (HR 1.67, 95% CI 1.26–2.23) than for non-smokers (HR 0.61, 95% CI 0.34–1.12).23

In this research, a total of 24 overweight patients, 15 with severe periodontitis, did not differ for CIMT. Most of the type II DM patients had a degree of severe periodontitis (22 & CIMT <0.8 and 25.9 & CIMT > 0.8). Only 15 subjects (27.0%) were patients with high total cholesterol, 12 subjects (22.0%) with hypertriglyceridemia low HDL 19 (35.1%) and high LDL 17 (0.31%). From the lipid profile, only triglycerides were significantly associated with CIMT values, while total cholesterol, LDL, and HDL values were associated but not significant.

This is similar to Praliya R.S et al a case-control study, suggest that Type-2 DM is associated with raised CIMT values, raised CIMT (>0.8mm) was found in 14(46.7%) in diabetic patients as compared to 3 (10%) in healthy, and positively significant related to Cholesterol total (r=0.741, p-value <0.05), LDL-C (r =0.624, p-value <0.05), and triglyceride level (r=0.588, p-value <0.05) 24.

From many kinds of literature, we know that dyslipidemia is an essential factor for atherosclerosis that has been shown to be associated with CIMT. Regression analysis demonstrated that the mean and maximum CIMT (CIMT[max]) are independently influenced by age, blood creatinine levels, and non-high-density lipoprotein (HDL) cholesterol levels.16

The association between triglycerides and cerebrovascular risk is well established from epidemiological studies, genome analyses, and Mendelian randomization studies. The American Heart Association has recognized triglycerides as an important biomarker of CV disease risk. However, randomized controlled clinical trials of therapies that primarily lower triglyceride levels have not consistently shown a reduction in major vascular events. Moreover, triglycerides per se may not be atherogenic but rather may be a marker for the concentration of atherogenic very-low-density lipoprotein (VLDL), so that further research is needed. 25

The Infarct area was related to the severity of periodontitis and CIMT but not significant (p: 0.184). Likewise, the severity of stroke assessed by the NIHSS, the associated fire was not significant (P: 0.022). Stroke severity assessed
by the NIHSS, influenced by many factors, including infarct area and presence of collaterals, is challenging to measure. So it requires more in-depth research, which can assess these factors.

The limitation of this study is that the subjects of this study are ischemic stroke, and we do not exclude according to the clinical severity. Carotid intima media thickness measurements were only once a time of; it is more meaningful to know the increase in CIMT if done serially. And we did not look at any other stroke risk factor values previously.

5. Conclusion

There is a significant association between the severity of periodontitis and the degree of atherosclerosis. Severe periodontitis is related to the increases of carotid intima media thickness (CIMT), which is a marker of the degree of atherosclerosis so that it becomes a risk factor for stroke.

Ethical Approval

The ethical approval for this study was issued by the Health Research Ethics Committee of Medical Faculty Diponegoro University No. 272 / EC / KEPK / RSDK / 2019

Conflicts of Interest

There is no conflict of interest.

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All financial resources are borne by the researcher

Author Contribution

In this research conceptualization, writing preparation of the original draft supported by Rethmaningsih, Iva Puspitasari, Renaldi, validation; formal analysis, investigation, data curation supported by Dodik Tugasworo, Jimmy Eko Budi Hartono, Methodology, writing-reviewing, and editing supported by Amin Husni and Maria Belladonna,

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