Association of Periodontitis and Arterial Stiffness in Type 2 Diabetic Patients

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ABSTRAK

Latar belakang: *periodontitis merupakan penyebab utama infeksi kronis pada pasien diabetes. Pasien diabetes memiliki risiko mengalami penyakit kardiovaskular empat kali lipat. Inflamasi kronis yang disebabkan oleh periodontitis merupakan faktor risiko kardiovaskular baru (non-tradisional) dan telah dikenal luas memiliki peran penting dalam aterogenesis. Pada subyek tanpa diabetes, didapatkan hubungan antara periodontitis dan kekakuan arteri; namun, hasil ini masih belum konsisten pada pasien diabetes. Tidak ada penelitian sebelumnya yang meneliti proporsi periodontitis maupun hubungannya dengan kekakuan arteri pada populasi pasien dengan diabetes tipe 2 di Indonesia.* ***Metode:*** *penelitian ini merupakan penelitian potong lintang yang melibatkan 97 pasien dengan diabetes tipe 2 yang datang ke klinik endokrinologi antara bulan April hingga bulan Agustus 2017. Periodontitis diukur berdasarkan kedalaman kantong (pocket depth), kehilangan perlekatan klinis (clinical attachment loss) dan perdarahan dengan melakukan pelacakan (probing) oleh ahli periodonti. Kecepatan gelombang nadi arteri karotis dan femoris (Carotid-femoral PWV) diukur dengan menggunakan alat SphygmoCor Xcel melalui teknik tonometri bantalan (cuff-based tonometry).* ***Hasil:*** *periodontitis ditemukan pada 99% pasien diabetes tipe 2 dan 78% di antaranya mengalami periodontitis berat. Tidak ada korelasi yang bermakna antara kedalaman kantong dan clinical attachment loss dengan cfPWV (r=0,024, p=0,407 and r=0,011, p=0,456). Sementara itu, terdapat korelasi positif antara kedalaman kantong dan PWV (r=0,294, p=0,041) pada pasien diabetes tipe 2 yang terkontrol dengan baik.* ***Kesimpulan:*** *sebagian besar pasien diabetes tipe 2 mengalami periodontitis berat, tetapi korelasi antara periodontitis dan kekakuan arteri tidak dapat disimpulkan dari penelitian ini.*

Kata kunci: *periodontitis, kedalaman kantong, kehilangan perlekatan klinis, kecepatan gelombang nadi (PWV).*

ABSTRACT

Background: *periodontitis is a major cause of chronic infection in diabetic patients. Diabetic patients have four-fold risk of having cardiovascular disease. Chronic inflammation caused by periodontitis, a non-traditional cardiovascular risk factor is widely known to play a major role in atherogenesis. Among non-diabetics, an association has been found between periodontitis and arterial stiffness, but in diabetic patients the result is inconsistent. No study has investigated either the proportion of periodontitis or its correlation with arterial stiffness in type 2 diabetes population in Indonesia.* ***Methods:*** *this study was a cross-sectional study involving 97 patients with type 2 diabetics, who were recruited on Endocrinology Clinic from April to August*

2017. Periodontitis was measured for pocket depth, clinical attachment loss and bleeding on probing by a periodontist. Carotid-femoral PWV (Pulse Wave Velocity) was measured using SphygmoCor Xcel with cuff-based tonometry technique. ***Results:*** *periodontitis was found in 99% type 2 diabetic subjects and 78% of them had severe periodontitis. There was no significant correlation found between pocket depth, clinical attachment loss and cfPWV (r=0.024, p=0.407 and r=0.011, p=0.456); whereas there was a weak positive correlation between pocket depth and PWV (r=0.294, p=0.041) in well-controlled type 2 diabetics.* ***Conclusion:*** *most of type-2 diabetics had severe periodontitis; however, the correlation between periodontitis and arterial stiffness could not be concluded in this study.*

Keywords: *periodontitis, pocket depth, clinical attachment loss, pulse wave velocity (PWV).*

INTRODUCTION

Periodontitis is the most common cause of chronic infection in diabetes worldwide and in Indonesia.[1-4] The relationship between diabetes and periodontitis is working both ways. Diabetes is known as a predisposing factor for developing periodontitis; while periodontitis may contribute to metabolic control derangement in diabetes. Mechanisms underlying this relationship involve biofilm formation and defective immune system. Oral plaque may form biofilm of Gram-negative bacteria that induce activation of specific and non-specific immune system.[5] Meanwhile in diabetes, immune system defects occur in all phase of inflammation. In diabetes, there is a down regulation of ICAM-1 and AGE-mediated crosslink disruption, which lead to PMN adhesion and chemotaxis disturbance. AGE also may disrupt interaction between leucocytes and endothelial cells.[6] Hyper-reactivity of monocytes after LPS exposure and AGE-mediated activation of Nf-kB results in increment of pro-inflammatory cytokine production in diabetes.[7] This abundant cytokine production may lead to premature apoptosis of PMNs and forbidding their bacterial killing ability. Loss of bacterial killing activity combined with abundant pro-inflammatory cytokine production cause extensive destruction of periodontal tissue and alveolar bone.

Oral endotoxin, bacteria and pro-inflammatory cytokine may leak into systemic circulation when severe destruction of periodontal tissue occurs or during oral hygiene procedure such as tooth brushing, scaling and even with gentle mastication. This leak can cause low-grade systemic inflammation that may play a role in inducing atherogenesis. Continuous inflammation will lead to lack of elastin production and increased production of collagen due to activation of fibroblasts. In addition, the matrix metalloproteinase (MMP) enzyme produced by activation of neutrophils and macrophages will degrade the vascular extracellular matrix which results in weakened collagen crosslinking and impairing elastin. Both of the above mechanisms are accompanied by endothelial impairment due to ROS contributing to the role in decreasing vascular distensibility, which is the initial stage of atherosclerosis. In compliant blood vessel, which has high shear stress, the endothelium will produce nitrite oxide (NO) a vasodilator agent.[8] Whereas low shear stress condition, which occurs in rigid arteries, will lead to endothelial dysfunction that may play a role in atherosclerosis initiation.[9] This increased inflammatory burden may exacerbate cardiovascular risk of type 2 diabetes patients with chronic infection such as periodontitis.

Periodontitis has been shown to be associated with clinically proven atherosclerosis and has a role in increasing cardiovascular risk.[10–12] This data is supported by a study, which shows that non-surgical periodontal management plays a role in improving the progression of atherosclerosis.[13] Several studies have attempted to link periodontitis with subclinical atherosclerosis, which is assessed by some surrogate marker modalities; however, the results are different in each study. Subclinical atherosclerosis can be measured by structural parameter such as carotid intima media thickness or by functional parameter. In general population, there is a linear relationship between the

severity of periodontitis and the increase in the thickness of tunica intima media.[14–16] These data are supported by reports of improvement of carotid thickness after periodontal treatment. On the other hand, studies using subclinical atherosclerotic functional parameters showed contradictory results.[14,16-18] Our study aimed to investigate the relationship between periodontitis and arterial stiffness measured by carotid femoral PWV (Pulse Wave Velocity) in type-2 diabetes population.

METHODS

Our study was a cross-sectional study involving 97 subjects. All of the subjects were recruited at an Endocrinology Outpatient Clinic between April and August 2017. The study protocol had been approved by an appropriate Ethics Commission under the number of 130/UN2.F1/ETIK/2017. The inclusion criteria were type-2 diabetic patients who were above 18 years old. Patients with history of cerebro-cardio-vascular diseases, autoimmune diseases, gestational diabetes, recent antimicrobial consumption and who had ongoing infection were excluded from the study to prevent bias from other sources of inflammation. All participants agreed to participate in our study and had signed the informed consent form before all examinations were performed. All subjects were interviewed to obtain basic medical history such as duration of diabetes, diabetes complications, comorbidities and medications. The height, weight and office blood pressure were measured. The laboratory tests, pulse wave velocity (PWV) measurement and periodontal examination were conducted in the same day.

Laboratory Measurement

Laboratory examination included measurement of quantitative c-reactive protein (CRP), which was considered as a sign of systemic inflammation and HbA1C. HbA1c measurement was performed using NGSP-certified high-performance liquid chromatography method and CRP measurement was done using ELISA technique.

Arterial Stiffness Measurement

Cuff-based tonometry technique using a device, SphygmoCor Xcel was used to measure arterial stiffness in this study. The measurement was conducted in a temperature-controlled room (20^{o}c) and all of the subjects had adequate rest for minimum 10 minutes before they proceeded to the measurement. During the measurement, all of the subjects were advised to remain still and refrain themselves from talking. Patients laid in supine position and femoral cuff was placed on their left leg with its lower border 5 cm above the upper border of the patella. PWV was calculated from the measurement of the pulse transit time generated using a cuff-based device placed between femoral and carotid artery (carotid-femoral PWV).

Periodontal Measurement

Periodontal examination was conducted by a certified periodontist. All participants underwent full-mouth examination. Periodontal probe used in this study was Aesculap® DB874R periodontal probe. Periodontal parameters used in this study included pocket depth (PD), clinical loss attachment (CAL), bleeding on probing (BOP) and plaque index (PI). Pocket depth was defined as the distance between gingival margin and the base of pocket measured by periodontal probe. Clinical loss attachment was measured using one fixed reference point (cemento-enamel junction). Both CAL and PD were recorded in millimeter (mm). The CAL and PD scores were based on maximum CAL and PD after full-mouth examination. Bleeding on probing were measured according to Saxer and Muhlemann[19] Classification. The final BOP score was the total score divided by the number of site examined. Oral hygiene was measured using plaque index according to Sillness and Loe.[19] The final score was the total score divided by the number of sites examined. All subjects were classified based on their CAL according to American Academy of Periodontology 1999 Criteria: (1) CAL of 1-2 mm: mild periodontitis, (2) 3-4 mm: moderate periodontitis and (3) CAL >5 mm: severe periodontitis.

Statistical Analysis

The obtained data were processed with statistical analysis using SPSS software program version 21.0. Descriptive statistic was conducted to obtain the baseline characteristics of the study

subjects including age, sex, duration of diabetes, HbA1c values, and quantitative CRP level. Goodness-to-fit test (Kolmogorov-Smirnov) was performed to acquire data distribution. All variables were not normally distributed and logarithmic transformation failed to normalize the data. Further statistical analysis in this study was done using non-parametric test.

Baseline characteristics were presented based on periodontitis severity, which were expressed in median (interquartile range/IQR) for numeric data and percentage (%) for nominal data. Correlation between PD and PWV as well as correlation between CAL and PWV were analyzed using Spearman Correlation Test. The interaction among other variables that were thought to interfere with the association including HbA1C level, hypertension and age could not be assessed using multivariate analysis because all variables were not normally distributed and transformation failed to normalize the data. Therefore, stratification analysis or by subgroup analysis based on HbA1c level, hypertension and age were performed to analyze correlation between PD and CAL; with PWV based on metabolic control, hypertension and age.

In subgroup analysis, HbA1C level was categorized as well-controlled and poor controlled level using a cut-off point of 7% HbA1c target. Hypertension was classified by the presence of hypertension in medical history, which was defined as objective proof of hypertension during blood pressure measurement or the patient was currently taking anti-hypertension drugs. As with age, the subjects were divided into two groups, i.e. those under 50 years and those above 50 years. The age of fifty years was used as a cut-off point since the significant change of arterial stiffness starts at the age of 50 years old in normal population.[20]

RESULTS

A total of 97 subjects were included in the study. Baseline characteristic of this study are summarized in **Table 1**. Female participants were comprised more than two-third of total participants. The median age of the subjects in this study was 51 years with an age range of 24 to 59 years. Most of the participants had severe periodontitis (75.3%) and generalized disease (71.2%).

Table 1. Baseline characteristic of the study

Variables	Values
Gender, n (%)	
- Male	29 (29.9)
- Female	68 (70.1)
Age (years), median (IQR)	51 (44.5 – 55.0)
BMI (kg/m^2), mean (SD)	26.6 (4.17)
Duration of Diabetes (years), median (IQR)	6 (4 – 12)
Periodontitis, n (%)	
- None	1 (1.0)
- Mild Periodontitis	7 (7.2)
- Moderate Periodontitis	16 (16.5)
- Severe Periodontitis	73 (75.3)
Extent, n (%)	
- Localized	28 (28.9)
- Generalized	71 (71.1)
PD (mm), median (IQR)	5 (1 – 6)
CAL (mm), median (IQR)	5 (4.5 – 7.0)
BOP, median (IQR)	0.8 (0.4 – 1.4)
PI, mean (SD)	1.6 (0.72)
PWV (m/s), mean (SD)	7.17(1.18)
HbA1C (%), median (IQR)	8.2 (6.7 – 9.5)
CRP (mg/L), median (IQR)	2.8 (1 – 4.8)

BMI = body mass index, BOP= bleeding on probing, CAL = clinical loss of attachment, CRP = c-reactive protein, PI = plaque index, PWV = pulse wave velocity

Metabolic and oral hygiene profile based on periodontitis severity are summarized in **Table 2**. One participant did not suffer from periodontitis; thus, she was not included in the descriptive analysis. The median age of the subject increased with the degree of periodontitis. The median BOP value in our study was 0.819, which belong to the mild gingivitis group. The mean plaque index in these patients was 1.619, indicating moderate category in oral hygiene. Subjects in the severe periodontitis group had poorer dental hygiene compared with subjects in mild and moderate periodontitis. BOP value also increased with the severity of periodontitis; however, subjects of the all three groups still had relatively mild gingivitis. The median duration of diabetes gained from interview in this study was 6 years. Median HbA1C was 8.2% with a range of 5.6 to 14.3%. Patients with moderate and severe

periodontitis showed longer duration of illness, poorer metabolic control as represented by higher HbA1C levels, older age and higher level of quantitative serum of CRP.

In this study, bivariate analysis was conducted to identify the correlation between PD, CAL and arterial stiffness. Correlation coefficient and p value between PD, CAL and PWV is displayed in **Figure 1**. Since the multivariate analysis to assess interaction between HbA1C, hypertension and age could not be performed, stratification by subgroup analysis was carried out by considering the risk factors found in the literatures that may affect the results of PWV.

HbA1C was divided into two groups based on the target of metabolic control in diabetes. The value of 7% was considered as the controlled level of HbA1C. In groups with controlled HbA1C, there was a weak correlation between pocket depth and PWV. While in uncontrolled HbA1C group, there was no significant correlation between PD and CAL against PWV. There was no significant correlation found in subgroup analysis for both hypertension and age. Correlation in subgroup analysis is summarized in **Figure 2**.

DISCUSSION

There is a notion that a positive correlation between PD and CAL with PWV has not been proven in this study (PD: r = 0.024, p = 0.407 and CAL: r = 0.011, p = 0.406). To our knowledge, no study on the association of PD and CAL with cfPWV in DM populations has ever been conducted. Heterogeneous subject characteristics, with different DM duration,

Table 2. Metabolic and oral hygiene profile according to periodontitis severity

Variables	Mild Periodontitis (n=7)	Moderate Periodontitis (n=16)	Severe Periodontitis (n=73)
Age (year), median (IQR)	45 (35 – 47)	50 (37 - 58)	52 (24 - 59)
BMI (kg/m^2), mean (SD)	26.0 (2.9)	29.1 (3.7)	25.8 (4.14)
Duration of diabetes (years), median (IQR)	5 (0.5 – 10.0)	5 (2.2 – 9.0)	7 (4.5 – 13.0)
PD (mm), median (IQR)	5 (4 – 7)	3 (1 – 5)	5 (2 – 6)
CAL (mm), median (IQR)	5 (2 – 7)	4.5 (3 – 5)	6 (5 – 7)
BOP, median (IQR)	0.6 (0.2 – 0.9)	0.9 (0.5 – 1.4)	0.8 (0.4 – 1.5)
PI, mean (SD)	1.2 (0.78)	1.1 (0.54)	1.7 (0.6)
PWV (m/s), median (IQR)	5.8 (5.6 – 7.9)	7.1 (6.0 – 7.9)	7.0 (6.3 – 8.1)
HbA1C (%), median (IQR)	7.5 (6.8 – 8.7)	7.9 (6.4 – 9.4)	7.9 (6.7 – 9.9)
CRP (mg/L) median (IQR)	1.3 (0.7 – 3.9)	2.7 (1.7 – 6.8)	2.8 (1.0 – 4.8)

BMI = body mass index, BOP= bleeding on probing, CAL = clinical loss of attachment, CRP = c-reactive protein, PI = plaque index, PWV = pulse wave velocity

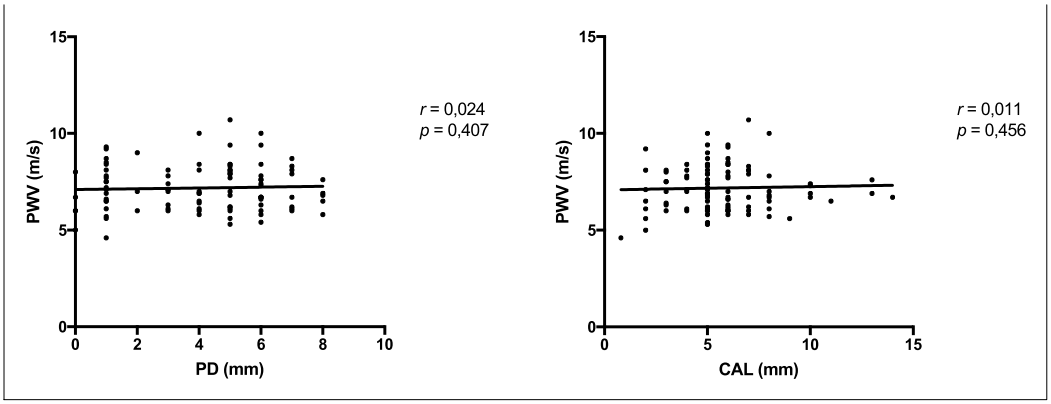

Figure 1. Correlation of PD and CAL with PWV

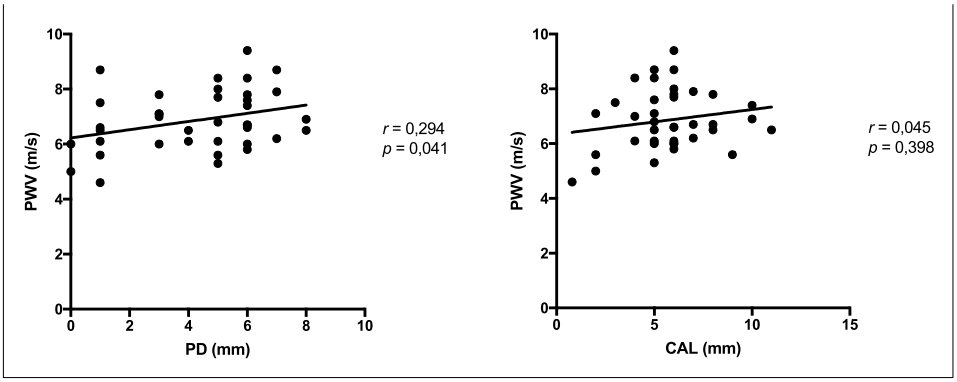

Figure 2. Correlation of PD and CAL with PWV in HbA1C > 7% group

different metabolic controls, long life span, comorbidity and drug use may contribute to such result.

However, there are some reports showing links between periodontitis and cardiovascular risk. Several studies have shown that patients with periodontal disease have a fourfold risk of coronary heart disease.[21,22] Periodontitis also has been shown to be associated with clinically proven atherosclerosis and has a role in increasing cardiovascular risk.[10–12] This data is supported by a study suggesting that non-surgical periodontal management plays a role in improving the progression of atherosclerosis.[13] Several studies have attempted to link periodontitis with subclinical atherosclerosis assessed by some surrogate marker modalities; however, the results are different in each study. Subclinical atherosclerosis could be measured by structural parameter such as carotid intima media thickness (cIMT), or by functional parameter such as PWV. In general population, there is a linear relationship between the severity of periodontitis and increase in the thickness of the tunica intima media.[14–16] These data has been supported by reports showing improvement of carotid thickness after periodontal treatment. On the other hand, studies using subclinical atherosclerotic functional parameters have indicated contradictory results as described above.[14,16–18]

Studies regarding arterial stiffness and periodontitis have shown contradictory results. Several studies have demonstrated significant connection between arterial stiffness and periodontitis.[16,23] Both studies were conducted in general population and excluding subjects with traditional risk factors of cardiovascular or adjusting cardiovascular risk factors such as hypertension and age. The positive correlation was found to be weak in one study[16] and the mean difference was small in another study; thus, its clinical significance was questionable.[23] Different results found in the two abovementioned studies with our study is likely to be influenced by the different characteristics of study subjects and the significant difference in the number of subjects involved. However, those results support the temporal relationship between risk of atherosclerosis and periodontitis in absence of other traditional risk factors. Subgroup analysis of our study had suggested a weak positive relationship between periodontitis and arterial stiffness in well-controlled diabetes group as shown by HbA1c level of <7%. Other two studies, which had suggested similar result with results of our study, come from Franek et al[14] and Miyaki et al[17]. Franek et al[14] showed that there was no difference between mean PWV in patients with periodontitis, gingivitis and healthy subjects; whereas significant difference was found in cIMT. Their study was conducted in type-2 diabetes population. Miyaki et al[17] also showed that there was no association between periodontitis and atherosclerosis measured by brachial ankle PWV (baPWV) after adjustment to traditional cardiovascular risk factors; however, the number of subjects involved was way less than the previous study.[16]

The contradictory result should be interpreted carefully. There are several factors that affect the value of PWV, including age, hypertension, duration of DM and HbA1c level.[1] Chronic

hyperglycemia exposure and enzymatic glycation that cause cross-reaction with collagen in the intimal layer of blood vessels will change the composition of blood vessel walls that reduce the elasticity of blood vessels. Increasing activity of local Renin-Angiotensin-Aldosterone in hypertension also causes vascular smooth muscle hypertrophy that will increase arterial stiffness.[24] As in the effect of medications, studies in the general population show that Angiotensin Converting Enzyme Inhibitors (ACEI), Aldosterone Receptor Blocker (ARB), statins and calcium channel blockers have been shown to decrease the value of PWV in both acute and chronic administration. Termination of the activation path of renin-angiotensin-aldosterone (RAA) will prevent vascular remodelling and improve aortic distensibility; while calcium channel blockers decrease arterial stiffness by vasodilation of blood vessels.[8] The effect of statins on cfPWV is still under debate. On the one hand, statins will decrease the cfPWV of the population at risk, but in the general population study, it has been known that statin administration for 6 months does not provide a significant decrease in aortic PWV.[25,26] No studies have examined the association of metformin with cfPWV in people with DM, but the underlying mechanism of cfPWV declining in diabetes patient possibly occurs through improvement of HbA1C level.

Hence, our study might show the temporal association between periodontitis and risk of atherosclerosis in patients without traditional cardiovascular risk factor as the subgroup analysis showed positive correlation between pocket depth and pulse wave velocity. This is also supported by two previous studies that have demonstrated the relationship between periodontitis and arterial stiffness if traditional risk factors are ruled out by design or by statistical analysis.[16,23] It may indicate that there is an association between periodontitis and risk of atherosclerosis; however, the association is weak and may be blunted by the influence of other uncontrolled and more prominent cardiovascular risk factors. As far as our concern, there is no study that has evaluated the association between periodontitis and arterial stiffness in well-controlled diabetic patients.

The main limitations of our study were heterogeneous subject characteristics such as age, different diabetes duration, metabolic control and diabetic complications. The effects of medication could not be disregarded as they are given in accordance with the indications, so that the cessation of such drugs would violate ethics. Our study was a hospital-based study, in which all subjects were recruited from an outpatient clinic setting; therefore, it may not represent the general diabetes population. Also, the cross-sectional design in this study could not show causal relationship between periodontitis and the risk of atherosclerosis. Further studies regarding association between periodontitis and arterial stiffness in well-controlled diabetes is needed.

CONCLUSION

In general, this study failed to show the relationship between periodontitis and arterial stiffness in type-2 diabetes patients. Such result may be blunted by more prominent traditional cardiovascular risk factors as the subgroup analysis showed the possible temporal association between periodontitis and arterial stiffness in patients with well-controlled diabetes. Further studies are required, particularly on the association between periodontitis and arterial stiffness in well-controlled diabetic patients.

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