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Oral Infection-Inflammatory Pathway, Periodontitis, Is a Risk Factor for Endothelial Dysfunction in Patients with Coronary Artery Disease

Brief title: Periodontitis and coronary artery disease

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Abstract

Objective: Several studies have shown that periodontitis is a risk factor for cardiovascular diseases. There is an association between inflammation and endothelial dysfunction. The purpose of this study was to evaluate endothelial function in patients with coronary artery disease (CAD) who had periodontitis.

Methods and results: We evaluated forearm blood flow (FBF) responses to acetylcholine (ACh), an endothelium-dependent vasodilator, and to sodium nitroprusside (SNP), an endothelium-independent vasodilator, in 101 CAD patients with periodontitis (37 men and 11 women, 63±12 yr) and without periodontitis (36 men and 17 women, 62±13 yr). FBF was measured by using strain-gauge plethysmography. Circulating levels of C-reactive protein and interleukin-6 were significantly higher in the periodontitis group than in the non-periodontitis group. FBF response to ACh was significantly smaller in the periodontitis group than in the non-periodontitis group. SNP-stimulated vasodilation was similar in the two groups. Periodontal therapy reduced serum concentrations of C-reactive protein from 2.7±1.9 to 1.8±0.9 mg/L ($P<0.05$) and interleukin-6 from 2.6±3.4 to 1.6±2.6 ng/L ($P<0.05$) and augmented ACh-induced vasodilation from 14.7±5.2 to 20.1±6.1 mL/min/100mL tissue ($P<0.05$) in patients with periodontitis. The SNP-stimulated vasodilation was similar before and after treatment. After administration of N^G-monomethyl-L-arginine, a nitric oxide synthase inhibitor, FBF response to ACh was similar before and after treatment.

Conclusion: These findings suggest that periodontitis is associated with endothelial dysfunction in patients with CAD through a decrease in nitric oxide bioavailability. Systemic inflammation may be, at least in part, a cause and predictor of progression of endothelial dysfunction.

Key words: periodontitis, coronary artery disease, endothelial function, inflammation

1. Introduction

Epidemiological studies have shown that periodontitis, an infection of the oral cavity caused by Gram-negative bacteria, is a risk factor for cardiovascular diseases.[1-4] However, not all of the studies have supported an association between periodontitis and cardiovascular outcomes.[5-7] Although the mechanisms by which periodontal disease is related to cardiovascular diseases are unclear, it is thought that systemic inflammation caused by periodontitis contributes to the development and maintenance of atherosclerosis through activation of a biochemical reaction cascade, initiation and development of plaque formation, and direct injury of the endothelium.

Endothelial dysfunction is the initial step in the development of atherosclerosis, leading to cardiovascular diseases, and plays an important role in the maintenance and development of cardiovascular diseases.[8] Several lines of evidence have shown that cardiovascular diseases are associated with endothelial dysfunction.[9-13] It is well known that there is an association between inflammation and endothelial dysfunction. Recently, we have reported that chronic infection with *Helicobacter pylori* impairs endothelium-dependent vasodilation in healthy male subjects.[14] Patients with periodontitis are ideal models for determining how endothelium-dependent vasodilation is affected by inflammation. Indeed, periodontitis has been shown to be associated with endothelial dysfunction in subjects without cardiovascular risk factors as well as hypertensive patients through a decrease in NO bioavailability,[15] suggesting that systemic inflammation might be, at least in part, a cause of endothelial dysfunction. In addition, periodontal therapy has been shown to improve endothelium-dependent vasodilation in patients with periodontitis.[16-18] However, there is little information regarding the effects of periodontitis on endothelium-dependent vasodilation in patients

with coronary artery disease (CAD).

The purpose of this study was to evaluate endothelial function in patients with CAD who had periodontitis and the effects of periodontal therapy on endothelial function in these patients.

2. Methods

2-1. Subjects

Patients with CAD who had periodontitis (n=48, 37 men and 11 women; mean age, 63±12 yr) and patients with CAD who did not have periodontitis as a control group (n=53, 36 men and 17 women; mean age, 62±13 yr) were enrolled in this study. The 48 patients with periodontitis were assigned in a 1:1 ratio to receive periodontitis treatment (n=24, 19 men and 5 women; mean age, 64±14 yr) or no periodontitis treatment (n=24, 18 men and 6 women; mean age, 63±13 yr) using a computer-generated permuted block randomization. Randomization was stratified by site. Patients with stenosis ≥70% in at least one proximal epicardial coronary artery and with objective evidence of myocardial infarction or at least one coronary stenosis ≥80% and classic angina without provocative testing were enrolled. Patients with refractory heart failure and cardiogenetic shock patients with ejection fraction <30%, and patients who had undergone revascularization, percutaneous coronary intervention or coronary artery bypass grafting within the previous 6 months and patients with myocardial infarction within the previous 6 months were excluded. Past and current smokers were also excluded. The Ethical Committee of Hiroshima University Graduate School of Biomedical Sciences approved the study protocol. Written informed consent for participation in the study was obtained from all subjects.

2-2. Study protocol

Each subject was requested to avoid making any changes in lifestyle, dietary habitus, or conventional therapy during the study. We measured the FBF responses to intra-arterial infusion of acetylcholine (ACh) and to sodium nitroprusside (SNP) before periodontal therapy in 48 patients with periodontitis and 53 control patients, and in 24 patients who were treated periodontitis and 24 untreated patients before and after 24 weeks of follow-up period. Subjects fasted the previous night for at least 12 hours. The study began at 8:30 AM. They were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature 22°C to 25°C) throughout the study. A 23-gauge polyethylene catheter (Hakkow Co., Tokyo, Japan) was inserted into the left brachial artery for the infusion of vasoactive agents, and to record arterial pressure with an AP-641G pressure transducer (Nihon Kohden Co., Tokyo, Japan) under local anesthesia (1% lidocaine). Another catheter was inserted into the left deep antecubital vein to obtain blood samples. Thirty minutes after maintaining the supine position, basal FBF was measured. Then, FBF responses to ACh (Daiichi Pharmaceutical Co., Tokyo, Japan), an endothelium-dependent vasodilator, and SNP (Maluishi Pharmaceutical Co., Tokyo, Japan), an endothelium-independent vasodilator were measured. ACh infusion was administered at a dose of 3.75, 7.5, and 15 μg/min for 5 minutes, and SNP infusion was administered at a dose of 0.375, 0.75, and 1.5 μg/min for 5 minutes. These studies were carried out in a randomized fashion. Each study proceeded after FBF had returned to baseline.

To examine the effect of periodontal therapy on release of NO, we measure FBF in the presence of the NO synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA)

(CLINALFA Co., Laufelfingen, Switzerland) in all subjects. The responses of forearm vasculature to ACh after intra-arterial the infusion of L-NMMA (8 μmol/min for 5 minutes) were evaluated.

Baseline fasting serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, malondialdehyde (MDA)-modified LDL, triglycerides, glucose, insulin, electrolytes, interleukin-6, and high-sensitivity C-reactive protein (hs-CRP) were obtained after a 30-minute rest period before the study. The 24-hr urinary excretion of 8-hydroxy-2'-deoxyguanosine (8-OHdG) was determined.

2-3. Definition and treatment of periodontitis

Periodontal status was measured by a self-reported questionnaire on periodontal symptoms, including gingival swelling and bleeding, purulent discharge, and tooth mobility, as previously described.[19] In addition to self-reported periodontal status, dentists who were unaware of any of the study protocols performed a routine oral examination for diagnosis of periodontitis and confirmed the presence of the disease. Chronic periodontitis was defined as the presence of at least 2 teeth with probing pocket depth ≥ 4 mm and with attachment loss ≥ 3 mm. The control patients had no periodontal disease history, no sign of periodontal disease, no probing pocket depth ≥ 3 mm, and no attachment loss ≥ 1 mm.

Patients received nonsurgical periodontal therapy that included oral hygiene instructions and subgingival scaling and root planning under local anesthesia as needed. Antibiotics were used for 4 to 7 days after intensive therapy. Then the patients performed mouth washing and teeth and subgingival brushing every day for 24 weeks.

To determine the periodontal status of the patients, probing pocket depth, clinical attachment level, and sites with gingival bleeding were evaluated before and after 24 weeks of treatment. Data for two patients in whom periodontitis was confirmed after 24 weeks of periodontal therapy and for one patient who dropped put of the study were excluded from the primary analysis.

2-4. Measurements of FBF

FBF was measured using a mercury-filled Silastic strain-gauge plethysmography (EC-5R, Hokanson, Inc., Bellevue, WA) as previously described.[11,20]

2-5. Analytical Methods

Samples of venous blood were placed in tubes containing sodium EDTA (1 mg/mL) and in polystyrene tubes. The EDTA-containing tubes were chilled promptly in an ice bath. Samples were stored at -80°C until the time of assay. Serum concentrations of total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, glucose, insulin, and electrolytes were determined by routine chemical methods. Serum concentration of hs-CRP was measured by a high sensitive nephelometry assay using a CRP kit (Dade Behring, Deerfield, IL). Serum concentration of interleukin-6 was measured by a high sensitivity ELISA (R&D System, Minneapolis, MN). The serum concentration of MDA-LDL was assayed by ELISA (anti-malondialdehyde-modified low-density lipoprotein antibody, SRL, Atsugi, Japan). The urinary excretion of 8-OHdG also was assayed by ELISA using 8-OHdG kits (Nihon Yushi, Fukuroi, Japan).

2-6. Statistical Analysis

Values are expressed as mean±SD. Values of $P<0.05$ were considered significant. The Mann-Whitney U test was used to evaluate differences between before and after periodontal treatment with respect to baseline parameters. Two-tailed Student paired t test was used to evaluate differences before and after treatment. Because of the skewed distributions of the measured hs-CRP and IL-6 levels, we treated these parameters as nonparametric variables and we analyzed the difference between two groups by the Mann-Whitney U test and the differences before and after treatment by Wilcoxon's signed rank sum test. Comparisons of dose-response curves of parameters during the infusion of the drug were analyzed by ANOVA for repeated measures. The data were processed using the software packages Stat View IV (SAS institute, Cary, CA) and Super ANOVA (Abacus Concepts, Berkeley, CA).

3. Results

3-1. Clinical characteristics in patients with and without peirodontitis

The baseline clinical characteristics of patients of periodontitis group and non-perodontitis group are summarized in Table 1. Serum concentrations of interleukin-6 and hs-CRP, indices of systemic inflammation, were significantly higher in patients with periodontitis than in patients without periodontitis. There was no significant difference in other parameters between the two groups.

3-2. Clinical characteristics in patients with periodontitis before and after periodontal therapy

The baseline clinical characteristics of the periodontitis treated group and untreated group are summarized in Table 2. There was no significant difference in baseline

clinical characteristics between the treated and untreated groups at 0 weeks of follow-up. The 24 weeks of treatment significantly decreased serum concentrations of interleukin-6 and hs-CRP, probing pocket depth, clinical attachment level, and sites with gingival bleeding. Periodontal therapy did not alter other parameters. In the untreated group, the baseline clinical characteristics were similar at 0 weeks and 24 weeks of follow-up.

3-3. Endothelial function in patients with and without peirodontitis

Intra-arterial infusion of ACh and SNP increased FBF in a dose-dependent manner in all subjects. The response of FBF to ACh was significantly less in patients with periodontitis than in control patients (Fig. 1, top). Vasodilatory responses to SNP were similar in the two groups (Fig. 1, middle). Intra-arterial infusion of L-NMMA significantly decreased basal FBF from 4.4±1.3 to 3.8±1.2 mL/min/100 mL tissue ($P<0.001$) in patients with periodontitis and from 4.5±1.2 to 3.8±1.1 mL/min/100 mL tissue ($P<0.001$) in control patients. After L-NMMA infusion, there was no significant difference between FBF responses to ACh in the two groups (Fig. 1, bottom).

3-4. Endothelial function in patients with periodontitis before and after periodontal therapy

The response of FBF to ACh was increased significantly by 24 weeks of treatment, whereas there was no significant difference between the FBF responses to ACh in the untreated group before and after the 24-week study period (Fig. 2, top). The increases in FBF during the infusion of SNP were similar at the beginning and the end of the 24-week study period in both groups (Fig. 2, middle). Intra-arterial infusion of

L-NMMA significantly decreased basal FBF from 4.5±1.4 to 3.9±1.1 mL/min/100 mL tissue ($P<0.001$) in the treated group and from 4.4±1.3 to 3.8±1.2 mL/min/100 mL tissue ($P<0.001$) in the untreated group at 0 weeks and from 4.6±1.5 to 4.0±1.2 mL/min/100 mL tissue ($P<0.001$) in the treated group and from 4.4±1.2 to 3.8±1.1 mL/min/100 mL tissue ($P<0.001$) in the untreated group at 24 weeks of follow-up. L-NMMA completely abolished the periodontal therapy-induced augmentation of FBF response to ACh (Fig. 2, bottom). No significant change was observed in arterial blood pressure or heart rate after intra-arterial infusion of either ACh or SNP in the presence and absence of L-NMMA in all patients. There was a significant correlation between interleukin-6 levels and hs-CRP levels ($r=0.54$, $P<0.001$). After periodontal therapy, changes in interleukin-6 and hs-CRP were parallel. There was no significant relationship among the vascular responses to ACh and SNP and serum concentration of interleukin-6 or hs-CRP or among the increase in FBF responses to ACh and SNP, and change in hs-CRP or interleukin-6.

4. Discussion

In the present study, we demonstrated that complication of periodontitis greatly increased the magnitude of endothelial dysfunction in patients with CAD who have endothelial dysfunction and that appropriate periodontal therapy improved endothelium-dependent vasodilation in patients with CAD who have periodontitis. Periodontitis impaired endothelium-dependent vasodilation but not endothelium-independent vasodilation in patients with CAD. Periodontal therapy augmented ACh-induced vasodilation in forearm circulation through an increase in NO production, whereas the vasodilator responses to SNP did not change after periodontal

therapy. These findings suggest that periodontal therapy has a predominately beneficial effect on endothelial cell function but not on smooth muscle cell function.

In our previous study, we showed that periodontitis impairs endothelium-dependent vasodilation in healthy young men who have no confounding factors of endothelial dysfunction, including hypertension, heart failure, atherosclerosis, hypercholesterolemia, diabetes mellitus, smoking, aging, and menstrual cycle, suggesting that periodontitis per se is a predictor of endothelial dysfunction.[15] Although we did not confirm the natural course of periodontitis in healthy young men, periodontitis-induced inflammation may be an initial step of endothelial dysfunction, leading to atherosclerosis.

It is well known that smoking is a potent predictor of the risk of periodontitis.[1-7] In addition, a large number of clinical and epidemiological studies have clearly shown that smoking is a risk factor of CAD and is associated with endothelial dysfunction.[21-24] The difficult interpretation of and discrepant results regarding the relationship between periodontitis and CAD are due to confounding effects of smoking. In a preliminary study, when 224 patients with CAD who had been admitted to our institute were divided into patients with and those without periodontitis, the ratio of smokers was significantly higher in patients with periodontitis than in patients without periodontitis (58% vs. 33%, P=0.02), while other cardiovascular risk factors were similar in the two groups. Therefore, in the present study, we excluded smokers to remove the strong confounding factor for both periodontitis and CAD. Endothelial function has been shown to be impaired in patients with CAD compared with that in healthy subjects.[9-13] In the present study, endothelium-dependent vasodilation was significantly smaller in CAD patients with periodontitis than in CAD patients without periodontitis, suggesting

that systemic inflammation may be, at least in part, a predictor of progression of endothelial dysfunction.

There are several possible explanations for the periodontitis-induced impairment of endothelium-dependent vasodilation in patients with CAD who had periodontitis. After infusion of the eNOS inhibitor L-NMMA, ACh-induced vasodilation was similar in the periodontitis group and the control group. These findings suggest that periodontitis decreases the production of NO in patients with CAD.

Chronic inflammation caused by periodontitis may contribute to endothelial dysfunction through a decrease in NO bioavailability, a decrease in NO production and/or an increase in NO inactivation. Under the condition of chronic inflammation, production of proflammatory cytokines results in activation of endothelial cells, leading to the excessive induction of adhesion molecules, cytokines, growth factors, and vasoconstrictors.[25,26] In addition, proflammatory cytokines such as tumor necrotic factor (TNF)-alpha and interleukin-6 downregulate the expression of eNOS.[27] TNF-alpha alone decreases the half-life of eNOS mRNA in human endothelial cells.[28] Administration of these cytokines attenuates endothelium-dependent vasodilation in vivo.[29] Interestingly, CRP also directly decreased eNOS mRNA and protein levels and enzymatic activity in human aortic endothelial cells.[30] Endothelial dysfunction promotes inflammation of the vascular wall, leading to a vicious circle between endothelial dysfunction and inflammation. These findings suggest that several pathways of proinflammatory factors in periodontitis may contribute to downregulation of the expression of eNOS and decrease in enzymatic activity, resulting in decrease in NO production.

Study limitations

In the present study, it has been clearly shown that endothelium-dependent vasodilation is less in patients with periodontitis than in patients without periodontitis and that periodontal therapy improves endothelial function in patients with periodontitis. However, the relationships between existence of periodontitis and prognosis of cardiovascular diseases, including myocardial infarction, heart failure and cardiovascular death are unclear. Prospective study is needed to determine whether patients with CAD who have periodontitis have a higher risk than patients with CAD who have no periodontitis for morbidity and mortality of cardiovascular events in the future.

The subjects enrolled in this study had mild to moderate periodontitis. Evaluation of severe periodontitis that requires surgical intervention may enable more specific conclusions concerning the roles of inflammation, especially inflammatory markers, and oxidative stress in endothelial function after periodontal therapy to be drawn.

In conclusion, both periodontitis and endothelial dysfunction independently or concomitantly lead to atherosclerosis, resulting in cardiovascular complications. We should pay attention to the existence of periodontitis in patients with CAD and vigorously treat periodontitis when we follow up patients with CAD. Periodontal therapy per se also is a good therapeutic approach for improving endothelial dysfunction. It is expected that treatment of periodontitis reduces the risk of mortality and morbidity of cardiovascular diseases through improvement in endothelial function. Future large-scale clinical studies are needed to determine the long-term effects of periodontal therapy on mortality and morbidity of cardiovascular diseases.

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Sources of Founding

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Conflict of Interest

None.

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Figure Legends

Figure 1. Effects of acetylcoline (top) and sodium nitroprusside (middle) on forearm blood flow (FBF) in patinets with and without periodontitis. Effects of acetylcoline on forearm blood flow (FBF) in patients with and without periodontitis in the presence of N^G-monomethyl-L-arginine (L-NMMA) (bottom).

Figure 2. Effects of acetylcoline (top) and sodium nitroprusside (middle) on forearm blood flow (FBF) before and after 24 weeks of follow-up in the control group and treatment group. Effects of acetylcoline on forearm blood flow (FBF) before and after 24 weeks of follow-up in the control group and treatment group in the presence of N^G-monomethyl-L-arginine (L-NMMA) (bottom).

Figure 1

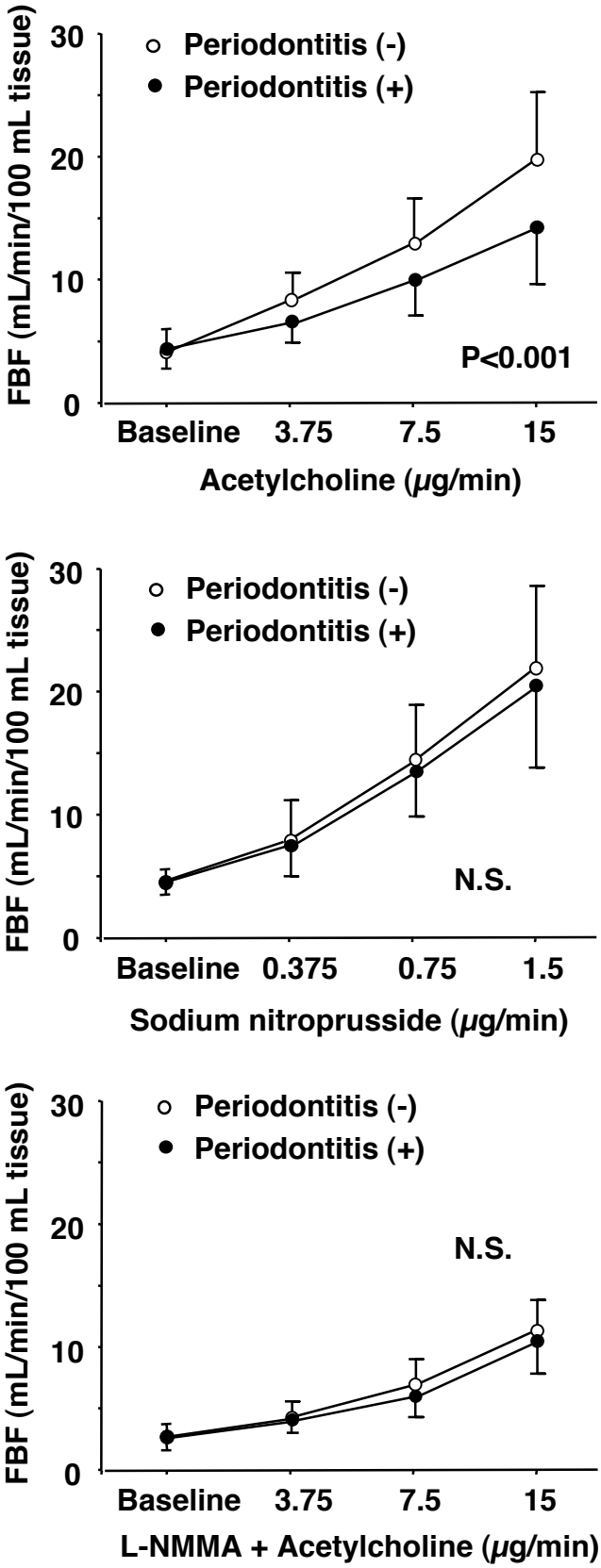
Periodontitis (-)
Periodontitis (+)
FBF (mL/min/100 mL tissue)
30
20
10
0
P<0.001
Baseline
3.75
7.5
15
Acetylcholine (μg/min)
Periodontitis (-)
Periodontitis (+)
FBF (mL/min/100 mL tissue)
30
20
10
0
N.S.
Baseline
0.375
0.75
1.5
Sodium nitroprusside (μg/min)
Periodontitis (-)
Periodontitis (+)
FBF (mL/min/100 mL tissue)
30
20
10
0
N.S.
Baseline
3.75
7.5
15
L-NMMA + Acetylcholine (μg/min)

Figure 2

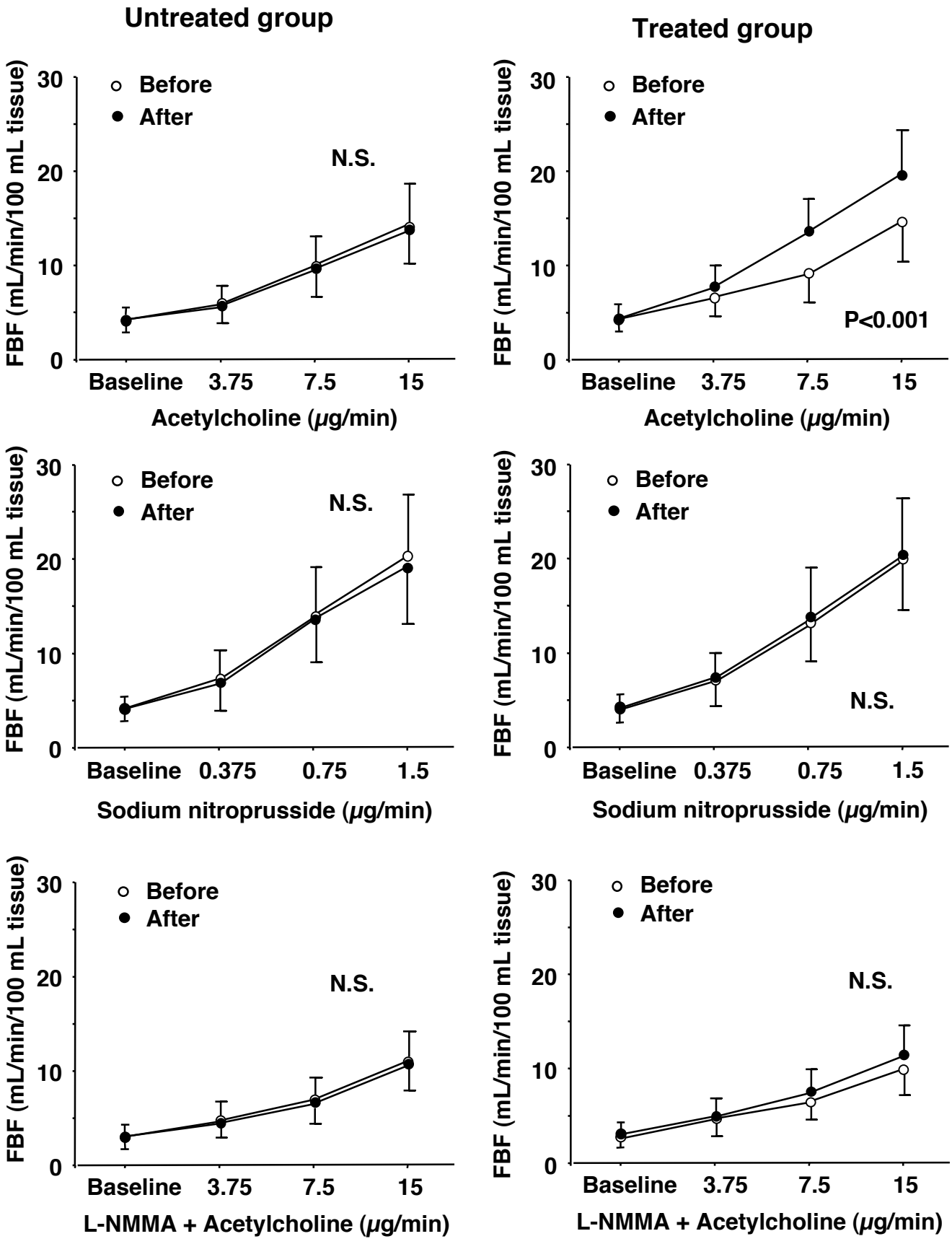
Untreated group
Treated group
Before
After
N.S.
P<0.001
FBF (mL/min/100 mL tissue)
0
10
20
30
Baseline
3.75
7.5
15
Acetylcholine (μg/min)
0.375
0.75
1.5
Sodium nitroprusside (μg/min)
L-NMMA + Acetylcholine (μg/min)

Table 1. Clinical Characteristics of Patients without Periodontitis (Control) and Patients with Periodontitis

Variables	Control (n=53)	Periodontitis (n=48)
Body mass index, kg/m^2	24.2 ± 2.9	24.3 ± 3.0
Systolic blood pressure, mm Hg	140.3 ± 16.8	141.2 ± 17.6
Diastolic blood pressure, mm Hg	82.7 ± 10.9	82.4 ± 11.5
Heart rate, bpm	72.5 ± 9.2	73.1 ± 8.7
Total cholesterol, mmol/L	4.86 ± 1.07	4.89 ± 1.14
Triglyceride, mmol/L	1.31 ± 0.74	1.29 ± 0.66
HDL cholesterol, mmol/L	1.20 ± 0.48	1.22 ± 0.51
LDL cholesterol, mmol/L	2.86 ± 0.97	2.91 ± 0.96
Glucose,mmol/dL	5.3 ± 1.9	5.4 ± 1.8
Insulin, pmol/L	45.8 ± 14.2	43.7 ± 18.7
Interleukin-6, ng/L	1.5 ± 2.9	2.7 ± 3.3*
High sensitivity CRP, mg/L	1.7 ± 1.1	2.6 ± 2.1*
MDA-LDL, U/L	60.3 ± 26.8	62.1 ± 31.3
Urinary 8-OHdG, ng/mg Cr	10.4 ± 4.5	10.6 ± 4.7
FBF, mL/min/100 mL tissue	4.5 ± 1.2	4.4 ± 1.3
Diseased vessel		
1 vessels, n (%)	26 (49)	23 (48)
2 vessels, n (%)	19 (34)	15 (31)
3 vessels, n (%)	8 (15)	10 (21)
Medical history		
Hypertension, n (%)	33 (62)	29 (60)
Dyslipedemia, n (%)	15 (28)	14 (29)
Diabetes mellitus, n (%)	10 (19)	8 (17)
Previous PCI, n (%)	22 (42)	18 (38)
Previous CABG, n (%)	5 (9)	4 (8)
Previous myocardial infaction, n (%)	6 (11)	4 (8)
Mecication		
ACE inhibitor, n (%)	14 (26)	16 (33)
ARB, n (%)	22 (42)	18 (38)
β -blocker, n (%)	8 (15)	7 (14)
Calcium antagonisit, n (%)	33 (62)	30 (63)
Diuretic, n (%)	8 (15)	5 (10)
Anti-platelet agents, n (%)	47 (87)	42 (88)
Statin, n (%)	41 (77)	32 (67)

HDL indicates high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; FBF, forearm blood flow; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
All results are presented as mean±SD. *P<0.05 versus control.

Table 2. Clinical Characteristics of Patients with Periodontitis before and after Periodontal Therapy

	Periodontitis			
	Untreated (n=24)		Treated (n=24)	
Variables	Before	After	Before	After
Body mass index, kg/m^2	24.3 ± 3.2	24.3 ± 3.3	24.2 ± 3.2	24.1 ± 3.1
Systolic blood pressure, mm Hg	141.3 ± 19.8	140.8 ± 19.1	141.3 ± 20.2	140.3 ± 19.3
Diastolic blood pressure, mm Hg	82.3 ± 12.7	81.9 ± 12.1	82.5 ± 13.3	80.7 ± 12.9
Heart rate, bpm	74.1 ± 9.2	75.3 ± 9.4	72.8 ± 9.5	73.3 ± 9.8
Total cholesterol, mmol/L	4.79 ± 1.21	4.77 ± 1.68	4.95 ± 1.25	4.88 ± 1.31
Triglyceride, mmol/L	1.28 ± 0.73	1.25 ± 0.64	1.30 ± 0.79	1.25 ± 0.67
HDL cholesterol, mmol/L	1.24 ± 0.73	1.23 ± 0.58	1.21 ± 0.62	1.20 ± 0.59
LDL cholesterol, mmol/L	2.93 ± 1.02	2.91 ± 0.99	2.88 ± 1.13	2.81 ± 0.87
Glucose, mmol/dL	5.4 ± 2.1	5.4 ± 1.9	5.3 ± 1.9	5.2 ± 2.0
Insulin, pmol/L	44.1 ± 20.9	45.3 ± 19.8	42.5 ± 21.2	43.5 ± 19.9
Interleukin-6, ng/L	2.7 ± 3.9	2.6 ± 4.4	2.6 ± 3.4	1.6 ± 2.6*
High sensitivity CRP, mg/L	2.6 ± 2.2	2.5 ± 2.1	2.7 ± 1.9	1.8 ± 0.9*
MDA-LDL, U/L	60.8 ± 32.3	59.7 ± 31.2	62.9 ± 34.1	60.8 ± 29.7
Urinary 8-OHdG, ng/mg Cr	10.6 ± 4.8	10.5 ± 4.6	10.5 ± 4.7	10.3 ± 4.40
FBF, mL/min/100 mL tissue	4.4 ± 1.3	4.4 ± 1.2	4.5 ± 1.4	4.6 ± 1.5
Dental examination				
Probing pocket depth (mm)	4.78 ± 0.72	4.89 ± 0.81	5.12 ± 0.79	3.29 ± 0.42*
Clinical attachment level (mm)	5.72 ± 1.02	5.87 ± 0.98	5.98 ± 1.13	4.28 ± 0.73*
Sites with gingival bleeding (%)	53.8 ± 17.3	57.2 ± 19.2	51.2 ± 18.1	17.8 ± 10.7*
Diseased vessel				
1 vessels, n (%)	12 (50)		11 (46)	
2 vessels, n (%)	7 (29)		8 (33)	
3 vessels, n (%)	5 (21)		5 (21)	
Medical history				
Hypertension, n (%)	13 (54)		16 (67)	
Dyslipedemia, n (%)	7 (29)		7 (29)	
Diabetes mellitus, n (%)	3 (13)		5 (21)	
Previous PCI, n (%)	10 (42)		8 (33)	
Previous CABG, n (%)	2 (8)		2 (8)	
Previous myocardial infaction, n (%)	2 (8)		2 (8)	
Mecication				
ACE inhibitor, n (%)	8 (33)		8 (33)	
ARB, n (%)	8 (33)		10 (42)	
β-blocker, n (%)	4 (17)		3 (13)	
Calcium antagonisit, n (%)	14 (58)		16 (67)	
Diuretic, n (%)	3 (13)		2 (8)	
Anti-platelet agents, n (%)	20 (83)		22 (92)	
Statin, n (%)	17 (71)		15 (63)	

HDL indicates high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; FBF, forearm blood flow; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
All results are presented as mean±SD. *P<0.05 versus before periodontitis therapy.