Mechanism by which periodontitis may contribute to atherosclerosis

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I. Introduction

Coronary artery disease is the major cause of premature death among men in industrialized countries, and its pathological basis is atherosclerosis. Atherosclerosis is the focal thickening of arterial intima and media. These cellular reactions may be a response to endothelial injury, mediated by cytokines and growth factor. Infections (including periodontal, *H. pylori* and *C. pneumoniae* infecions) may be one cause of such injury; as may smoking, hypertension, hyperlipidemia and oxydant stress. Gram-negative bacteria or the associated lipopolysaccharide (endotoxin) can induce inflammatory cell infiltration into major blood vessels, vascular smooth muscle proliferation, vascular fatty degeneration and intravascular coagulation. The remarkable similarities of bacterially induced vascular pathology and the natural history of atherogenesis has led certain investigators to suggest that, in addition to genetic, lifestyle and dietary influences, infections of unknown origin may contribute to the cardiovascular pathology[1].

The role of periodontal disease in the etiology of cardiovascular disease has recently received considerable attention. Several observational epidemiologic studies[2-9] have found that poor periodontal health status is associated with an increased risk for cardiovascular disease.

Several possible mechanisms may operate to explain the association between periodontal infections and atherosclerosis. These may include: (1) direct effects of infectious agents in atheroma formation[10-12] (2) indirect or host-mediated effects triggered by infection[13-21] (3) common genetic predisposition for periodontal disease and atherosclero-

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sis[22-23] and (4) common risk factors, such as lifestyle.

Periodontal pathogens are not only capable of directly invading the periodontal tissues, but the loss of epithelial integrity within the periodontal pocket creates ample opportunity for direct bacterial translocation and bacteremia[24-25]. Thus, periodontitis is a chronic infection which can result in repeated systemic exposure to Gram-negative bacteria, lipopolysaccharide, and other bacterial products.

Within the periodontium, the monocyte responds to the bacterial LPS (lipopolysaccharide, endotoxin) from Gram-negative anaerobic bacteria, especially black-pigmented species such as Porphyromonas and Bacteroides, by secreting three key pro-inflammatory mediators: PGE_2 , IL-1β and TNF-α. These paracrines have deleterious effects on the periodontium by eliciting vasodilation and increasing vasopermeability, inflammatory cell recruitment, connective tissue degradation, and bone destruction. Periodontitis-affected tissues serve as a reservoir of cytokines and prostaglandins which can enter the circulation and induce systemic effects[3].

Therefore, periodontal disease, once established, provides a biological burden of endotoxin (lipopolysaccharide) and inflammatory cytokines which serve to initiate and exacerbate atherosclerosis and thromboembolic events.

The levels of inflammatory mediators present within the gingival crevicular fluid provide a sensitive and quantitative assessment of the host-based underlying inflammatory response. Furthermore, there are close associations between the GCF levels of PGE_2 and IL-1 and the systemic monocytic response to LPS. That is, the level of PGE_2 secreted by peripheral blood monocytes in culture in response to LPS correlates within the PGE_2 levels present within the GCF[26]. However, to date there is no published documentation of periodontitis-induced elevation of serum pro-inflammatory cytokines.

The aim of the present study is to investigate that the pro-inflammatory cytokines in GCF may be dumped systemically falling within the detectable range of biological serum assay.

II. Materials and Methods

1. Patient Selection

36 admitted to the Department of Cardiology, Seoul National University Hospital with unstable angina pectoris or acute myocardial infarction (AMI) or the previous history of ischemic heart disease were included in this study. Of these people, 24 patients who were diagnosed as atherosclerosis in the coronary angiography became the case group. 12 patients who were not diagnosed as atherosclerosis became the control group. Edentulous patients were excluded from this study. Informed consent was obtained from all patients before examination.

2. Medical History

Patients from both groups were interviewed about their medical status. Data on hypertension, diabetes, smoking status, family history of coronary heart disease, and previous history of ischemic heart disease were recorded.

3. Clinical measurements

At Ramfjord' s teeth (#16,21,24,36, 41,44), gingival index (GI), plaque index (PI), probing pocket depth (PPD), clinical attachment level (CAL) were measured. Probing pocket depth and clinical attachment level were measured at 6 sites per tooth (mesiobuc-

cal, direct buccal, distobuccal, mesiolingual, direct lingual, distolingual).

4. Gingival crevicular fluid sampling and analysis of inflammatory mediator

The levels of interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), prostaglandin E_2 (PGE_2) were determined. GCF was sampled from the deepest pocket of two teeth with the deepest pocket of the Ramfjord' s teeth using Periopaper® filter strips (Pro Flow, Inc. Amityville, NY, USA). GCF strips were placed for 30s into the periodontal pocket and after removal placed into cryovials and quickly transferred to liquid nitrogen. The amount of each mediator was determined performing enzyme-linked immunoadsorbent assays (ELISAs) specific for each cytokine using commercially available kits (R&D Systems, Minneapolis, MN).

5. Peripheral blood samples and analysis of inflammatory mediators

Peripheral blood of each patient was collected. A standard venipuncture was used to collect 50 ml of whole blood in heparinized tubes and centrifuging at 300g for 30 min. Cytokine levels in the plasma samples were determined by ELISA using commercially available kits for IL-1β, IL-6, TNF-α, PGE_2.

6. Laboratory Analysis

Blood samples were taken on admission from all patients. Serum total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol), C-reactive protein (CRP), white blood cell (WBC) counts were determined.

7. Statistical Analysis

Means and proportions for major risk factors and clinical parameters and the amount of cytokines were calculated. The significance of any difference in means was tested by using Student t test, and the significance of any difference in proportions was tested by using chi square test (or Fisher' s exact test). The relation of independent variables to atherosclerosis (dependent variables) was assessed using logistic regression analysis. The correlation between cytokines in GCF and those in plasma was tested by determining Pearson' s correlation coefficients.

III. Results

Study population characteristics are shown in Table 1. For age, family history, diabetes, hypertension, previous history of ischemic heart disease, current smoker, no significantly different distributions

Table 1. Characteristics of study samples

	Atherosclerosis (n=24)	Control (n=12)
Age (years)	59.0 ± 9.1 (45-75)	51.4 ± 8.1 (35-65)
Male/Female	18/6	8/4
Family History	10 (43.5%)	2 (16.7%)
DM	7 (29.2%)	3 (25%)
HT	14 (58.3%)	4 (33.3%)
Previous History	11 (45.8%)	4 (33.3%)
Current Smoker	15 (62.5%)	4 (33.3%)

Table 2. Periodontal status (mean ± SD)

	Atherosclerosis	Control	p-value
GI	1.02 ± 0.39	0.61 ± 0.58	0.017*
PI	1.48 ± 0.82	1.41 ± 0.82	0.817
PPD	4.48 ± 0.98	3.90 ± 1.26	0.140
CAL	4.76 ±1.20	4.05 ± 1.26	0.110

GI ; gingival index, PI ; plaque index, PPD ; probing pocket depth, CAL ; clinical attachment level
*p<0.05

Table 3. Cytokine levels in gingival crevicular fluid (GCF) (ng/ml ± SEM)

	Atherosclerosis	Control	p-value
IL-1β	98.62 ± 19.68	34.66 ± 7.61	0.005*
IL-6	8.22 ± 1.48	12.97 ± 5.50	0.421
TNF-α	3.87 ± 0.42	6.12 ± 0.79	0.009*
PGE_2	711.47 ± 40.47	541.44 ± 60.14	0.022*

*p<0.05

Table 4. Cytokine levels in plasma (ng/mL ± SEM)

	Atherosclerosis	Control	p-value
IL-1β	0.13 ± 0.29	-0.69 ± 0.60	0.176
IL-6	5.36 ± 0.88	5.02 ± 1.44	0.828
TNF-α	8.09 ± 0.72	14.08 ± 5.44	0.300
PGE_2	375.80 ± 166.68	396.38 ± 154.83	0.946

Table 5. Serum lipid/lipoprotein, c-reactive protein, and WBC (mean ± SEM)

	Atherosclerosis	Control	p-value
Total cholesterol(mg/dL)	186.17 ± 5.00	214.08 ± 22.99	0.258
Triglycerides(mg/dL)	143.38 ± 17.91	151.50 ± 27.97	0.800
LDL cholesterol(mg/dL)	115.58 ± 4.86	136.40 ± 19.89	0.329
HDL cholesterol(mg/dL)	44.33 ± 1.82	47.75 ± 4.35	0.480
CRP (mg/dL)1.72 ± 0.58	0.94 ± 0.56	0.396	
WBC ($\times 10^9$/L)	7.93 ± 0.54	6.61 ± 0.63	0.149

LDL; low-density lipoprotein, HDL; high-density lipoprotein, CRP; C-reactive protein, WBC; white blood cell

were observed. But, the atherosclerosis group tended to be older, have more often family history, diabetes, hypertension, previous history, smokers.

Table 2 shows clinical measurements for periodontal status. In gingival index appearing the present inflammatory status of the gingiva, the difference was statistically significant (*P=0.017*). Atherosclerosis group showed more severe inflammation than the control group. But, probing pocket depth and clinical attachment level reflecting the long-term destruction of the periodontium didn' t show the statistically significant difference. And in plaque index appearing the present oral hygiene, there was no statistically significant difference.

Table 3 presents the mean concentrations of the cytokines in GCF. In the atherosclerosis group, IL-

Table 6. Correlation coefficients for cytokine levels in GCF with cytokine levels in plasma

	Atherosclerosis	Control	All
gIL-1 with			
PGE_2	-0.126	0.415*	0.368*
gIL-6 with			
IL-6	-0.190	0.509*	-0.004
gTNF-α with			
IL-1	-0.610*	-0.239	-0.477**
gIL-6	-0.596*	0.187	-0.206
$gPGE_2$ with			
TNF-α	-0.392	-0.312	-0.388*
IL-1 with			
IL-6	-0.146	-0.487*	-0.285
TNF-α	0.161	-0.505*	0.142

*p<0.05, **p<0.01

Table 7. Unadjusted (crude) odds ratios for atherosclerotic risk factors

Variable	Atherosclerosis	Control	Crude odds ratio	p-value
Gender				
Male	18 (75%)	8 (67%)	1.5	0.696
Female	6 (25%)	4 (33%)		
Family history				
Yes	10 (43%)	2 (17%)	3.9	0.149
No	13 (57%)	10 (83%)		
HT				
Yes	14 (58%)	4 (33%)	2.8	0.157
No	10 (42%)	8 (67%)		
DM				
Yes	7 (29%)	3 (25%)	1.2	1.000
No	17 (71%)	9 (75%)		
Previous history				
Yes	11 (46%)	4 (36%)	1.5	0.721
No	13 (54%)	7 (64%)		
Current smoker				
Yes	15 (63%)	4 (33%)	3.3	0.098
No	9 (37%)	8 (67%)		
PPD				
PPD≥4 mm	17 (71%)	6 (50%)	2.4	0.281
PPD<4 mm	7 (29%)	6 (50%)		

PPD; probing pocket depth

1β was more than 3-fold higher (*P=0.005*), comparing to the control group. PGE_2 was also more than 1.5-fold higher in the atherosclerosis group (*P=0.022*). However, TNF-α was more than 2-fold higher in control group (*P=0.009*). IL-6 didn't show the statistically significant difference.

The cytokine levels in plasma didn't show the statistically significant difference (Table 4).

In the serum lipid/lipoprotein, C-reactive protein, WBC, there was no statistically significant difference between the atherosclerosis group and the control group (Table 5).

Table 6 presents the correlation coefficients for cytokine levels in GCF with that levels in plasma. There was no correlation between the corresponding cytokine in GCF and the cytokine in plasma.

The unadjusted odds ratios for several potential risk factors for atherosclerosis appear in Table 7. Gender, Family history, hypertension, diabetes, previous history, smoking, and probing pocket depth did not appear to influence the observed frequency of atherosclerosis in this dataset.

The final full logistic regression models appear in Table 8. Only IL-1β and TNF-α in GCF were associated significantly with atherosclerosis (P=0.0177, 0.0309 respectively). Especially, IL-1β in GCF was associated strongly with atherosclerosis (odds ratio=273.385). IL-1β was associated positively with atherosclerosis and TNF-α was associated negatively with atherosclerosis (parameter estimate=5.6109, -0.7761 respectively). Gingival index had the correlation with IL-1β in GCF (P=0.023). Thus, gingival index was deleted from the model. Hypertension was also associated positively with IL-1β ein GCF (P=0.0455) and previous history of ischemic heart disease was associated negatively with TNF-α (P=0.4868) in GCF. Therefore, hypertension and previous history were deleted from the model.

IV. Discussion

In the gingival index (GI) which may indicate the present inflammation status, the atherosclerosis group showed higher level than the control group. However, plaque index (PI) indicating the present status of oral hygiene, probing pocket depth (PPD) and clincal attachment level (CAL) which indicate long-term destruction of the periodontal tissue showed no difference between the atherosclerosis group and the control (Table 2). It is consistent with the results of Kweider et al[27]. They compared fibrinogen and white cell count in patients with gingivitis or periodontitis and in periodontally healthy controls. In this study, it appeared that individuals with poorer gingival index scores had higher fibrinogen scores and white cell counts, irrespective whether they had been classified as periodontal patients or controls. In the present study, indicators of periodontal disease such as GI, PI, PPD, CAL are the means of the values measured in the Ramfjord' s

Table 8. Multivariate logistic regression models for atherosclerosis

Variable	Parameter Estimate	Standard Error	Probability Chi-Square	Odds Ratio	95% Confidence Levels
Age	0.1073	0.0657	0.1021	0.003	(0.979 1.266)
Gender	2.3260	1.6683	0.1633	10.237	(0.389 269.303)
Smoking	2.7840	1.7191	0.1054	16.184	(0.557 470.346)
PPD	-2.6129	1.5221	0.1860	0.134	(0.007 2.639)
gIL-1β*	5.6109	2.3654	0.0177*	273.385*	(2.650)999.99)
gTNF-α*	-0.7761	0.3596	0.0309*	0.460*	(0.227 0.931)
gPGE2	0.9718	1.1340	0.3915	2.643	(0.286 24.397)

† Hosmer and Lemeshow Doodness-of-Fit Test ; P=0.6884

*: p〈0.05

PPD ; probing pocket depth, gIL-1β ; IL-1β in GCF, gTNF-α; TNF-α in GCF, gPGE2; PGE2 in GCF

teeth. Thus, it may not reflect the periodontal status of the full mouth. According to Offenbacher' s study[21], the extent of periodontal disease was more associated with the preterm low birth weight than the severity of periodontal disease. That is, it seems to be valuable to record the status of the full mouth. And the edentulous patients were excluded from this study. Therefore, the association between periodontal health and CVD factors may be underestimated.

The most striking observation in this study is the quantitative dominance of IL-1β Sand PGE_2 within the GCF of the atherosclerosis group (Table 3). IL-1β and PGE_2 mediate inflammation and connective tissue destruction. It is also consistent with the current concept of molecular pathogenesis which places emphasis on the central role of the LPS-elicited monocytic activation pathway[28]. However, TNF-α is higher in the control than the atherosclerosis group (P=0.009). It is not consistent with the other study[15]. By the way, IL-1β and PGE_2 in GCF is higher in the atherosclerosis group is not consistent with the fact that there is no difference of the periodontal status between the atherosclerosis and control. This may result from the fact that clinical measurements in this study may not reflect the periodontal status of the full mouth. And, although not statistically significant, other indicators of disease such as PI, PPD and CAL demonstrated a consistent trend for the atherosclerosis group having worse periodontal disease than the controls. It seems to be due to small sample size. In plasma levels of the cytokines, there were no statistically significant differences (Table 4). It is consistent with Prabhu et al[14]. They demonstrated no significant differences between healthy controls and patients with periodontitis in the systemic immune response of the cytokine levels and their m RNA expression. And, in this study, the cytokines in GCF were not correlated with those in plasma (Table 6). In conclusion, the cytokines in GCF may not be dumped systemically.

Serum lipid/lipoprotein levels, C-reactive protein and white cell count of the atherosclerosis group did not differ from those of the control (Table 5). This might be due to the medical treatment given to the patients with atherosclerosis.

In logistic regression models, only IL-1β and TNF-α in GCF were associated significantly with atherosclerosis (Table 8). It is evident that after adjusting for all the other factors in the model, IL-1β in GCF demonstrated more than 273-fold the odds of atherosclerosis. The elevation of IL-1β levels in GCF resulting from periodontitis is positively associated with atherosclerosis. However, elevated IL-1β in GCF, itself, may not be dumped systemically falling within the detectable range of biological serum assay.

Further research may be conducted to explain why the elevation of cytokines in GCF is positively associated with the atherosclerosis, although there is no elevation of cytokines in plasma. And, the other mechanism by which periodontitis may be proposed to contribute to atherosclerosis-the effect of the periodontal pathogens or lipopolysaccharide on major blood vessels-must be clarified.

Beck et al. proposed the hypothetical working model for the biological basis of the observed association between periodontal disease and atherosclerosis, coronary heart disease[3]. They emphasized that there may be an underlying hyperinflammatory trait in response to stimuli that is manifested by an excessive production of pro-inflammatory cytokines and lipid mediators by monocytes and other cell types. This hyperinflammatory trait MØ may be induced by genetic, behavioral and environmental exposure and may serve as a common antecedent to both cardiovascular and periodontal risk. The effect of a genetic factor such as the hyperinflamma-

tory MØ phenotype on periodontitis and atherosclerosis remains to be elucidated.

V. Conclusions

1. The elevation of cytokines, especially IL-1β in GCF resulting from periodontitis is positively associated with the atherosclerosis.
2. The cytokine produced locally in periodontium may not be dumped systemically to blood circulation.

VI. References

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-국문초록-

치주염이 동맥경화에 기여하는 기전에 관한 연구

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그람 음성균의 감염에 의한 만성 염증질환인 치주염이 동맥경화를 동반한 허혈성 심장질환 (협심증이나 심근 경색)을 일으킬 수 있는 위험인자로 작용할 수 있다는 보고가 있었다. 그러나, 그 기전에 관해서는 명확하게 알려져 있지 않다. 작용기전의 하나로서, 치주염에 의해 치주조직에서 국소적으로 생긴 염증성 싸이토카인 (IL-1β, IL-6, PGE_2, TNF-α)이 혈행을 따라 이동하여 심혈관에서 동맥경화를 일으킬 수 있다는 가설이 제시되고 있는데, 이 가설을 검증해 보고자 한다.

서울대학교 병원 순환기 내과에 불안정 협심증이나 심근경색으로 입원한 환자 및 과거 이 질환의 병력을 갖고 있거나 검진 목적으로 내원하여 관상동맥 조형술을 받은 환자들 중 동맥경화로 진단받은 사람을 실험군(24명)으로 하고, 동맥경화로 진단받지 않은 사람을 대조군(12명)으로 하였다. 치주질환의 활성도를 나타내는 치은 지수, 치태 지수, 치주낭 깊이, 부착 상실을 측정하였다. Paper strip을 실험대상 치아 (Ramfjord' s teeth)들 중에서 가장 깊은 치주낭을 가진 두 개의 치아를 택하여 각 치아의 가장 깊은 치주낭에 30초간 삽입한 후 밀폐된 plastic tube에 넣고 ELISA kit를 이용하여 IL-1β, IL-6, TNF-α, PGE_2의 농도를 측정하였다. 환자의 plasma에서도 동일한 싸이토카인의 농도를 측정하였다. 설문조사를 통해 동맥경화의 위험 인자로 간주되어온 고혈압, 당뇨, 가족력, 심근경색이나 협심증의 기왕력, 흡연의 유무를 기록하였다. 혈액검사를 하여 total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, WBC, CRP (C-reactive protein)의 농도를 측정하였다.

치주조직에 대한 임상 검사 결과 치은의 염증상태를 나타내는 지표인 치은 지수에서만 실험군이 대조군에 비해 유의할 정도 (P=0.0174)로 높게 나타났고, 만성적인 염증의 결과로 인한 치조골의 상실 정도를 나타내는 치주낭 깊이나 부착 상실에서는 유의할 만한 차이를 보이지 않았다. 치주낭에서 측정한 염증성 싸이토카인 중 IL-1β, PGE2가 실험군에서 유의할 만한 차이 (P=0.005, 0.022)를 보이며, 더 높은 농도로 나타났고, TNF-α는 대조군에서 유의성 있게 (P=0.009) 높게 나타났다. 그러나, plasma의 싸이토카인이나, serum lipid/lipoprotein, C-reactive protein, WBC는 유의할 만한 차이를 보이지 않았다. 또한 치은열구액내의 싸이토카인과 혈장내에 이에 상응하는 싸이토카인 간에 상관관계는 관찰되지 않았다. 다변량 로지스틱 회귀분석 결과, 치은열구액내의 IL-1β와 TNF-α 만이 동맥경화와 유의성 있는 관련성을 보였고, 특히 IL-1β의 교차비는 273으로 상당한 관련성을 보여주었다.

결론적으로, 치주조직에서 국소적으로 생긴 염증성 싸이토카인이 그대로 혈행으로 이동하여 혈장내의 싸이토카인 농도를 높이는 것은 아니다. 그러나, 치주염으로 인해 치은열구액내에 국소적으로 증가된 염증성 싸이토카인은 동맥경화와 상당한 관련성을 가진다.

주요어: 치주염, 동맥경화, 치은열구액, 싸이토카인