



Examining the Relationship: *Porphyromonas gingivalis* Presence in Subgingival and Atherosclerotic Plaques of Cadavers

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Abstract

Background: Atherosclerosis and periodontitis are chronic inflammatory diseases characterized by inflammation and tissue destruction. *Porphyromonas gingivalis*, a key pathogen in periodontal disease, is implicated in initiating inflammation and tissue damage.

Objectives: Given the potential link between periodontitis and the development of atherosclerotic plaques, this study aimed to investigate the presence of *P. gingivalis* DNA in subgingival and atherosclerotic plaques obtained from cadavers at the Tehran Forensic Medicine Center.

Methods: In this cross-sectional study, cadavers with a postmortem interval of 6 hours and atherosclerotic plaques in their coronary arteries, along with subgingival plaques exhibiting pocket depths exceeding 5 mm, were examined. Subgingival plaque samples were collected from the deepest sites, while atherosclerotic plaque samples were harvested. Real-time PCR was employed to detect the presence of *P. gingivalis* in all samples, and the McNemar test was used for data analysis.

Results: A total of 25 cadavers were included in the analysis, and both subgingival and atherosclerotic plaque samples were assessed. *P. gingivalis* DNA was identified in 40% of subgingival plaque samples and 16% of atherosclerotic plaque samples. Moreover, all positive atherosclerotic plaque samples also tested positive for *P. gingivalis* in the subgingival plaque. McNemar's analysis revealed a statistically significant difference between the subgingival and atherosclerotic samples (P-value = 0.03). Additionally, a correlation coefficient of 0.53 was obtained.

Conclusions: While the study has certain limitations, the findings indicate a significant association between the presence of *P. gingivalis* in subgingival and coronary atherosclerotic plaques. Further investigations are warranted to elucidate the precise role of this periopathogen in atherosclerotic plaque formation.

Keywords: *Porphyromonas gingivalis*, Plaque, Atherosclerotic, Dental Plaque, Coronary Vessels

1. Background

Atrioventricular septal defect (AVSD) is a progressive chronic inflammatory process that can thicken vascular walls (1, 2). Cardiovascular diseases (CVD) are primarily caused by AVSD, the leading cause of global mortality, projected to affect approximately 23.4 million individuals (3). Several risk factors, including hypertension, hypercholesterolemia, diabetes, extreme obesity, smoking, physical inactivity, and chronic

bacterial infections, have been linked to the development of AVSD (4). Recent studies over the past two decades have indicated that microorganisms and conventional risk factors play a role in the initiation and progression of atherosclerotic plaques (4-7). Notably, periodontal pathogens such as *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and *Porphyromonas gingivalis* (*P. gingivalis*) have been strongly associated with coronary artery disease and myocardial infarction (8). *P. gingivalis*, the primary

pathogen in chronic periodontitis, contributes to the pathogenesis of atherosclerosis through the presence of lipopolysaccharides (LPS) as endotoxins and its ability to translocate into systemic blood vessels from the oral cavity (8). The DNA of *P. gingivalis* is commonly found in atheromatous plaques of individuals with periodontal diseases (9).

Periodontitis is a chronic asymptomatic inflammatory disease characterized by a slow progression. It occurs following the colonization of gram-negative anaerobic bacteria in the tooth or subgingival margin, resulting in damage to the supporting tissues (3, 5, 10). The chronic inflammatory responses triggered by periodontitis have been considered potential risk factors for AVSD (7). Studies have shown that patients with periodontitis and ulcerated epithelium in the pocket wall experience transient bacteremia (7, 11, 12).

Among the numerous bacterial species in human subgingival plaque, *P. gingivalis* is the primary causative agent of chronic periodontitis. This bacterium produces various virulence factors that modulate the host's inflammatory response and contribute to the destruction of periodontal tissues (13). Evidence suggests that periodontal pathogens are involved, either directly or indirectly, in platelet accumulation, increased levels of low-density cholesterol, lipoprotein deposition in the vascular wall, endothelial damage in the heart and carotid arteries, and elevated levels of inflammatory mediators in the blood and tissues (4). Persistent low-level bacteremia associated with chronic periodontitis can lead to the invasion of bacteria into endothelial cells, causing endothelial dysfunction and triggering pro-inflammatory and pro-atherogenic responses. Periodontal pathogens activate pro-inflammatory cytokines and chemokines, forming foam cells, which is an early stage in the development of atherosclerosis (14).

Numerous studies have emphasized the critical role of anaerobic bacteria, including *P. gingivalis* and *A. actinomycetemcomitans*, in developing CVD. For instance, Gaetti-Jardim et al. found a significant association between *P. gingivalis* in subgingival plaques of patients with periodontitis and atherosclerotic plaques in the same individuals (4). While some studies have reported a similar correlation (1, 3), others have not found a significant relationship between *P. gingivalis* in subgingival and atherosclerotic plaques in patients with periodontitis (9, 15).

2. Objectives

Given the conflicting findings regarding the potential involvement of *P. gingivalis* in coronary artery diseases (CAD), which continue to be the leading cause of mortality worldwide (2-4, 16), the present study aimed to investigate the presence of *P. gingivalis* DNA in autopsy samples of subgingival and atherosclerotic plaque obtained from corpses transferred to the Tehran Forensic Medicine Organization.

3. Methods

3.1. Patients

This descriptive cross-sectional correlational study was conducted on deceased individuals transferred to the Forensic Medicine Organization to determine the cause of death. All procedures were performed following the ethical guidelines laid down by the Declaration of Helsinki. The study population consisted of 16 (64%) males and 9 (36%) females, with an average age of 56. Inclusion criteria required individuals to have at least ten teeth and two pockets with a depth exceeding 5 mm. Additionally, these individuals were diagnosed with coronary atherosclerotic plaques during the autopsy, performed within 6 hours postmortem. Comprehensive data, including systemic conditions, age, weight, height, history of drug addiction, and smoking habits, were extracted from the cadavers' records. Before commencing the study, ethical approvals and permissions were obtained from the appropriate authorities at the Forensic Medicine Organization. Written consent was obtained from the families of the cadavers involved in this research study.

3.2. Sample Collection

The autopsies were performed by experienced forensic experts who meticulously examined the condition of the coronary arteries. Identification of coronary arteries with atherosclerotic plaques was confirmed. Subsequently, probing of all tooth surfaces was conducted using a Williams probe. Subgingival plaque samples were collected from the deepest regions of pockets exceeding 5 mm, employing sterile paper points. These samples were then carefully transferred to Eppendorf tubes containing trypticase soy broth (TSB) medium. Forensic experts excised atherosclerotic plaques measuring at least 1 × 1 mm and promptly placed them in separate Eppendorf tubes containing TSB. Each of the 25 eligible cadavers contributed one subgingival plaque sample and one atherosclerotic plaque sample. All collected samples were promptly stored at -20°C and transported to the Microbiology

Department of Shahid Beheshti University of Medical Sciences to analyze *P. gingivalis* DNA using the real-time polymerase chain reaction (PCR) method.

3.3. DNA Extraction and Real-time PCR

Bacterial DNA extraction was performed on all plaque samples using the high-pure PCR template preparation kit (Roche, Germany, Lot No. 10362400), following the manufacturer's instructions. The Nanodrop instrument (WPA Biowave II Nanospectrophotometer, USA) determined the total DNA concentration. Qualitative real-time PCR was conducted using the BIOFACT Sybr Green master mix (CAT. NO.: PR901638) on a real-time PCR system (QuantStudio™ 6 Flex Real-Time PCR System, Thermo Fisher Scientific). The real-time PCR reactions were prepared in a final volume of 20 μ L, comprising 2 μ L of extracted genomic DNA as the template, 10 μ L of master mix, and 0.4 M each of the forward and reverse primers. The primer sequences used were as follows: 3'-AGGCAGCTTGCCATACTGCG-5' (forward) and 3'-ACTGTTAGCAACTACCGATGT-5' (reverse) (17). PCR-grade water was utilized as a negative control instead of template DNA.

The conditions for the qualitative real-time PCR were as follows: An initial denaturation step at 95°C for 10 minutes, followed by 45 cycles of denaturation at 95°C for 15 seconds, annealing at 50°C for 30 seconds, and extension at 72°C for 30 seconds. The accumulation of PCR products at each cycle was monitored by measuring the increase in fluorescence intensity of the dsDNA-binding Sybr Green.

3.4. Data Analysis

The quantitative variables were described using mean, standard deviation, minimum, and maximum, whereas qualitative variables were explained in percentages. McNemar's test was used for pairwise comparison of PCR results in two samples. The results' correlation and the agreement's Kappa coefficient were calculated in the whole group and subgroups. A P-value < 0.05 was considered statistically significant.

4. Results

This research aimed to investigate the presence of *P. gingivalis* DNA in subgingival and atherosclerotic plaques collected from 25 eligible corpses. Among the examined corpses, three individuals (12%) were identified as smokers, while seven individuals (28%) had a history of alcohol or drug addiction.

The molecular tests revealed that 40% (10 samples) of subgingival plaques and 16% (4 samples) of atherosclerotic plaques tested positive for *P. gingivalis* DNA. Among the 21 negative samples of atherosclerotic plaques (84%), six corresponding subgingival plaque samples were reported as positive. All four positive atherosclerotic plaque samples were also positive for bacterial DNA in the subgingival plaque samples (Table 1).

In 15 out of the 25 examined samples (60%), bacterial DNA was not detected in either the subgingival or atherosclerotic plaques. Conversely, bacterial DNA was detected in both the subgingival and atherosclerotic plaques in 4 cases. Thus, there was an agreement between the two groups in nineteen cases. The McNemar test was employed to compare the two groups (atherosclerotic and subgingival samples) within each patient, and the results revealed statistically significant differences (P-value = 0.03).

Nine of the examined corpses had a medical history of diabetes and cardiovascular diseases. The subgingival and atherosclerotic plaques contained bacterial DNA in two of these cases. Applying the McNemar test in these cases did not reveal a significant difference between the atherosclerotic and subgingival groups (correlation coefficient $r = 0.500$). Therefore, within each patient with a history of cardiovascular disease and diabetes, there was no significant distinction between the atherosclerotic and subgingival plaque samples.

As presented in Table 2, the Spearman correlation coefficient demonstrated a moderate correlation ($r = 0.53$) between the atherosclerotic and subgingival groups. Table 3 provides an overview of the Kappa agreement coefficient, pairwise comparisons using the McNemar test, and corresponding P-values, assessing the agreement between the atherosclerotic and subgingival groups. The Kappa test revealed poor inter-group agreement (44%). However, a modest agreement was observed between the subgingival and atherosclerotic samples across all subjects. Notably, this agreement coefficient increased among individuals with a history of cardiovascular disease and diabetes, BMI over 25 kg/m², and age over 55 years. Furthermore, McNemar's test indicated no statistically significant difference between the results of the two atherosclerotic and subgingival plaque samples in high-risk individuals (P-value > 0.05).

5. Discussion

Reviewing research conducted over the past two decades reveals that certain microorganisms and

Table 1. Cross Table of the Frequency of *Porphyromonas gingivalis* Bacteria in Atherosclerotic and Subgingival Samples ^a

Variable	Atherosclerosis		Total
	Negative	Positive	
Subgingival			
Negative	15	0	15
Positive	6	4	10
Total	21	4	25

^a Values are presented as count (%).

Table 2. Correlation Coefficient Between the Results of Two Atherosclerotic and Subgingival Groups

Variables	Atherosclerosis		Total
	Negative	Positive	
Subgingival			
Negative			
Count	15 (60)	0	15
Expected Count	12.6	2.4	15
Positive			
Count	6	4	10
Expected Count	8.4	1.6	10
Total			
Count	21	4	25
Expected Count	21	4	25
Measure of Agreement			
Value of Kappa	0.444		

common risk factors can contribute to the development of atherosclerotic plaques. One such bacterium is *P. gingivalis*, an anaerobic Gram-negative bacterium known for its role in initiating inflammation and tissue destruction in periodontal disease (13, 18).

Periodontitis, characterized by oral microbiota dysbiosis, is a multifactorial inflammatory disease that destroys periodontal tissues and bone (19). Numerous studies have established a significant association between chronic periodontitis and other conditions like rheumatoid arthritis, diabetes, and cardiovascular disease (20, 21).

The inflammatory atherosclerosis hypothesis posits that atherosclerosis is an inflammatory response triggered by agents that cause damage to the endothelial cells of blood vessel walls (7). In addition to directly infecting cardiac tissue, certain infectious agents can induce and sustain inflammation, indirectly contributing to cardiovascular disease (1, 22). Other risk factors for atherosclerosis include hypertension, hypercholesterolemia, diabetes, obesity, smoking, and physical inactivity (4).

The association between oral health and atherosclerosis was initially suggested by Mattila et al., who found a strong correlation between poor dental hygiene and acute myocardial infarction (23). Mendez et al. identified periodontitis as an independent risk factor for peripheral vascular disease. The presence of periodontopathic bacteria, including *P. gingivalis* and *Streptococcus sanguis*, in atherosclerotic lesions was first reported in a study investigating the impact of various infections on the development of carotid artery plaques (24).

The oral cavity serves as a significant reservoir of diverse microorganisms that can enter the bloodstream of individuals with periodontitis through activities like chewing and tooth brushing, which occur multiple times a day (25, 26).

Research indicates that the prevalence of *P. gingivalis* in healthy adults ranges from 16.8% to 25%, highlighting its presence even in individuals without apparent periodontal issues. For instance, a study published in the *Journal of Clinical Microbiology* reported a detection rate of 25% in healthy subjects, contrasting with a higher prevalence of 79% in individuals with

Table 3. Summary of Kappa Agreement Coefficient, Pairwise Comparison of Two Groups and P-Value for Agreement Between Atherosclerotic and Subgingival Groups

Variables	Subgingival	Atherosclerosis	McNemar; P-Value	Kappa
Total			0.03	0.44
Positive	10 (40)	4 (16)		
Negative	15 (60)	21 (84)		
CVD+^a			0.50	0.53
Positive	4 (44.4)	2 (22.2)		
Negative	5 (55.6)	7 (77.8)		
BMI > 25			0.25	0.52
Positive	6 (46.2)	3 (23.1)		
Negative	7 (53.8)	10 (76.9)		
Age > 55			0.13	0.46
Positive	6 (42.9)	10 (71.4)		
Negative				

^a CVD+ = people with diabetes + people with cardiovascular disease.

periodontitis. This disparity underscores the potential subclinical presence of *P. gingivalis* in healthy populations, suggesting a complex relationship between this bacterium and oral health (27).

In the present study, *P. gingivalis* was detected in 45% of subgingival plaque samples and 16% of atherosclerotic plaque samples. A pairwise comparison of atherosclerotic and subgingival samples within each patient revealed a statistically significant difference in the results. Six of the 21 atherosclerotic samples negative for *P. gingivalis* had positive subgingival samples. Furthermore, all four positive atherosclerotic plaque samples also tested positive in examining subgingival plaques. The correlation between the atherosclerotic and subgingival groups was modest (correlation coefficient $r = 0.5$), and the agreement between the atherosclerotic and subgingival groups, as assessed by the Kappa test, was 44%. Atarbashi-Moghadam et al. reported the presence of *P. gingivalis* in 43.47% of subgingival and 13.04% of atherosclerotic plaque samples, which was statistically significant. This study is the same as the current study regarding sample size, the microbiological investigation method, the statistical test, and the results. It confirms the relationship between *P. gingivalis* in subgingival and atherosclerotic plaques (1).

In the study by Altayeb et al., the load of periodontal bacteria in atherosclerotic plaque samples was much higher in patients with periodontitis compared to the healthy group, and pathogens play a role in periodontitis, especially *P. gingivalis* and *Tannerella forsythia*, were also found in atherosclerotic plaques. This study showed that the presence of these bacteria in atherosclerotic plaques is attributed to the severity of

periodontitis and bacterial load of subgingival plaques. The presence of periodontal pathogens in atherosclerotic plaques showed a relationship between periodontitis and cardiovascular diseases, which is consistent with the results of the present study (3).

Gaetti-Jardim et al. conducted a study that aligns with the present research, as they found no significant association between the presence of periopathogenic bacteria in atherosclerotic plaques and factors such as age, sex, number of teeth, or smoking. *P. gingivalis* was the most frequently detected bacterium (53.8%) in atherosclerotic plaque samples from patients with periodontitis. The authors of that study suggested that the presence of periopathogenic bacteria in atherosclerotic plaques of individuals with periodontitis indicates a non-random occurrence and implies their potential involvement in cardiovascular diseases, consistent with the current study's findings (4).

In another study by Marcelino et al., they reported the presence of *P. gingivalis* in 75% of subgingival plaque samples and 50% of atherosclerotic plaque samples, corroborating the present study and confirming the relationship between *P. gingivalis* in subgingival and atherosclerotic plaques (28).

Szulc et al. also found the presence of *P. gingivalis* in 74% of subgingival plaque samples and 23% of atherosclerotic plaque samples. Their findings demonstrated the frequent occurrence of *P. gingivalis* in atherosclerotic plaques of patients with periodontitis, which is consistent with the current study (7).

On the other hand, Cairo et al. reported the presence of *P. gingivalis* in 53% of subgingival plaque samples (15).

However, they did not detect it in any of the atherosclerotic plaque samples. They did not observe a relationship between the presence of periodontal bacteria in subgingival plaques and the development of atherosclerotic plaques, which contradicts the results of the present study. This discrepancy could be attributed to the smaller sample size in their study, which may have hindered the detection of a relationship between the presence of *P. gingivalis* in subgingival plaques and atherosclerotic plaques. Furthermore, the methods employed in the two studies differ, as Cairo et al. collected samples from the carotid arteries of living individuals. In contrast, our study collected samples from the coronary arteries of deceased individuals (15). Aimetti et al. reported the presence of *P. gingivalis* in 63% of subgingival plaque samples and did not report the presence of this bacterium in any of the atherosclerotic plaque samples. They found no relationship between *P. gingivalis* in subgingival and atherosclerotic plaques. They took their sample from carotid artery plaques. The discrepancy between the results can be attributed to the different immune responses of the host, the different study populations, and the different sample collection techniques (11).

Additional analyses conducted in our study revealed that when considering only the high-risk group of individuals with a history of cardiovascular disease and diabetes, there was no statistically significant difference between the atherosclerotic and subgingival plaque samples. However, the small size of our study may have influenced these findings. Given that advanced age, high BMI, and underlying systemic conditions such as diabetes and smoking are significant risk factors for cardiovascular diseases, it is imperative to prioritize these factors and conduct further investigations in future studies.

One limitation of our research was the difficulty in obtaining suitable samples. Rigor mortis posed challenges in opening the mouth, thereby hindering access to posterior teeth during subgingival plaque sampling. Additionally, the small sample size and focus solely on the DNA of *P. gingivalis* bacteria were areas that could be improved in our study. Future studies can explore the examination of other periopathogenic bacteria in similar contexts. Furthermore, our study only examined the existence of an agreement between samples without investigating cause-and-effect relationships. It is worth considering that by focusing on larger sample sizes and minimizing data dispersion in terms of age, sex, and systemic conditions, a stronger agreement between subgingival and atherosclerotic

samples can potentially be achieved, particularly within high-risk groups.

Future studies could use next-generation sequencing to fully characterize all oral and atherosclerotic plaque specimens to better understand the role of periopathogenic bacteria in atherosclerotic plaque development and progression. This approach would provide valuable insights into the intricate mechanisms underlying the involvement of periopathogenic bacteria in atherosclerosis.

5.1. Conclusions

In conclusion, despite the limitations of our study, the results highlight a significant relationship between the presence of *P. gingivalis* in subgingival and atherosclerotic plaques in coronary arteries. Patients with chronic periodontitis exhibited positive detection of this pathogen in their atherosclerotic plaques, indicating a potential link between periodontal disease and cardiovascular health. These findings underscore the importance of emphasizing effective periodontal therapy as a potential intervention for improving cardiovascular outcomes in individuals with cardiovascular disease. Further research with larger sample sizes and comprehensive analysis of other periopathogenic bacteria is warranted to better understand this association and establish causality.

Footnotes

Authors' Contribution: H. R. D.: Conceptualization, validation, supervision, project administration; N. E.: Conceptualization, validation, writing-review and editing, supervision, project administration, Visualization; Sh. K. J.: Investigation, resources, visualization; H. G.: Methodology, formal analysis, resources; B. H.: Investigation, formal analysis, Data curation; S. M.: Writing-original draft, writing-review and editing, Visualization; M. S.: Writing-original draft, writing-review and Editing.

Conflict of Interests Statement: The authors state that they have no conflicts of interest.

Data Availability: All datasets generated for this study are included in the article.

Ethical Approval: This study is approved by the Faculty of Dentistry, Islamic Azad University of Tehran ([IR.IAU.DENTAL.REC.1397.047](https://doi.org/10.30616/IR.IAU.DENTAL.REC.1397.047)).

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Informed Consent: Written consent has been obtained from the families of the cadavers involved in this research study.

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