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Periodontal disease in association with Myocardial Infarction with Non-Obstructive Coronary Arteries and Microvascular Coronary Artery Disease

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Abstract

Objective. We sought to evaluate any association of periodontitis in patients with angina despite non-obstructive coronary artery disease (CAD).

Methods. Electronic records of all patients (n=103,955) labeled as ACS were screened and the patients diagnosed with myocardial infarction with non-obstructive coronary arteries (MINOCA) were enrolled as group 1 and age-matched controls with no CAD were labeled as group 2.

Results. Female gender (OR (95%CI): 1.04 (0.93 – 1.59); p=0.004), diabetes mellitus (OR (95%CI): 0.25 (0.05– 0.63); p=0.02), peripheral arterial disease (OR (95%CI): 0.78 (0.63 – 0.91); p=0.001), dyslipidemia (OR (95%CI): 1.45 (0.47 – 2.93); p=0.015), smoking, moderate (OR (95%CI): 5.42 (1.91 – 22.69); p=0.04) and severe periodontitis (OR (95%CI): 2.58 (1.72 – 3.26); p=0.027) were independent predictors of MINOCA. There was an increased graded risk (relative risk (RR)) of MINOCA with periodontitis + diabetes mellitus (RR (95%CI): 0.91 (0.34 – 1.23); p=0.032), periodontitis + peripheral arterial disease (RR (95%CI): 0.85 (0.47 – 1.46); p=0.025), periodontitis + renal disease (RR (95%CI): 1.04 (0.85 – 1.23); p=0.04), and periodontitis + smoking (RR (95%CI): 0.94 (0.77 – 1.06); p=0.006).

Conclusion. This study demonstrated that moderate to severe periodontitis might be independently associated with the increased incidence of MINOCA among the general population. Furthermore, it discovered various predictors of MINOCA among the general population.

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Introduction

Periodontal disease (PD) is a major public health problem and is associated with various systemic diseases[1]. Given that cardiovascular disease (CVD) shares common risk factors with periodontitis [2], several studies have demonstrated the causal relationship between the two. Whilst many studies have investigated the potential link of oral hygiene with CVD, the outcomes have been limited to atherosclerotic CVD, including acute coronary syndrome (ACS), or heart failure (HF) [3]. Several mechanisms have been proposed to explain the link between periodontitis and myocardial infarction with non-obstructive coronary arteries (MINOCA). One theory is that bacteria from the mouth may enter the bloodstream and cause inflammation in the arteries, which can lead to coronary thrombus causing MI. Additionally, the inflammation associated with periodontal disease may contribute to the development of atherosclerosis, which is the buildup of plaque in the arteries. To our knowledge, the relationship between periodontitis with MINOCA and microvascular angina has not been investigated. We, therefore, sought to evaluate any association of periodontitis in patients with angina despite non-obstructive coronary artery disease (CAD). In addition, we compared the prevalence of periodontitis in the age-matched general population with no CVD.

Methods

This prospective observational study was conducted at our institute (Abbas Institute of Medical Sciences) according to the World Medical Declaration of Helsinki. Ethical approval was sought before data collection (study ID # AIMS/13/22). All patients gave written informed consent.

Electronic records of all patients (n=103,955) labeled as ACS were screened from January 2018 to December 2021. All patients diagnosed with MINOCA were enrolled as group 1 and age-matched controls with no CAD were labeled as group 2. Anyone who had undergone recent (within 2 weeks) periodontal treatment was excluded because dental examination might interfere with wound healing. Patients requiring endocarditis prophylaxis were also excluded.

The extent of periodontitis is influenced by other non-cardiac diseases, including immunocompromised state, lipid, and glycogen storage diseases, systemic inflammatory diseases, auto-immune connective tissue diseases, leukocyte adhesion deficiency, and hypophosphatemia; therefore, to prevent attrition bias, we excluded patients with major concomitant diseases. All patients underwent a dental check-up from the cardiology outpatient clinic. Patients underwent intraoral clinical examination by a single periodontist to eliminate inter-observer variability.

MINOCA was defined according to the ESC working group position paper on myocardial infarction with non-obstructive coronary arteries, following a clinical diagnosis (Symptoms of ischemia, rise and fall of troponins, and/or electrocardiographic changes consistent with ischemia) of acute myocardial infarction (AMI) and demonstration of non-obstructive coronary arteries (<50% coronary stenosis) [4]. Periodontal disease was defined according to the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10), as mentioned by Park *et al.* [5]. The dental examination involved patient history, oral inspections, and probing periodontal pockets with a World Health Organization probe [6]. Depth of the periodontal pocket was defined as the distance from the marginal gingiva to the sulcus ground. Bleeding from gums upon probing, calculus, and the periodontal screening index (PSI) were examined for each tooth. The highest score of PSI was recorded for every patient: scores of 1 and 2 were defined as gingivitis; scores of 3 or ≥4 were labeled as moderate and severe periodontitis, respectively [7]. Primary outcome was to assess the association between periodontal disease and MINOCA. Secondary outcomes included predictors of MINOCA in this cohort and graded risk of MINOCA and periodontitis with CV risk factors.

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA.). Categorical data were presented as numbers (n) and percentages (%) and mean ± standard deviation (SD) were used for continuous variables. Chi-square test was performed for categorical data and Student's t-test or Mann-Whitney U test was used for continuous data where appropriate. Univariate and multivariate regression analyses were performed to determine independent predictors of MINOCA and severe periodontitis. All tests were 2-tailed, and a p-value of <0.05 was considered significant.

Results

The study population comprised 6,237 patients with MINOCA (group 1) and 6,000 age-matched healthy adults (group 2) who had no major cardiovascular events. Baseline patient characteristics are tabulated in **Table 1.** Approximately 70% of participants brushed their teeth at least once a day, used toothpaste as the method of cleaning, and 11% had regular dental visits in both groups.

Table 1. Baseline characteristics

Characteristics	Group 1 (n=6,237)	Group 2 (n=6,000)	p-value
Age (years)	38 ± 12	41 ± 21	0.301
Females	54.5%	37.2%	<0.001
Income levels			
High	11.4%	10.9%	0.832
Middle	31.9%	33.5%	0.547
Low	56.7%	55.6%	0.915
Anthropometric measures			
BMI (kg/m2)	25 ± 4	25 ± 7	0.994
Systolic blood pressure (mmHg)	136 ± 37	137 ± 32	0.741
Diastolic blood pressure (mmHg)	83 ± 16	82 ± 25	0.522
Physical activity	23.5%	16.5%	
Comorbidities			
Diabetes Mellitus	37.9%	25.3%	<0.001
Hypertension	31.5%	27.1%	0.021
Dyslipidemia	27.8%	21.6%	0.007
Smoker	34.5%	32.1%	0.328
Peripheral arterial disease	11.8%	6.4%	0.002
Renal disease	2.7%	2.2%	0.614
Laboratory findings (mg/dL)			
HDL	35 ± 9	34 ± 5	0.563
LDL-C	144 ± 43	132 ± 58	0.004
Triglycerides	113 ± 23	111 ± 43	0.269
Creatinine	0.8 ± 0.1	0.8 ± 0.2	0.951
Oral care			
Frequency of cleaning			
Once a day	69.8%	71.3%	0.638
Twice or more a day	17.5%	23.7%	0.054
Less than once a day	12.7%	5%	<0.001
Method of cleaning			
Tooth paste	71.1%	68.4%	0.159
Any other	28.9%	31.6%	0.208
Regular dental visits	10.9%	11.1%	0.902
Severity of periodontal disease			
Normal	68.8%	82.3%	<0.001
Gingivitis	11.5%	7.5%	0.032
Moderate periodontitis	10.9%	5.7%	<0.001
Severe periodontitis	8.8%	4.5%	<0.001

Female gender (OR (95%CI): 1.04 (0.93 – 1.59); p=0.004), diabetes mellitus (OR (95%CI): 0.25 (0.05– 0.63); p=0.02), peripheral arterial disease (OR (95%CI): 0.78 (0.63 – 0.91); p=0.001), dyslipidemia (OR (95%CI): 1.45 (0.47 – 2.93); p=0.015), smoking, moderate (OR (95%CI): 5.42 (1.91 – 22.69); p=0.04) and severe periodontitis (OR (95%CI): 2.58 (1.72 – 3.26); p=0.027) were independent predictors of MINOCA. This is shown in **Supplementary Table 1**. There was an increased graded risk (relative risk (RR)) of MINOCA with periodontitis + diabetes mellitus (RR (95%CI): 0.91 (0.34 – 1.23); p=0.032), periodontitis + peripheral arterial disease (RR (95%CI): 0.85 (0.47 – 1.46); p=0.025), periodontitis + renal disease (RR (95%CI): 1.04 (0.85 – 1.23); p=0.04), and periodontitis + smoking (RR (95%CI): 0.94 (0.77 – 1.06); p=0.006). This is shown in **Supplementary Table 2.** Central illustration for this manuscript is shown in **Figure 1.**

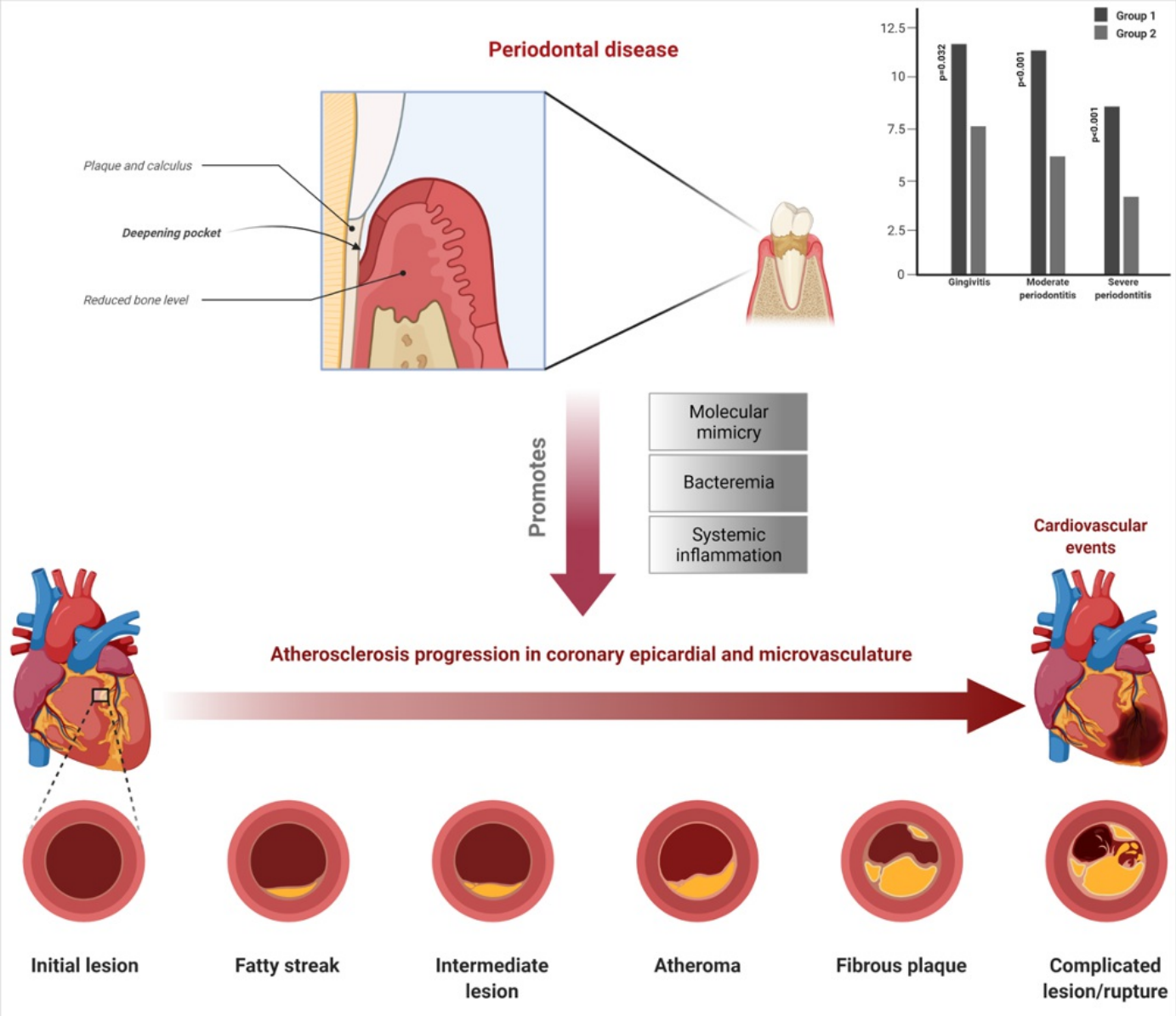

Figure 1. Proposed mechanism of periodontitis with atherosclerotic epicardial and microvasculature

Discussion

The present study demonstrated that moderate to severe periodontitis might be independently associated with the increased incidence of MINOCA among the general population. Furthermore, it discovered various predictors of MINOCA among the general population such as DM, dyslipidemia, PAD, smoking, and female gender. To the best of our knowledge, this is the first study to demonstrate a potential link between MINOCA and PD.

While the exact mechanisms underlying the observed associations between MINOCA and periodontal disease remain unclear, several potential explanations exist, as shown in Figure 1. One such possibility pertains to the invasion of endothelial cells by periodontal pathogens, which has been demonstrated by polymerase chain reaction assays for atherosclerotic plaques [8]. This bacterial presence may influence atherosclerosis due to some pathogens such as*P. gingivalis* triggering foam cell formation, resulting in a state of secondary inflammation that leads to endothelial dysfunction [9][10].

Another suggested mechanism might be the precipitation of a systemic inflammatory response by the periodontal pathogens, resulting in chronically elevated levels of various cytokines [11]. This may also explain our findings since systemic inflammation has been shown to play a role in the pathogenesis of coronary artery spasm [12] and multiple plaque rupture [13], both of which are underlying causes of MINOCA[4]. It is known that periodontitis, diabetes, renal disease, smoking and peripheral arterial disease have independent increased risks of CAD [2][6]. In addition, this study shows an incremental risk of MINOCA in patients with periodontitis. Therefore, we conclude that there might be an incremental risk of MINOCA with periodontitis, and it is an independent predictor of non-obstructive CAD. In addition, CV risk factors (Supplementary Table 2) do have an incremental graded risk of MINOCA. This is consistent with a study demonstrating that common CV risk factors have an incremental risk for incident CAD and all-cause mortality [14]. Keeping in view the increased risk, patients with these risk factors should be treated as high risk and recommended for aggressive risk factor modification strategies, as they can lead to non-obstructive CAD.

Previous studies have demonstrated some relationships between PD and the risk of adverse cardiovascular outcomes [15]. Looking at both the specific patient population[6] and the general population [16], the outcomes of interest have been limited to heart failure, myocardial infarction, CAD, and atherosclerosis, the latter two of which were both predominantly coronary obstructive events. To the best of our knowledge, the present study is the first investigation focusing on the relationships between PD and the risk of MINOCA, which is a non-obstructive phenomenon.

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Competing interests

Authors declare no competing interests.

Appendix

Supplementary Table 1. Age-adjusted multivariate regression analysis for predictors of MINOCA

Predictor	OR (95%CI)	p-value
Female gender	1.04 (0.93 – 1.59)	0.004
Diabetes mellitus	0.25 (0.05– 0.63)	0.02
Peripheral arterial disease	0.78 (0.63 – 0.91)	0.001
Dyslipidemia	1.45 (0.47 – 2.93)	0.015
Smoking	4.35 (1.14 – 14.65)	0.035
Moderate periodontitis	5.42 (1.91 – 22.69)	0.04
Severe periodontitis	2.58 (1.72 – 3.26)	0.027

Supplementary Table 2. Association between MINOCA with periodontitis and common cardiovascular risk factors

Variables	Multivariate model; Relative Risk (95% CI)	p-value	Variables	Multivariate model; Relative Risk (95% CI)	p-value
Periodontitis alone	0.93 (0.34 – 1.56)	0.026	No periodontitis	2.49 (1.31 – 3.05)	0.37
Periodontitis + DM	0.91 (0.34 – 1.23)	0.032	No periodontitis + DM	0.74 (0.26 – 1.24)	0.002
Periodontitis + PAD	0.85 (0.47 – 1.46)	0.025	No periodontitis + PAD	2.15 (1.27 – 2.64)	0.084
Periodontitis + renal disease	1.04 (0.85 – 1.23)	0.04	No periodontitis + Renal disease	1.45 (1.12 – 1.68)	0.063
Periodontitis + Smoking	0.94 (0.77 – 1.06)	0.006	No periodontitis + Smoking	0.97 (0.65 – 1.21)	0.027

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