Received: 16 July 2021 | Revised: 14 October 2021 | Accepted: 19 October 2021

DOI: 10.1002/JPER.21-0418

JOURNAL OF Periodontology

ORIGINAL ARTICLE

Association between peri-implantitis and cardiovascular diseases: A case-control study

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Abstract

Background: This study assesses the association between peri-implantitis and cardiovascular diseases (CVD).

Methods: One hundred and twenty-eight patients with dental implants were recruited to evaluate the prevalence of peri-implantitis in patients with or without CVD (CVD group, n = 82, control group, n = 46, respectively). Diagnosis of peri-implantitis followed the 2017 World Workshop guidelines and the severity was defined as mild, moderate, and severe form when the radiographic bone loss (RBL) was <2, 2 to 4, and >4 mm. Multivariable logistic regression was performed to test the association between two diseases.

Results: A trend of higher prevalence of peri-implantitis defined by detectable RBL beyond the physiologic bone remodeling was found in the CVD group (64.6%) when compared with the controls (56.5%). A significant higher prevalence (48.8%) of moderate to severe peri-implantitis was identified in CVD compared with controls(30.4%) with a significant crude association between moderate to severe peri-implantitis and CVD (odds ratio = 2.18, 95% CI, 1.02 to 4.67; $P = 0.04$). The CVD group had a trend of higher prevalence of deep pockets (≥7 mm) and higher numbers of sites with bleeding on probing (>66%) when compared with controls ($P > 0.05$). However, after controlling for multiple confounders including age, hypertension, smoking, family history of heart attack, and periodontitis, the significant association was not found.

Conclusions: CVD group had significantly higher prevalence of moderate to severe peri-implantitis (RBL ≥2 mm). The association between the two diseases did not exist after controlling multiple confounders for CVD. Future studies with a larger sample size controlling for the patient- and implant-related confounders are needed to better understand the link between peri-implantitis and CVD.

KEYWORDS
cardiovascular diseases, dental implants, heart disease risk factors, peri-implantitis

1 | INTRODUCTION

Peri-implantitis has been exhaustively investigated in contemporary dentistry. A variety of risk indicators for peri-implantitis has been identified, including its association with systemic conditions, but this potential association remains unclear (other than diabetes).[1] It is characterized by the inflammation within the peri-implant mucosa following plaque accumulation and the subsequent progressive bone loss.[2] Mirroring gingivitis, peri-implant mucositis preceding peri-implantitis presents with soft tissue inflammation without corresponding bone loss after physiologic remodeling.[3] The disease entities are collectively considered as the peri-implant diseases, a biological complication surrounding dental implants and the collateral restorative components.[4] An unanimity of the prevalence of peri-implantitis in the scientific literature is still lacking as a result of varying case definitions.[5] namely the different cut-off threshold of bone loss. Correspondingly, a recent systematic review pointed out the wide variety of the prevalence of peri-implantitis as 1% to 47%, with a negative relationship between the prevalence and threshold of bone loss.[6]

Cardiovascular diseases (CVD) are the leading cause among the non-communicable diseases (NCD) for global disease burden (one-third of the total mortality, 45% of NCD-induced mortality).[7] In the US population, not only is CVD the leading cause of death, it also creates the highest medical expenditures and social burden among age-related chronic conditions.[8,9] The term "Total Cardiovascular Disease" is used by the American Heart Association (AHA) to describe collective conditions including stroke, congenital heart disease, rhythm disorders, subclinical atherosclerosis, coronary heart disease (CHD), heart failure, valvular disease, venous diseases, and peripheral disease. The most recent statistical report disclosed the high prevalence of 48% overall and 9% when hypertension is excluded (CHD, heart failure, and stroke only) among US adults.[10]

CVD has been linked to periodontitis based on epidemiological evidence.[11] The evidence suggests a biological mechanism linking severe periodontitis to CVD through bacteremia and the subsequent mounting systemic inflammatory burden.[12] Similar to periodontitis, the chronic inflammation around dental implants harbors pathogenic bacteria[13–15] and increased proinflammatory cytokines.[16,17] In light of the potential significant inflammatory burden around implants with severe inflammation or at multiple sites, it was hypothesized in the current investigation that chronic inflammation at peri-implantitis sites might induce low-grade systemic inflammation and increase the risk for developing CVD via a potential infectious axis similar to that between periodontitis and CVD. The association between two diseases was never investigated before, hence, the aim of this study was to explore the relationship between peri-implantitis and CVD and potential background confounders.

2 | MATERIALS AND METHODS

2.1 | Study population

This study protocol was approved by the Institutional Review Board at the University of Michigan (HUM00130676) and conducted from April 2018 until June 2020 at the Department of Periodontics and Oral Medicine, School of Dentistry in collaboration with the Frankel Cardiovascular Center, Michigan Medicine. The screening process was described in the Appendix S1 (in online *Journal of Periodontology*). Participants with the following criteria were included: 1) aged ≥25 years, 2) at least one implant in function ≥6 months, 3) no known episode of peri-implant infection causing significant abscess or facial swelling within the past year, 4) no known mechanical complications affecting the implant restorations within the past year, 5) enrolled in the controls non-CVD group were those without any established CVD diagnosis, 6) enrolled in the CVD group were those with an established diagnosis of CVD or atherosclerotic cardiovascular diseases (ASCVD) including coronary heart disease, cerebrovascular disease, and peripheral artery disease *after* implant placement, and those who had received interventions to prevent a subsequent CVD event or with a history of a cardiovascular event (myocardial infarction, stroke, stable, or unstable angina, transient ischemic attack, or coronary or other arterial revascularization including coronary artery bypass graft or coronary transluminal angioplasty with or without a stent) *after* implant placement. The diagnosis of CVD was assigned by cardiologists at the Frankel Cardiovascular Center based on findings of ischemic changes in the electrocardiogram, findings in coronary angiography, or a history of a previous CVD event proved by the medical records. The subjects with the following conditions were excluded: 1) head/neck radiotherapy, chemotherapy, or immunosuppressed therapy in the past 6 months; 2) pregnant or lactating female; 3) >2 weeks use of antibiotics in the past 3 months; 4) patients taking medications known to modify the bone metabolism (e.g., IV bisphosphonates, long-term use of corticosteroids, or hormone replacement therapy); 5) drug addiction or alcohol intoxication; 6) treatment for peri-implantitis in the past 3 months. All subjects recruited to the clinical assessment/data collection (one-time appointment) were phone-interviewed first

and confirmed that they had at least one implant placed before they were diagnosed with CVD.

2.2 | Clinical and radiographic assessment/Data collection

The health history was acquired by a constructed questionnaire including age, sex, ethnicity, BMI, diagnosis of type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, osteoporosis, rheumatoid arthritis, or other major diseases. Lifestyles including smoking (pack/day and years of cessation) and alcohol consumption (units/week) were documented. The medication list and the family medical history were also recorded. The questionnaires were administered orally and confirmed study subjects fully understood the questions. Physical assessments were performed, including pulse, blood pressure, and extra-/intraoral exam. Fasting glucose level (mg/dL) was collected using glucometer* and categorized to reflect glycemic control at the time of visit, including <100 (normal), 100 to 125 (prediabetes), 126 to 153 (well-controlled), 154 to 183 (moderate-controlled), and >183 (poor-controlled).[18] Serum samples were collected to evaluate the lipid profile, including total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). With the lipid profile acquired, metabolic syndrome, 10-year ASCVD risk, and the stages of cardiometabolic disease were assessed. The collection procedures and laboratory/data analyses are described in Supplementary Appendix S2 (in online *Journal of Periodontology*).

The dental history was recorded, including the number of remaining teeth, frequency of supportive periodontal therapy (SPT), the time of implant insertion, implant locations, and history of treating peri-implantitis based on the electronic dental records at the University of Michigan, School of Dentistry or confirmed with subject's private dentists. All the implants and remaining natural teeth were evaluated by radiography using long-cone paralleling techniques. The bone loss apical to the most coronal portion of the intraosseous part of the implant or the anticipated level after initial bone remodeling was measured in millimeters to the first visible bone-to-implant contact (BIC) using in-house software.† The implant with the most severe bone loss was identified as the "most diseased" implant and included in the final analysis if more than one implant were present. As a result, implant conditions were divided into two subgroups, including healthy and peri-implantitis. In the subgroup of peri-implantitis, the time of peri-implantitis onset (the first evidence of RBL beyond initial bone remodeling) was evaluated by the past history of radiographs in the electronic dental records at the University of Michigan or private practice in order to test the hypothesis of the current investigation. Subjects with peri-implantitis being observed after the diagnosis of CVD or with unknown history were excluded from the final analysis. Clinical assessments were recorded at six sites around the "most diseased" (tested) implant, including peri-implant probing depth (PD), clinical attachment level (CAL) with the reference of implant crown margin, bleeding on probing (BOP) (±), suppuration (±), modified plaque index (modPI) (0, 1, 2, 3), and modified gingival index (modGI) (0, 1, 2, 3).[19] The implant-related characteristics of the tested implant (e.g., implant system and surface type, implant diameter and length, bone/tissue level, connection and restoration type, years of restoration, and opposing dentition status) and the total number of diseased implants in the whole mouth were documented. A full-mouth periodontal chart was obtained to record PD, CAL, BOP, furcation involvement, and mobility. All assessments were made by one self-calibrated examiner with an inter-examiner reliability of κ 0.82.

2.3 | Diagnosis of peri-implantitis and periodontitis

Following the guidelines of 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions,[2,20] the peri-implant health was defined by the absence of soft tissue inflammation and the absence of additional bone loss. Peri-implant mucositis was diagnosed when peri-implant signs of inflammation (redness, swelling, BOP within 30 seconds following probing) were present without bone loss. Peri-implantitis was diagnosed when there was baseline radiograph present where bone loss is detectable beyond initial bone remodeling, exceeding the mean measurement error of 0.5 mm (detectable bone loss), in combination with an increased PD, BOP, and/or suppuration. In the absence of a baseline radiograph, ≥3 mm of radiographic bone loss (RBL) was identified as peri-implantitis. To discern the inflammatory burden of peri-implantitis, the severity of peri-implantitis was classified in the current study as mild (RBL, detectable to 2 mm), moderate (RBL, 2-4 mm), and severe (RBL > 4 mm) peri-implantitis based on the previous investigations.[21,22]

Periodontitis of the remaining natural teeth was diagnosed where ≥2 non-adjacent teeth presented with interdental CAL or buccal CAL ≥3 mm with PD ≥3 mm at ≥2 teeth except for gingival recession or caries. Staging and grading[23] were included in the stratified analysis to evaluate the impact of periodontal disease severity on the

* Accu-Chek® Aviva Glucometer, Roche Diabetes Care, Indianapolis, IN
† axiUm Dental Software, Exan, Henry Schein, Las Vegas, NV

systemic inflammatory burden concomitant with the peri-implant disease. If only one area (adjacent teeth) presented with interdental CAL or teeth with periodontal stability/remission, the case was categorized as "periodontally healthy".

2.4 | Statistical analysis

An unmatched case-control study design with a predetermined case-to-control ratio (2:1) was implemented. Based on the previous studies, the prevalence of peri-implantitis (defined by detectable bone loss) in the control group was assumed to be 40%.[22,24,25] With a hypothetical peri-implantitis rate of 67% in CVD group, a power calculation to satisfy the two-tailed confidence level of 95% and a power of 80% was performed to acquire a sample size of 134 (89 CVD and 45 controls) using OpenEpi, version 3 calculator. All the categorical variables were reported as frequency (n) and percentage (%). All the quantitative variables were reported as means and standard deviations. Continuous parameters were analyzed using the Student *t-test* or Mann-Whitney depending on the normality test. Multivariable logistic regression with a hierarchical modeling was used to evaluate the adjusted odds ratio (ORs) of the association between peri-implantitis and CVD. The demographic variables were entered, followed by systemic-, oral health-related, and implant-related variables into the univariate regression hierarchically. Confounding variables contributing to the significant explanatory power by P value < 0.05 in the univariate analysis were retained in the final logistic regression model. Sensitivity analyses of different CVD categories in the regression model were performed. Additional stratified analyses were performed to evaluate the potential interaction between different confounding variables. The significance level was defined as P value < 0.05, and all the analyses were completed by statistical software.[‡] Data are available from the authors upon request.

3 | RESULTS

3.1 | Demographic characteristics

A total of 132 participants who met the inclusion criteria were recruited. However, four subjects in the CVD group were excluded due to the lack of radiographic evidence for the occurrence of peri-implantitis before the CVD diagnosis. Consequently, 82 CVD and 46 controls were included in the final statistical analysis (details in Supplementary Appendix S3). Demographic variables between two groups are shown in Table 1. The mean age among the CVD group was significantly higher than the control group (75.0 ± 8.3 versus 69.3 ± 10.1, $P < 0.01$). No significant difference in sex distribution between the two groups was found ($P = 0.08$), yet the majority of the CVD group was composed of males (65.9%). Smoking history was significantly different between the two groups ($P = 0.03$) that two-thirds of controls had never smoked compared with 36% in the CVD group. Concerning the cardiovascular risk factors, the CVD group exhibited a significantly higher prevalence of hypertension than the controls (59.8% versus 39.1%, $P = 0.03$). A family history of heart attack was reported in 58.5% of individuals in the CVD group, which was significantly higher than the control group (34%, $P = 0.01$). The use of aspirin, anticoagulant, and stain lip-lowering medication was more prevalent in the CVD group ($P < 0.05$). The results of lipid panel analyses and the resulting 10-year ASCVD risk and stages of cardiometabolic disease were shown in the Supplementary Table S1 in online *Journal of Periodontology*. Among the lipid profile, TC, LDL-C, cholesterol/HDL ratio, and LDL/HDL ratio were significantly higher in the control group compared with the CVD group ($P < 0.05$).

3.2 | Diagnosis of CVD

The categories of the CVD diagnosis among the CVD group were shown in Table 2. The most common type was coronary heart disease (CHD) (29.3%), followed by arrhythmias (28%), cerebrovascular disease (CeVD) (14.6%), and peripheral artery disease (PAD) (7.3%). Among the patients with arrhythmia, half of the participants received the intervention of pacemakers (14.6% in the total CVD group).

3.3 | Prevalence of peri-implantitis

The prevalence of peri-implant health was 9.8% (n = 8) among the CVD group and 8.7% (n = 4) among the controls (Table 3). The corresponding prevalence of peri-implant mucositis was 25.6% (n = 21) and 34.8% (n = 16), respectively. Peri-implantitis with detectable bone loss was identified in 64.6% (n = 53) of the CVD group and 56.5% (n = 26) of controls. Among them, 11.3% (n = 6) in the CVD group and 7.7% (n = 2) in controls were diagnosed without the baseline radiographs. A prevalence of moderate to severe peri-implantitis (with RBL ≥2 mm) among the CVD group was 48.8% (n = 40) which was significantly higher than 30.4% (n = 14) among the controls ($P = 0.04$). Although not statistically significant, a higher percentage of BOP >66% (% calculated by BOP sites

[‡] IBM® SPSS® Statistics for MAC, 24.0 version, IBM, Armonk, NY

TABLE 1 Demographic variables and CVD risk factors

Variable	Controls (non-CVD) (n = 46) n (%)	CVD (n = 82) n (%)	P value
Age [mean ± SD (range)]	69.3 ± 10.1 (43–86)	75.0 ± 8.3 (50–91)	**0.004**[a,b]
Age			
40 to 49 years	3 (6.5)	0 (0)	< **0.01**[a]
50 to 59 years	2 (4.3)	5 (6.1)	
60 to 69 years	16 (34.8)	12 (14.6)	
70 to 79 years	17 (37.0)	41 (50)	
≥80 years	8 (17.4)	24 (29.3)	
Sex			0.08
Female	23 (50)	28 (34.1)	
Male	23 (50)	54 (65.9)	
Ethnicity			0.08
White	36 (78.3)	74 (90.2)	
Black	3 (6.5)	3 (3.7)	
Hispanic	3 (6.5)	0 (0)	
Asian or American Indian/Alaskan Native/Pacific Islander	4 (8.7)	5(6.1)	
Smoking			**0.03**[a]
Never-smoker	28 (60.9)	30 (36.6)	
Current smoker	2 (4.3)	4 (4.9)	
Ex-smoker	16 (34.8)	47 (5	
≤5 years	1 (6.3)	3 (6.3)	0.52
5 to 10 years	2 (12.5)	3 (6.3)	
10 to 15 years	2 (12.5)	2 (4.2)	
>15 years	11 (68.8)	40 (85.1)	
Alcohol			0.59
Non-drinker	14(30.4)	31 (37.8)	
Social drinker	15 (32.6)	17 (20.7)	
<7 units/week	12 (26.1)	21 (25.6)	
7 to 14 units/week	4 (8.7)	9 (11)	
>14 units/week	0 (0)	1 (1.2)	
BMI			0.85
Normal	17 (37)	23 (28)	
Overweight	15 (32.6)	30 (36.6)	
Obese	12 (26.1)	21 (25.6)	
Severe obese	2 (4.3)	3 (3.7)	
Diabetes mellitus[c]	8 (17.4)	24 (29.3)	0.14
Hypertension[c]	18 (39.1)	49 (59.8)	**0.03**[a]
High cholesterol[c]	16 (34.8)	38 (46.3)	0.20
Osteoporosis or bone-related disease[c]	7 (15.2)	15 (18.3)	0.64
Rheumatoid arthritis[c]	3 (6.5)	6 (7.3)	0.87
Metabolic syndrome[d]	20 (43.5)	45 (54.9)	0.22
Comorbidity			
1 comorbidity	14 (30.4)	27 (32.9)	0.77
2 comorbidity	10 (21.7)	17 (20.7)	0.89
3 comorbidity	9 (19.6)	25 (30.5)	0.18
Family health history			
Heart attack	17 (37)	48 (58.5)	**0.01**[a]
Stroke	21 (45.7)	29 (35.4)	0.33
Hypertension	25 (54.3)	48 (58.5)	0.46
Diabetes	18 (39.1)	40 (48.8)	0.27
Cancer	28 (60.9)	52 (63.4)	0.62
Medications			
Hypoglycemics	5 (10.9)	20 (24.4)	0.06
Aspirin	11 (23.9)	37 (45.1)	**0.02**[a]
Anticoagulant	2 (4.3)	27 (33.0)	**<0.01**[a]
Statin	13 (28.3)	49 (59.8)	**<0.01**[a]
Angiotensin II receptor blocker	8 (17.4)	16 (19.5)	0.77
ACE inhibitor	8 (17.4)	16 (19.5)	0.77
Calcium channel blocker	4 (8.7)	15 (18.3)	0.14
Beta-blocker	11 (23.9)	33 (40.2)	0.06
Diuretics	7 (15.2)	24 (29.3)	0.07
Fasting glucose level[e]			0.28
Normal (< 100 mg/dL)	14 (35.8)	14 (21.9)	
Prediabetes (100–125 mg/dL)	22 (55)	37 (57.8)	
Well-controlled (126-153 mg/dL)	3 (7.5)	12 (18.8)	
Moderate controlled (154-183 mg/dL)	1 (2.5)	1 (1.6)	

[a] *P* value in bold indicated the statistical significance ($P < 0.05$).
[b] *P* value obtained from *t*-test without the assumption of equal variance; other *P* values were obtained from Chi-square test.
[c] Patient-self-reported history of disease.
[d] Metabolic syndrome was determined by BMI and lipid profile acquired from serum samples.
[e] Indicated the glycemic control at the time of visit.
Data may be missing for some individuals.

circumferentially around implant) was found in the CVD group (53.7%) compared with controls (39.1%). Similarly, a higher percentage of deep PD (≥7 mm) was found among the CVD group (14.6% versus 8.7%, $P > 0.05$, CVD versus controls), and the difference lies within the subset of severe peri-implantitis with RBL >4 mm (50% versus 37.5%, CVD versus controls). There were no statistically significant differences found in the implant-related

TABLE 2 Categories of CVD diagnoses within the CVD group

Category	n (%)
Coronary heart disease	24 (29.3)
Cerebrovascular disease	12 (14.6)
Peripheral artery disease	6 (7.3)
Rhythm disorders	23 (28.0)
Cardiac pacemaker insertion	12 (14.6)
Valvular disease	6 (7.3)
Subclinical atherosclerosis	2 (2.4)
Thoracic or abdominal aortic aneurysm	2 (2.4)
Cardiomyopathy and heart failure	7 (8.5)

characteristics between two groups; however, the mean value of the total number of diseased implants in the oral cavity was found significantly higher in the CVD group ($P = 0.048$).

3.4 | Characteristics of periodontal health

The CVD group exhibited a significantly higher incidence of periodontitis (76.4%) compared with the control group (48.9%) with an OR = 3.4 (95% CI, 1.52 to 7.52; $P < 0.01$) (Table 4). The majority of the disease severity observed in both groups was generalized Stage 2. Based on the indirect evidence of progression (%RBL and case phenotype), the majority of individuals diagnosed with periodontitis were Grade B after grade modifying for smoking/diabetes, and they were significantly higher in the CVD group (87.3% versus. 54.4%, $P = 0.01$). Tooth loss was significantly higher in the CVD group ($P < 0.01$). One-third of the participants in the CVD group lost >10 teeth compared with the control group; on the contrary, half of the participants in the control group lost < 5 teeth. Complete edentulism in the CVD group was also significantly higher compared with the control group (12.2% versus. 2.2%, $P = 0.05$). Interestingly, the frequency of SPT among the two groups showed no difference ($P = 0.35$).

3.5 | Multivariable logistic regression

The crude odds ratio (OR) from the bivariate logistic regression for the association between peri-implantitis (> detectable bone loss) and CVD was 1.48 (95% CI, 0.71 to 3.11; $P = 0.30$). A significant association was found between the moderate to severe peri-implantitis (RBL ≥2 mm) and CVD (crude OR = 2.18; 95% CI, 1.02 to

TABLE 3 Prevalence of peri-implant disease and dental implant-related characteristics

Variable	Controls (non-CVD) (n = 46) n (%)	CVD (n = 82) n (%)
Peri-implant health	4 (8.7)	8 (9.8)
Peri-implant mucositis	16 (34.8)	21 (25.6)
Peri-implantitis		
> detectable bone loss	26 (56.5)	53 (64.6)
Moderate to severe[b]	14 (30.4)[a]	40 (48.8)[a]
Severe[c]	8 (17.4)	14 (17.1)
Peri-implant pocket depths		
≤3 mm	5 (10.9)	5 (6.1)
4 to 6 mm	37 (80.4)	65 (79.3)
≥7 mm	4 (8.7)	12(14.6)
BOP[d]		
<33%	7 (15.2)	10 (12.2)
33% to 66%	21 (45.7)	28 (34.1)
>66%	18 (39.1)	44 (53.7)
Suppuration	7 (15.2)	7 (8.5)
Total implant number		
Single	13 (28.3)	19 (23.2)
Multiple	33 (71.7)	63 (76.8)
Implant prosthesis		
Fixed prosthesis	45 (97.8)	70 (85.4)
Overdentures	1 (2.2)	12 (14.6)
Implant type		
Bone-level	42 (91.3)	68 (82.9)
Tissue-level	4 (8.7)	14 (17.1)
Years of restoration		
<5 years	17 (39.5)	18 (22.8)
5 to 10 years	13 (30.2)	27 (34.2)
10 to 15 years	7 (16.3)	26 (32.9)
>15 years	6 (14.0)	8 (10.1)
Total diseased implants (full mouth)[e]		
< 5 implants	22 (47.8)	44 (53.7)
≥ 5 implants	4 (8.7)	11 (13.4)
Mean± SD (Range)[f]	2.34 ± 1.88 (1-10)[a]	3.25 ± 2.43 (1-12)[a]

[a]indicated the significant difference between two groups in the Chi-square test or t-test ($P < 0.05$).
[b]Moderate to severe peri-implantitis: RBL ≥2 mm, RBL = radiographic bone loss.
[c]Severe peri-implantitis: RBL > 4 mm.
[d]BOP = bleeding on probing.
[e]Including the tested implant which is the "most diseased" implant.
[f]Mean ± SD (range) was calculated by excluding healthy implants.

TABLE 4 Periodontal health variables

Variable	Non-CVD (n = 45) n (%)	CVD (n = 72) n (%)	P value
Periodontal health	23 (51.1)	17 (23.6)	**< 0.01**[a]
Periodontitis	22 (48.9)	55 (76.4)	
Severity[b]			**< 0.01**[a]
Stage 1	10 (41.7)	3 (4.5)	
Stage 2	7 (29.2)	52 (78.8)	
Stage 3	2 (8.3)	3 (4.5)	
Stage 4	5 (20.8)	9 (12.5)	
Extent[b]			**0.04**[a]
Localized	12 (54.5)	26 (29.1)	
Generalized	10 (45.5)	39 (70.9)	
Grade[b]			**0.01**[a]
Grade A	7 (31.8)	3 (5.4)	
Grade B	12 (54.5)	48 (87.3)	
Grade C	3 (13.6)	4 (7.3)	
Teeth loss number			**<0.01**[a]
< 5 teeth	23 (51.1)	25 (30.5)	
5-10 teeth	18 (40)	28 (34.1)	
> 10 teeth	4 (8.9)	29 (35.4)	
Complete edentulism	1 (2.2)	10 (12.2)	**0.05**[a]
SPT[c] frequency			0.35
Episodic	23 (51.1)	46 (59.7)	
Regular	22 (48.9)	31 (40.3)	

[a]P value in bold indicated significance in the chi-square test ($P < 0.05$).
[b]Based on the criteria from the Classification of 2017 World Workshop.
[c]SPT: Supportive Periodontal Therapy.

4.67; $P = 0.04$). Particularly, the significance was found evident in the subgroup of moderate peri-implantitis (RBL, 2 to 4 mm) with crude OR = 3.10 (95% CI, 1.08 to 8.91; $P = 0.04$). A sensitivity test was performed to differentiate the effect of CVD diagnosis by omitting rhythm disorders, the association between moderate to severe peri-implantitis and CVD was statistically significant with a crude OR of 2.71 ($P = 0.016$). Second sensitivity test of unadjusted association only included atherosclerotic CVD (CHD, CeVD, PAD, and subclinical atherosclerosis) reached a borderline significance (OR = 2.29, $P = 0.06$).

Among relevant confounding factors, age, hypertension, family history of heart attack, smoking, presence of periodontitis, number of tooth loss, use of aspirin, anticoagulant, and statin medication, LDL-C level were found significantly influencing the association between the moderate to severe peri-implantitis (RBL ≥2 mm) and CVD ($P < 0.05$). The total number of diseased implants reached a borderline significance in the result of univariate analysis ($P = 0.06$). To avoid over fitting regression models, the final logistic regression model included those significant confounding factors with the most clinical relevance, including age, hypertension, smoking, family history of heart attack, and periodontitis. After controlling for those confounders, the significant association between the moderate to severe peri-implantitis and CVD was not observed (OR = 1.40, 95% CI, 0.53 to 3.75; $P = 0.5$) (Table 5). The result of sensitivity test excluding rhythm disorders after controlling for same confounders was not statistically significant (OR = 1.77, $P = 0.29$); similarly, sensitivity test only included CHD, CeVD, PAD, and subclinical atherosclerosis failed to reach significance (OR = 1.29, $P = 0.66$). All the interaction between different confounding variables were not significant in the regression modeling. Additional stratified analysis was performed to explore the effect of periodontal condition on the association between moderate to severe peri-implantitis and CVD, and the results remained non-significant (Table 6).

4 | DISCUSSION

To evaluate the potential risk that low-grade chronic inflammation induced by peri-implantitis may pose to CVD, participants in the CVD group were recruited only when dental implants were placed before the CVD diagnosis. More importantly, the presence of peri-implantitis was identified radiographically before the CVD diagnosis to ensure the temporal relationship between the "exposure" and "disease". This case-control study revealed a significant higher prevalence of moderate to severe peri-implantitis (RBL ≥2 mm) in the CVD group (48.8% versus 30.4%, $P = 0.04$). With a more definitive cut-off threshold of bone loss (2 mm),[21,22] the inflammatory burden of peri-implantitis can be distinguished and the probability of false positives can be decreased. Our data showed that moderate to severe peri-implantitis (RBL ≥2 mm) was significantly associated with the risk for CVD with an OR of 2.18 ($P = 0.04$). By excluding the rhythm disorders, the association between moderate to severe peri-implantitis and CVD was statistically significant with a crude OR of 2.71 ($P = 0.016$). Another sensitivity test only included ASCVD related to inflammtion (CHD, CeVD, PAD, and subclinical atherosclerosis) exhibited a borderline significance (OR = 2.29, $P = 0.06$). Although the association after controlling for multiple confounders was not significant in both sensitivity test, it implies the potential link may exist between the more severe peri-implantitis and atherosclerotic cardiovascular disease that is directly related to the chronic inflammation.

TABLE 5 Multivariable logistic regression model for the prediction of CVD

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Moderate to severe peri-implantitis (RBL[a] ≥2 mm)	**2.18 (1.02 to 4.67)[b]**	1.4 (0.53 to 3.75)
Age		**1.09 (1.03 to 1.16)[b]**
Hypertension		0.99 (0.38 to 2.54)
Family history of heart attack		**2.7 (1.09 to 6.65)[b]**
Smoking		
Non-smoker		reference
Ever-smoker		**3.34 (1.29 to 8.62)[b]**
Periodontitis		2.11 (0.77 to 5.81)

[a]RBL = radiographic bone loss.
[b]Odds ratio (OR) in bold denoted the significance in the multivariable logistic regression ($P < 0.05$).

TABLE 6 Stratified analyses of periodontal condition on the association between moderate to severe peri-implantitis and CVD

Category	Model 1 Moderate to severe peri-implantitis[a] (unadjusted)		Model 2 Moderate to severe peri-implantitis[a] (adjusted for multiple variables[b])	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Periodontitis	2.34 (0.85 to 6.42)	0.1	1.89 (0.59 to 6.06)	0.29
Periodontally healthy	1.02 (0.2 to 5.29)	0.98	0.23 (0.02 to 2.98)	0.26

[a]Moderate to severe peri-implantitis = radiographic bone loss ≥2 mm and BOP ± suppuration.
[b]Adjusted for age, hypertension, smoking, and family history of heart attack.

However, after controlling for multiple confounders for CVD, the significant association was no longer observed (adjusted OR = 1.4, $P = 0.5$). This is probably due to the limited sample size that are unable to accommodate multivariable modeling. Even though a pre-determined 2:1 case-to-control ratio was implemented in this study to increase the effect measure[26]; the lower number of cases in the severe peri-implantitis category that might attenuate the overall study power. Another possible explanation is that cardiovascular risk factors, such as hypertension, dyslipidemia, hyperglycemia, obesity, and others, may outweigh the low-grade local inflammation triggered by peri-implantitis alone. Similar to periodontal inflammation, the local effect could be diluted by the rest of body system and its effect is noticed only when it is maximal[27] or escalated in the situation of multiple implants with peri-implantitis. The total number of diseased implants was found significantly higher in the CVD group. Although the result of final regression model was not influenced by this factor, but it was commensurate with the thesis that increased sites of inflammation around diseased implants elevated the risk of cardiovascular inflammation.

Considered the dominant cause of CVD, including MI, heart failure, stroke, and claudication, atherosclerosis is characterized as an inflammatory process involving the host's immune response interacting with other conventional CVD risk factors to initiate, disseminate, and activates lesions throughout the cardiovascular system.[28] Yet, CVD cannot be fully explained by those classic risk factors, such as diet, high blood pressure, high BMI, high cholesterol, poor glycemic control, metabolic syndrome, smoking, or lack of physical activity.[27] Evidence has mounted that low-grade chronic inflammation is associated with the increased prevalence of cardiovascular risk factors but also an independent risk factor for the development of atherosclerotic plaque and CVD.[29] It is well known that a number of chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and many others are associated with an increased risk of CVD.[30,31] Similarly, periodontitis is another chronic inflammatory condition related to CVD and behaves as an independent risk factor for CVD development.[32] Inflammation of the periodontium was associated with the risk of future cardiovascular events.[33] The association between periodontitis and CVD may be attributed to the chronic transient bacteremia and increased systemic mediators of inflammation, including C-reactive protein and oxidative stress.[12] Our findings also supported the positive association between periodontal disease severity/extent (including number of teeth loss) and CVD, which is in line with the evidence from epidemiological studies.[34,35]

Peri-implantitis is considered as a biological complication around dental implants exhibiting signs of inflammation and increased PD over time.[1,36] It is a multifactorial disease triggered by multiple predisposing factors (e.g., inadequate treatment planning, insufficient keratinized mucosa or bone volume, poor 3D implant position, and prosthetic design, history of periodontitis, poor oral hygiene, episodic maintenance smoking, diabetes, and immune susceptibility).[2] Interestingly, there are similarities between peri-implantitis and periodontitis, including the common key anaerobic periodontopathogens, such as *Porphyromonas gingivalis, Fusobacterium nucleatum*, and *Tannerella forsythia*.[13,37,38] and soft tissue reactions to plaque formation, such as the B- and T-cell dominated inflammatory cell infiltrate and tissue breakdown.[39–42] In light of the similarities between the two diseases, the low-grade chronic inflammation that arises from the continuous bacterial insult propagating to distant tissues may be shared, particularly when the ongoing inflammation manifests in a more severe form. Although it was not statistically significant, our observations that severe peri-implant inflammation characterized by deep pockets and BOP% >66% was more prevalent in the CVD group, supported this potential association between the local and systemic inflammatory burden. The impact of periodontitis on the association between moderate to severe peri-implantitis and CVD was investigated by the stratified analysis. Significant association between peri-implantitis and CVD was not found in the cohort of periodontitis or in the periodontal healthy patients. The potential "synergistic" relationship between periodontitis and peri-implantitis escalating the systemic inflammatory burden is still unclear within the scope of current case-control study.

The higher prevalence of statin (cholesterol-lowering agents) treated patients in the CVD (59.8%) than the control group (28.3%) (Table 1) may explain the finding that a significantly higher level of total cholesterol (TC), LDL-C, cholesterol/HDL, and LDL/HDL ratio was found in the control group (Supplementary Table S1). Literature has linked the lipid disorder or dyslipoproteinaemia to the systemic inflammation, atherosclerosis, and local periodontal inflammation.[43,44] In this study, intermediate to high 10-year ASCVD risk assessing the comprehensive profile of age, systolic blood pressure, TC, HDL-C, smoking, T2DM, and hypertension treatment was found in 72% of participants of the control group. Again, these findings resonate with the postulation that the CVD risk from local peri-implant persistent inflammation could be diluted by other cardiometabolic risks.

The limitations of the current investigation included the inability to establish the causality between peri-implantitis and CVD by the nature of a case-control design. Secondly, the sample size in this study was insufficient to differentiate all the potential confounders for the association between peri-implantitis and CVD in the final regression modeling, especially among the severe peri-implantitis subgroup. Thirdly, confounding bias cannot be ruled out because the CVD cases were established regardless of disease severity and the time elapsed since the diagnosis. Future prospective studies with a larger sample size controlling for the patient- and implant-related confounders are warranted to observe the suspected risk for CVD in patients with severe peri-implantitis.

5 | CONCLUSIONS

Our results suggest that the CVD group had higher prevalence of moderate to severe peri-implantitis (RBL ≥2 mm). In addition, the CVD group exhibited a trend of higher prevalence of deep pockets (≥7 mm) and higher numbers of BOP sites (>66%) in patients with peri-implantitis. However, the association between the two diseases was not statistically significant after controlling multiple confounders for CVD. Future studies with a larger sample size controlling for the patient- and implant-related confounders are needed to better understand the link between peri-implantitis and CVD.

ACKNOWLEDGMENTS

This work has been supported by the Delta Dental Research Fund from The Delta Dental Foundation at Michigan and the Graduate Student Research Fund at the University of Michigan. The authors would like to thank Dr. Hussam Askar, Dr. Jad Majzoub, Mr. James Sugai, Ms. Veronica Slayton, Ms. Donna Brennan, Ms. Cynthia Miller, and Ms. Alicia Baker, Department of Periodontics and Oral Medicine, the University of Michigan, for their contributions to this research investigation.

AUTHOR CONTRIBUTIONS

I-Ching Wang, William V. Giannobile, Jeffery Johnston, J. Christopher Fenno, Hom-Lay Wang: Contributed to the conception and design of the study, acquisition of the data, drafting of the article, critical revision of the article, and final approval of the version to be published. Alice Ou: Contributed to the acquisition of data and final approval of the version to be published. Bo Yang: Contributed to the conception and design of the study and final approval of the version to be published. All authors gave final approval and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The author Dr. Jeffery Johnston, Vice President, Chief Science Officer, and Director of the Research and Data Institute at Delta Dental of Michigan declared the conflicting

interests that this work has been funded by Delta Dental. The remaining authors have no specific conflict of interest related to the present research.

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How to cite this article: Wang IC, Ou A, Johnston J, et al. Association between peri-implantitis and cardiovascular diseases: A case-control study. *J Periodontol*. 2022;93:633–643. https://doi.org/10.1002/JPER.21-0418