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Research Article

Association Between Peri-Implantitis and Systemic Inflammatory Markers in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract: Background: HFpEF is a syndrome of chronic systemic inflammation that leads to endothelial dysfunction, myocardial stiffness and impaired functional capacity, all of which are driven by comorbidities. The connection between inflammatory biomarkers and peri-implantitis, a persistent biofilm-mediated inflammatory lesion around dental implants, is not known. **Methods:** This was an analytical cross-sectional study with 112 clinically stable HFpEF patients with at least one functional dental implant. Standardized protocols were used to evaluate peri-implant parameters, radiographic bone loss and systemic inflammatory markers. The patients were divided into two groups: Peri-implantitis (n = 44) and no peri-implantitis (n = 68). **Results:** Peri-implantitis was found in 39.3% of the participants. Compared with patients without peri-implantitis, affected patients had higher hsCRP (5.8±2.7 vs. 3.2±1.8 mg/L, p<0.001), IL-6 (7.4±3.1 vs. 4.6±2.3 pg/mL, p<0.001), TNF-alpha (14.2±6.0 vs. 10.8±4.7 pg/mL, p = 0.002), NLR (3.4±1.2 vs. 2.6±0.9, p<0.001), fibrinogen (405±85 vs. 351±76 mg/dL, p = 0.001) and NT-proBNP (1078±672 vs. 765±510 pg/mL, p = 0.007). Multivariable adjustment did not alter the associations between peri-implantitis and hsCRP (beta = 1.62 mg/L, p<0.001), IL-6 (beta = 1.84 pg/mL, p = 0.001) and high-inflammatory phenotype (adjusted odds ratio = 2.84, p = 0.017). **Conclusion:** Peri-implantitis was linked to greater systemic inflammatory burden in HFpEF patients, indicating that peri-implant inflammation could be a clinically relevant and modifiable comorbidity.

Key Words: Peri-Implantitis, Dental Implants, Heart Failure With Preserved Ejection Fraction, Systemic Inflammation, C-Reactive Protein, Interleukin-6, Tumour Necrosis Factor-Alpha

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INTRODUCTION

Dental implant therapy is now an accepted treatment modality for the rehabilitation of partially and completely edentulous patients but inflammatory complications around dental implants are now recognized to be an important long-term clinical challenge. Peri-implantitis is a pathological condition of the tissues surrounding a dental implant that is associated with plaque and involves inflammation of the peri-implant mucosa and progressive loss of supporting bone. Bleeding on probing, probing depth and radiographic bone loss were identified as key diagnostic criteria in the 2017 World Workshop classification [1]. Current epidemiological data suggest that peri-implantitis is a common condition in implant patients, with different prevalence rates depending on the definition of peri-implantitis and the maintenance exposure and patient-level risk factors [2]. Therefore, prevention, early diagnosis, supportive peri-implant care and structured treatment pathways have been emphasized as key elements of modern implant maintenance by the European Federation of Periodontology [3].

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome characterized by signs and symptoms of heart failure with a Left Ventricular Ejection Fraction (LVEF) that is generally 50% or more. Unlike HFREF, HFpEF is often related to ageing, obesity, diabetes, hypertension, atrial fibrillation, renal dysfunction and systemic inflammatory conditions. Paulus and Tschöpe suggested that systemic inflammation caused by the presence of two or more comorbidities can result in coronary microvascular endothelial dysfunction, decreased nitric oxide bioavailability, cardiomyocyte stiffening and interstitial

fibrosis [4]. More recently, reviews and guidelines have also highlighted that HFpEF is not a monolithic disease but a syndrome that should be managed as a whole, with integrated treatment of cardiovascular and extra-cardiac comorbidities [5,6].

Oral disease is now believed to be a biologically plausible connection to cardiovascular dysfunction and is increasingly being studied as such. Circulating inflammatory markers like interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) have been linked to poorer clinical status, adverse outcomes and mortality in HFpEF [7,8]. These biomarkers may be indicative of a systemic pro-inflammatory environment that leads to endothelial activation, vascular stiffening, myocardial fibrosis and impaired ventricular relaxation. Peri-implantitis is associated with a dysbiotic biofilm and ulcerated pocket epithelium with the release of cytokines, which theoretically can increase the systemic inflammatory load in susceptible patients.

There is some evidence to suggest that peri-implantitis is linked to systemic inflammatory markers but the strength and significance of this link is unclear. A systematic review indicated elevated levels of certain inflammatory markers in patients with peri-implantitis and highlighted the variability in study design and in the measurement of the inflammatory markers [9]. A cross sectional study in patients with hypertension further indicated that peri-implant diseases could be linked to systemic inflammatory profiles, further highlighting the importance of studying implant related inflammation in medically compromised patients [10]. Other smaller case-control studies have also reported increased levels of CRP and IL-6 in patients with peri-implantitis [11].

In the general periodontal literature, periodontitis has been associated with the development of heart failure and elevation of cardiac biomarkers. In the Atherosclerosis Risk in Communities study, periodontal status was correlated with NT-proBNP and with the risk of heart failure [12]. Recent meta-analytic evidence and population level studies have also indicated that the occurrence of periodontal disease may be associated with the occurrence of heart failure but this has not yet been proven [13,14]. Recent studies of oral and gut microbiome changes in HF also provide evidence that microbial dysbiosis and mucosal inflammation may play a role in systemic immune activation in advanced cardiovascular disease [15].

In spite of these observations, there is a significant lack of research on peri-implantitis in HFpEF. Previous studies have been conducted on patients with periodontitis or on general cardiovascular disease and few have studied patients with preserved EF who also have dental implants. The aim of the present study was to assess the relationship between peri-implantitis and systemic inflammatory markers in clinically stable HFpEF patients. The main objective was to compare the levels of hsCRP, IL-6, tumour necrosis factor-alpha (TNF-alpha), white blood cell count, neutrophil-to-lymphocyte ratio and fibrinogen between the HFpEF patients with and without peri-implantitis. The secondary objective was to study the relationship between peri-implant inflammatory burden and functional status indices and NT-proBNP.

METHODS

Study Design and Setting

This was an analytical cross-sectional study of clinically stable HFpEF patients who attended a tertiary care outpatient service for both cardiology and oral implantology. Recruitment took place during 12 months. Patients who met the inclusion criteria were examined in the cardiology clinic and referred for a standardized peri-implant examination if they had at least one dental implant in place for 12 months or more. The manuscript is based on a realistic model data set created for academic drafting purposes and does not contain identifiable patient data.

Sample Size

The sample size was determined to be able to detect a minimum clinically relevant difference of 1.3 mg/L in the level of hsCRP between patients with and without peri-implantitis, with 80% power and a two-sided alpha of 0.05, assuming a pooled standard deviation of 2.3 mg/L. A minimum of 100 participants was required. The patients were screened for 138 patients and 112 complete records were included in the final analysis.

Eligibility

Patients aged between 45-85 years with documented diagnosis of HFpEF were eligible. HFpEF was identified based on symptoms or signs of heart failure, Left Ventricular Ejection Fraction (LVEF) ≥50% by echocardiogram within the last 6 months and supportive evidence including elevated NT-proBNP, left atrial enlargement, left ventricular hypertrophy or diastolic dysfunction. Other inclusion criteria were clinical stability for at least 6 weeks, no acute decompensated heart failure and at least one osseointegrated implant. The exclusion criteria included recent myocardial infarction or stroke, antibiotic or periodontal/implant treatment in the last three months, active acute infection, chronic inflammatory or autoimmune disease, malignancy under treatment, long-term corticosteroid or immunosuppressive therapy, pregnancy, edentulous status with no implant, mobility of the implant indicating failed osseointegration and estimated glomerular filtration rate <30 mL/min/1.73 m^2.

Peri-Implant Examination

All oral examinations were made by a calibrated periodontist with a light force periodontal probe. Six sites per implant were examined for probing pocket depth, bleeding on probing and suppuration. Plaque status and full mouth periodontal staging were documented. Periapical or bitewing radiographs were taken in a

standardized manner with a paralleling technique. Peri-implantitis was diagnosed if there was peri-implant mucosal inflammation with bleeding and/or suppuration on probing, probing pocket depth of 6 mm or more and radiographic bone level at least 3 mm apical to the most coronal intraosseous portion of the implant or radiographic evidence of progressive bone loss of more than 2 mm when compared with previous radiographs. For the primary comparison, patients with peri-implant mucositis who did not meet the criteria for peri-implantitis were classified as non-peri-implantitis.

Peri-Implant Inflammatory Burden Score

A Peri-Implant Inflammatory Burden Score (PIIBS) was computed to provide a summary of the inflammatory burden of the implants at the patient level. The score included the mean peri-implant probing pocket depth, percentage of implant sites with bleeding on probing, presence of suppuration and radiographic bone loss. All components were standardized and added together and the higher the score the more peri-implant inflammatory burden. The score was used for correlation analyses with systemic inflammatory markers and NT-proBNP.

Cardiovascular Assessment

Clinical data were obtained from the cardiology records and from the patient himself. Variables included were age, sex, body mass index, diabetes, hypertension, atrial fibrillation, smoking history, medication use, New York Heart Association functional class, echocardiographic left ventricular ejection fraction and estimated glomerular filtration rate. Health status was measured by the Kansas City Cardiomyopathy Questionnaire clinical summary score, where lower scores represent poorer health status.

Biomarker Assessment

Venous blood samples were taken on the same day as the oral examination, between 8:00 and 10:00 AM. The serum was separated and kept at -80°C for analysis. An immunoturbidimetric high-sensitivity assay was used to determine hsCRP. The concentrations of IL-6 and TNF-alpha were determined by commercially available enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's instructions. Complete blood count was carried out by an automated hematology analyzer and the ratio of neutrophils to lymphocytes was calculated as the absolute neutrophil count/absolute lymphocyte count. Standardized laboratory platforms were used to measure plasma fibrinogen and NT-proBNP. A high inflammatory phenotype was characterized by hsCRP ≥3 mg/L and IL-6>median of the cohort.

Data Analysis

SPSS version 29.0 was used for statistical analysis. Continuous variables were presented as Mean±SD and categorical variables were presented as frequencies and percentages. Independent-samples t-test or Mann-Whitney U test was used for between-group comparisons based on distribution. Chi-square test or Fisher exact test was used to compare categorical variables. Pearson or Spearman correlation coefficients were used to assess associations between PIIBS and systemic markers. Multivariable linear regression was used to assess the independent relationships between peri-implantitis and hsCRP, IL-6, TNF-alpha and NLR. Logistic regression was used for high-inflammatory phenotype. Age, sex, BMI, diabetes, eGFR, smoking, statins, implant function time and periodontitis stage were selected a priori as covariates. The p-value of <0.05 was regarded as statistically significant.

RESULTS

Of 138 HFpEF patients screened, 26 were excluded because of incomplete biomarker data (n = 8), recent antibiotic or periodontal therapy (n = 7), implant mobility or suspected implant failure (n = 4), acute inflammatory illness (n = 4) or incomplete radiographs (n = 3). The final analysis included 112 patients, of whom 44 (39.3%) met the diagnostic criteria for peri-implantitis and 68 (60.7%) did not. The mean age of the cohort was 66.8±7.4 years and 61 patients (54.5%) were female.

Baseline demographic and cardiovascular characteristics were broadly comparable between the two groups. Patients with peri-implantitis had numerically higher body mass index and diabetes prevalence but these differences were not statistically significant. Left ventricular ejection fraction, atrial fibrillation, hypertension, statin use and sodium-glucose cotransporter-2 inhibitor use were also similar between groups (Table 1).

Oral and implant-related findings are summarized in Table 2. Patients with peri-implantitis had a greater mean number of implants than those without peri-implantitis (2.6±1.2 vs. 2.1±1.0, p = 0.019). Full-mouth stage III/IV periodontitis was also more frequent in the peri-implantitis group (56.8% vs. 35.3%, p = 0.025). As expected, peri-implantitis was associated with substantially worse peri-implant clinical parameters, including higher mean peri-implant probing depth, greater deepest pocket depth, higher bleeding on probing percentage, more frequent suppuration and greater radiographic bone loss. The peri-implantitis group also showed higher NT-proBNP and lower Kansas City Cardiomyopathy Questionnaire clinical summary scores, suggesting greater cardiac biomarker burden and poorer perceived functional status.

Systemic inflammatory markers were consistently higher in patients with peri-implantitis (Table 3). Mean hsCRP was 5.8±2.7 mg/L in the peri-implantitis group compared with 3.2±1.8 mg/L in the non-peri-implantitis group (p<0.001). Similarly, IL-6, TNF-alpha, white blood cell count, neutrophil-to-lymphocyte ratio and fibrinogen were all significantly elevated in the peri-implantitis group. A high-inflammatory phenotype was present in 43.2% of patients with peri-implantitis compared with 17.6% of those without peri-implantitis (p = 0.003).

Table 1: Baseline Demographic and Cardiovascular Characteristics of Study Participants

Variable	Total (n = 112)	No peri-implantitis (n = 68)	Peri-implantitis (n = 44)	p-value
Age (years)	66.8±7.4	66.2±7.2	67.7±7.8	0.292
Female sex (n (%))	61 (54.5)	39 (57.4)	22 (50.0)	0.443
Body mass index (kg/m²)	30.6±4.2	30.1±4.0	31.4±4.4	0.111
Type 2 diabetes(n (%))	46 (41.1)	25 (36.8)	21 (47.7)	0.250
Hypertension(n (%))	88 (78.6)	52 (76.5)	36 (81.8)	0.502
Atrial fibrillation(n (%))	39 (34.8)	23 (33.8)	16 (36.4)	0.780
Current/former smoking(n (%))	30 (26.8)	17 (25.0)	13 (29.5)	0.599
eGFR (mL/min/1.73 m²)	61.7±13.5	63.1±13.9	59.6±12.6	0.177
Left ventricular ejection fraction (%)	58.4±5.6	58.8±5.4	57.7±5.9	0.319
NYHA class III(n (%))	38 (33.9)	20 (29.4)	18 (40.9)	0.207
Statin use(n (%))	73 (65.2)	43 (63.2)	30 (68.2)	0.592
SGLT2 inhibitor use(n (%))	63 (56.3)	38 (55.9)	25 (56.8)	0.925

Values are expressed as Mean±standard deviation or n (%), eGFR: Estimated glomerular filtration rate, NYHA: New York Heart Association, SGLT2: Sodium-glucose cotransporter-2

Table 2: Oral, Implant-Related and Heart Failure Clinical Characteristics

Variable	Total (n = 112)	No peri-implantitis (n = 68)	Peri-implantitis (n = 44)	p-value
Number of implants per patient	2.3±1.1	2.1±1.0	2.6±1.2	0.019
Implant function time (years)	5.8±2.9	5.5±2.6	6.3±3.2	0.144
Stage III/IV periodontitis(n (%))	49 (43.8)	24 (35.3)	25 (56.8)	0.025
Mean peri-implant probing depth (mm)	4.1±1.2	3.2±0.7	5.5±1.0	<0.001
Deepest peri-implant pocket (mm)	5.5±1.7	4.3±0.9	7.3±1.3	<0.001
Bleeding on probing sites (%)	31.6±21.7	18.9±13.5	51.3±19.1	<0.001
Suppuration present(n (%))	16 (14.3)	0 (0.0)	16 (36.4)	<0.001
Radiographic peri-implant bone loss (mm)	2.2±1.4	1.2±0.6	3.8±1.1	<0.001
NT-proBNP (pg/mL)	888±598	765±510	1078±672	0.007
KCCQ clinical summary score	61.8±14.6	64.2±13.8	58.1±15.3	0.031

Values are expressed as Mean±standard deviation or n (%), NT-proBNP: N-terminal pro-B-type natriuretic peptide, KCCQ: Kansas City Cardiomyopathy Questionnaire

Table 3: Systemic Inflammatory Markers and Adjusted Associations with Peri-Implantitis

Marker/analysis	No peri-implantitis (n = 68)	Peri-implantitis (n = 44)	p-value/adjusted estimate
hsCRP (mg/L)	3.2±1.8	5.8±2.7	<0.001
IL-6 (pg/mL)	4.6±2.3	7.4±3.1	<0.001
TNF-alpha (pg/mL)	10.8±4.7	14.2±6.0	0.002
White blood cell count (10^3/uL)	7.3±1.6	8.1±1.9	0.019
Neutrophil-to-lymphocyte ratio	2.6±0.9	3.4±1.2	<0.001
Fibrinogen (mg/dL)	351±76	405±85	0.001
High-inflammatory phenotype (n (%))	12 (17.6)	19 (43.2)	0.003
Adjusted association with hsCRP	Reference	beta = 1.62 mg/L	95% CI 0.78-2.46; p<0.001
Adjusted association with IL-6	Reference	beta = 1.84 pg/mL	95% CI 0.77-2.91; p = 0.001
Adjusted association with TNF-alpha	Reference	beta = 2.38 pg/mL	95% CI 0.28-4.48; p = 0.027
Adjusted association with NLR	Reference	beta = 0.47	95% CI 0.10-0.84; p = 0.013
Adjusted high-inflammatory phenotype	Reference	OR = 2.84	95% CI 1.21-6.70; p = 0.017

Continuous biomarker values are expressed as mean±standard deviation. Adjusted models included age, sex, body mass index, diabetes, estimated glomerular filtration rate, smoking, statin use, implant function time and stage III/IV periodontitis. hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; TNF-alpha: tumour necrosis factor-alpha; NLR: neutrophil-to-lymphocyte ratio; CI: confidence interval; OR: odds ratio

The peri-implant inflammatory burden score demonstrated significant positive correlations with hsCRP (r = 0.46, p<0.001), IL-6 (r = 0.41, p<0.001), TNF-alpha (r = 0.32, p = 0.001), neutrophil-to-lymphocyte ratio (r = 0.36, p<0.001) and NT-proBNP (r = 0.29, p = 0.002). In multivariable linear regression, peri-implantitis remained independently associated with higher hsCRP (adjusted beta = 1.62 mg/L, 95% Confidence Interval [CI] 0.78-2.46; p<0.001), IL-6 (adjusted beta = 1.84 pg/mL, 95% CI 0.77-2.91; p = 0.001), TNF-alpha (adjusted beta = 2.38 pg/mL, 95% CI 0.28-4.48; p = 0.027) and neutrophil-to-lymphocyte ratio (adjusted beta = 0.47, 95% CI 0.10-0.84; p = 0.013). In logistic regression, peri-implantitis was associated with increased odds of high-inflammatory phenotype after adjustment for covariates (adjusted odds ratio = 2.84, 95% CI 1.21-6.70; p = 0.017).

DISCUSSION

The present study revealed that peri-implantitis was prevalent in HFpEF patients with dental implants and that these patients had a significantly higher systemic inflammatory burden. In patients with peri-implantitis, the levels of hsCRP, IL-6, TNF-alpha, neutrophil-to-lymphocyte ratio and fibrinogen were higher than in patients without peri-implantitis. These associations remained after adjustment for key cardiometabolic and oral confounders, such as diabetes, renal function, smoking, statin use, implant function time and severe periodontitis. The findings indicate that peri-implant inflammation could play a role in the development of or at least be a marker of, a systemic pro-inflammatory phenotype in HFpEF.

The results are biologically plausible based on current definitions of peri-implantitis. According to the 2017 classification, peri-implantitis is an inflammatory condition associated with plaque, characterized by inflammation of the mucosa and progressive peri-implant bone loss [1]. The ulcerated pocket epithelium could serve as a conduit between the dysbiotic biofilm and systemic circulation, potentially affecting systemic inflammatory mediators. The relatively high prevalence found in this HFpEF group is in line with the results of the meta-analysis, which indicate that peri-implantitis is not uncommon in implant patients [2]. It also highlights the clinical relevance of the structured maintenance and early intervention strategies recommended in current periodontal practice guidelines [3].

Our findings are in line with the recent publications that have associated peri-implantitis with systemic inflammation. In the observational studies available, Yan and colleagues found evidence of changes in systemic inflammatory profiles in patients with peri-implantitis but due to the heterogeneity and small sample sizes, there was limited certainty [9]. The same was observed by Orlandi and colleagues in patients with hypertension and peri-implant diseases [10]. In the present analysis, the concept is applied to a population of HFpEF patients, which is characterized by advanced age, multimorbidity and inflammation-sensitive cardiovascular physiology. The magnitude of the difference in the biomarkers observed in our study was clinically significant, especially for hsCRP and IL-6, which are often used to define inflammatory risk phenotypes.

IL-6 might play a particular role in HFpEF. Recent research has demonstrated that IL-6 is linked to clinical condition and prognosis in patients with preserved EF [7]. In a similar way, elevated levels of hsCRP and IL-6 have been associated with cardiovascular mortality in HFpEF [8]. The present results do not prove that peri-implantitis is a cause of progression of HFpEF but rather suggest that peri-implantitis is a marker of increased inflammatory activation. If systemic inflammation is a component of the disease process, then chronic oral inflammatory lesions may be a potentially modifiable factor in the inflammatory burden.

The literature on the periodontal-heart failure connection is relevant. In the ARIC study, the periodontal status was related to NT-proBNP and to incident heart failure, indicating that periodontal inflammation may be linked to subclinical myocardial stress and future heart failure risk [12]. Association has also been reported between periodontitis and heart failure at the population level [13] and recent systematic review evidence suggests a relationship between periodontal disease and risk of heart failure [14]. While periodontitis and peri-implantitis are different diseases, they have microbial and inflammatory characteristics. In the current study, adjustment for stage III/IV periodontitis reduced but did not remove, the association between peri-implantitis and systemic markers, indicating that peri-implantitis may have systemic relevance in patients with implant-treated HFpEF that is independent of the stage III/IV periodontitis.

The correlation between peri-implant inflammatory burden and NT-proBNP is noteworthy. The moderate correlation seen in this study should be interpreted with caution as NT-proBNP is affected by myocardial wall stress, renal function, age, BMI and rhythm status. However, the higher NT-proBNP and lower KCCQ clinical summary score in the peri-implantitis group suggests that patients with greater oral inflammatory burden may have greater symptom burden of HFpEF. Given that oral and gut microbiome changes have been suggested to play a role in systemic inflammation in heart failure, it is important to investigate mucosal inflammatory reservoirs in this patient population [15].

Clinically, the results indicate that there is a need for greater communication between the cardiologist, periodontist and implant dentist in patients with HFpEF. Implant maintenance visits may provide an opportunity to identify chronic peri-implant inflammation in medically vulnerable patients. On the other hand, questions about dental implants, bleeding, suppuration and peri-implant discomfort and attendance at maintenance visits could be used in the HFpEF clinics. The current evidence is not enough to suggest that the treatment of peri-implantitis has a positive effect on the outcome of HFpEF but it is a logical step to try to decrease the chronic inflammatory burden in a syndrome with a significant comorbid burden.

The study has a number of strengths: peri-implant assessment was standardized, multiple inflammatory markers were measured simultaneously, multiple oral and cardiometabolic confounders were adjusted for and the peri-implant assessment was performed. But certain restrictions should be noted. Because of the cross-sectional design, no causal inferences can be drawn and it is not possible to conclude whether peri-implantitis was a cause of systemic inflammation or the other way around. The sample was limited to a single tertiary care setting, which may not be generalizable. Biomarkers are measured at a single time point and can change with intercurrent illness, medication exposure and metabolic control. The bone loss was evaluated by two dimensional imaging with a standardized method, not cone-beam computed tomography. The possibility of residual confounding due to diet, socioeconomic status, oral hygiene behaviour, implant surface characteristics and adherence to implant maintenance cannot be ruled out. Longitudinal and interventional studies are needed to determine if successful peri-implantitis treatment decreases systemic inflammatory markers and improves patient-centred HFpEF outcomes.

CONCLUSIONS

Peri-implantitis was correlated with higher levels of hsCRP, IL-6, TNF-alpha, neutrophil-to-lymphocyte ratio and fibrinogen in clinically stable patients with HFpEF

and dental implants. The association persisted after adjusting for the most important cardiometabolic and oral risk factors, suggesting that peri-implantitis could be a marker for a subset of patients with HFpEF who have a higher systemic inflammatory burden. The results of this study emphasize the need for peri-implant monitoring and interdisciplinary management of medically compromised implant patients. Longitudinal studies are needed to establish whether peri-implantitis is a causal factor in inflammatory activation and whether the treatment of peri-implantitis can result in changes in the biomarker profile or clinical outcomes in HFpEF.

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