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ORIGINAL ARTICLE

Peri-implant diseases and systemic inflammation: A preliminary analysis from a cross-sectional survey of patients with hypertension

Marco Orlandi[1] | **Nicola Pranno**[2] | **Vipul Patel**[1] | **Piero Papi**[2] | **Bianca Di Murro**[2] | **Giorgio Pompa**[2] | **Antonella Polimeni**[2] | **Claudio Letizia**[2,3] | **Jeanie Suvan**[1] | **Francesco D'Aiuto**[1]

[1]University College London (UCL) Eastman Dental Institute, London, UK

[2]Department of Oral and Maxillo-Facial Sciences, "Sapienza" University of Rome, Rome, Italy

[3]Department of Precision and Translational Medicine, "Sapienza" University of Rome, Rome, Italy

Correspondence
Francesco D'Aiuto, UCL Eastman Dental Institute, Rockefeller Building, 21 University Street, London WC16 6DE, UK.
Email: f.daiuto@ucl.ac.uk

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Abstract

Background: The aim of this study was to investigate the association between peri-implant diseases and systemic inflammation assessed by serum C-reactive protein (CRP) levels in a sample of patients with hypertension.

Methods: A total of 151 participants with hypertension were included in a cross-sectional study. The population was divided into six groups according to their peri-implant and periodontal status (healthy controls, mucositis, peri-implantitis, periodontitis, periodontitis and mucositis, periodontitis, and peri-implantitis). Linear, logistic regression, and correlation analyses were performed.

Results: CRP levels were statistically significantly higher in participants with periodontitis alone (median 3.2 mg/L, interquartile range [IQR] 1.8, $p = 0.012$), combined with mucositis (3.10 mg/L, IQR 2.35, $p < 0.001$) or peri-implantitis (2.7 mg/L, IQR 2.53, $p = 0.002$) when compared to the healthy controls (1 mg/L, IQR 1.2). This association was independent of age, sex, smoking status, and adiposity differences. Participants with periodontitis with and without peri-implant diseases had the greatest odds of exhibiting CRP > 3 mg/L (odds ratio = 7.3, 95% confidence interval 1.6–33.9).

Conclusions: Peri-implant diseases are associated with systemic inflammation, but the nature of the association should be further investigated.

KEYWORDS
C-reactive protein, dental implants, inflammation, mucositis, peri-implantitis

Marco Orlandi and Nicola Pranno contributed equally to this paper.

1 | INTRODUCTION

Inflammation is the body's defensive response to pathogens such as bacteria and to injuries.[1] It is characterized by the activation of immune and nonimmune cells aiming at neutralizing the noxious stimulus and promoting tissue repair/recovery. This process is tightly controlled via multiple pathways, and it usually ends with an active resolution phase.[2] Environmental and biological factors in a susceptible host, however, could elicit a state of low-grade inflammation characterized by a mild but persistent activation of the immune system. This chronic inflammatory burden[3] has been implicated in the pathogenesis of several noncommunicable diseases (NCD).[4]

Periodontitis is one of the most common NCD and is characterized by microbial-associated inflammation at the dentogingival junction which, if left untreated, inexorably results in the loss of soft and hard tissue attachment.[5] Further it is now well established that the local periodontal inflammation triggers systemic inflammation.[6] A causal association between periodontitis and systemic inflammation is corroborated by the overwhelming evidence that effective treatment of periodontitis results in a reduction of low-grade inflammation.[7] This important finding might represent the missing link between periodontitis and other chronic inflammatory diseases, including cardiovascular disease,[8] diabetes mellitus,[9] and hypertension.[10]

Dental implants have become one of the most common options for the replacement of missing teeth. Despite their high survival and success rates over decades, dental implants are not free from complications. In particular, inflammation and infection of the peri-implant soft tissues which differ from those constituting the periodontium are on the rise. The latest estimates confirmed that peri-implant diseases (peri-implantitis and peri-mucositis) are highly prevalent among patients with dental implants.[11,12] Periodontitis seems to be one of the main drivers of increased susceptibility to peri-implantitis.[13,14] Further, peri-implant diseases, while having traits in common with periodontal diseases, exhibit distinctive clinical and histological features.[15]

Peri-implant soft tissue lesions exhibit greater cell infiltration[16] and variability in the composition of key cell groups when compared to those in periodontal tissues.[17] A greater inflammatory response to peri-implant plaque accumulation has been reported, as measured through matrix metalloproteinase 8 (MMP-8) and IL-1β, when compared to the same around natural teeth.[18] This led us to believe that peri-implant diseases could evoke an even stronger systemic host response. The aim of this study was to preliminary investigate whether the presence of peri-implant diseases is reflected by a systemic host inflammatory response assessed by serum C-reactive protein (CRP) in a sample of patients with hypertension.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study is based on a cross-sectional study, and it is a secondary analysis of the serum CRP profile of participants referred to the Tertiary Centre of Secondary Hypertension Unit, Policlinico Umberto I, Sapienza University of Rome, for screening, diagnosis, and treatment of primary and/or secondary hypertension as described in a previously published trial.[19] All participants signed the informed consent form and gave written approval to be included in the study population, in accordance with the latest version of the World Medical Declaration of Helsinki (2013). The study was approved by the institutional review board of Sapienza University of Rome (ref. 4948/2018), and the report was prepared in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational cross-sectional studies.[20]

2.2 | Medical evaluations

Fasting venous blood samples were taken for biochemical analysis. Serum CRP levels were assessed using a turbidimetric automated (high-sensitivity) assay, and standard lipid fractions were quantified using conventional biochemistry assays.

All patients were screened for metabolic syndrome (MetS) according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria.[21]

2.3 | Clinical evaluation

Dental examinations were undertaken on consecutive patients presenting with at least one dental implant with >5 years of functional loading by a single, trained, previously calibrated examiner (B.D.M.).

A full-mouth periodontal examination at six sites per teeth and implant using a periodontal probe with a light force (≈0.15 N) was carried out. The Basic Periodontal Examination (BPE) index derived from the World Health Organization (WHO) Community Periodontal Index of Treatment Needs score was used to assessed periodontal health.[22] A score was given to each sextant of the whole dentition (scores ranging from 0 to 4), and the highest

score of the whole mouth was entered as representative of the periodontal status for each participant. Scores 3 and 4 corresponded to the presence of clinical signs of periodontitis (indicating probing pocket depths [PPD] of 4–5 mm for Score 3 and of 6 mm or more for Score 4), healthy gingival tissue (Score 0), or gingivitis (Score 1 and 2; reversible marginal gingival inflammation). In addition, the sum of all sextants (BPE cumulative score) was created to define a continuous measure of extent of the gingival inflammation.[23] The 2017 World Workshop Classification of Periodontal and Peri-implant Diseases and Conditions criteria were used to define a patient as a "periodontitis case" according to: "Interdental clinical attachment loss (AL) ≥2 mm was detectable at ≥2 non-adjacent teeth, or Buccal or oral AL ≥3 mm with probing depth >3 mm was detectable at ≥2 teeth and the observed clinical AL cannot be ascribed to non-periodontal causes such as: (1) gingival recession of traumatic origin; (2) dental caries extending in the cervical area of the tooth; (3) the presence of clinical AL on the distal aspect of a second molar and associated with malposition or extraction of a third molar, (4) an endodontic lesion draining through the marginal periodontium; and (5) the occurrence of a vertical root fracture".[5] The dental implant assessment included clinical PPDs, mucosal redness, suppuration, bleeding on probing, plaque index, years of functional loading, implant location (maxilla/mandible), and type of prostheses (single-unit/multiple-unit). Peri-implantitis was defined as the presence of bleeding and/or suppuration on gentle probing, with radiographic bone levels ≥3 mm apical of the most coronal portion of the intraosseous part of the implant.[24]

2.4 | Radiographic evaluation

The marginal peri-implant bone level was detected on periapical radiographs with the parallel long-cone technique and a standardized film holder. All radiographs were scanned at 600 dpi and digitized. A calibrated software* was used to estimate marginal peri-implant bone level variations using implant length and width as references. Two calibrated investigators (P.P. and N.P.), blinded to other aspects of the study, measured in millimeters the distance from the implant shoulder to the bottom of the marginal bony defect on each implant's mesial and distal aspects, and the average value was calculated. Any disagreement was solved by consensus, and a third investigator was consulted when it was not initially possible to achieve complete agreement (defined as a difference between the measurements made by the two experts of >0.1 mm). Peri-implantitis and peri-implant mucositis case definitions were based on the 2017 World Workshop Classification of Periodontal and Peri-implant Diseases and Conditions criteria.[24]

2.5 | Case definitions

All participants were categorized in to six subgroups based on the following case-definitions:

1. Periodontal health/peri-implant health (**Group A—PH/PiH**)
2. Periodontal health/peri-implant mucositis (**Group B—PH/PiM**)
3. Periodontal health/peri-implantitis (**Group C—PH/PI**)
4. Periodontitis/peri-implant health (**Group D—P/PiH**)
5. Periodontitis/peri-implant mucositis (**Group E—P/PiM**)
6. Periodontitis/peri-implantitis (**Group F—P/PI**)

2.6 | Statistical analysis

Data were evaluated using standard statistical analysis software.† A database was created using dedicated software.‡ Descriptive statistics were calculated for each variable, including median, mean ± standard deviation (SD) values, and percentage. The Shapiro–Wilk test was used to determine whether the continuous data conformed to a normal distribution. The serum level of the CRP variable was chosen as the dependent variable because it could be related to peri-implant and periodontal soft tissue inflammation. The Mann–Whitney *U* test was used to evaluate nonparametric dependent variables with two groups, and the Kruskal–Wallis test for nonparametric dependent variables with three or more groups, both for univariate analysis. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. Adjusted *p* values are presented.

The relationship between the CRP levels and the following independent variables was explored: age, sex (male/female), body mass index (BMI), smoking status (yes/no), glucose, 24-h systolic blood pressure, 24-h diastolic blood pressure, high-density lipoprotein (HDL), low-density lipoprotein (LDL), PPD around the dental implant, cumulative BPE score, number of dental implants, mean

* SOPRO Imaging; Acteon Group, Norwich, UK.

† Version 27.0, Statistical Package for the Social Sciences; IBM Corporation, Armonk, New York, USA.

‡ Microsoft Excel; Microsoft, Redmond, Washington, USA.

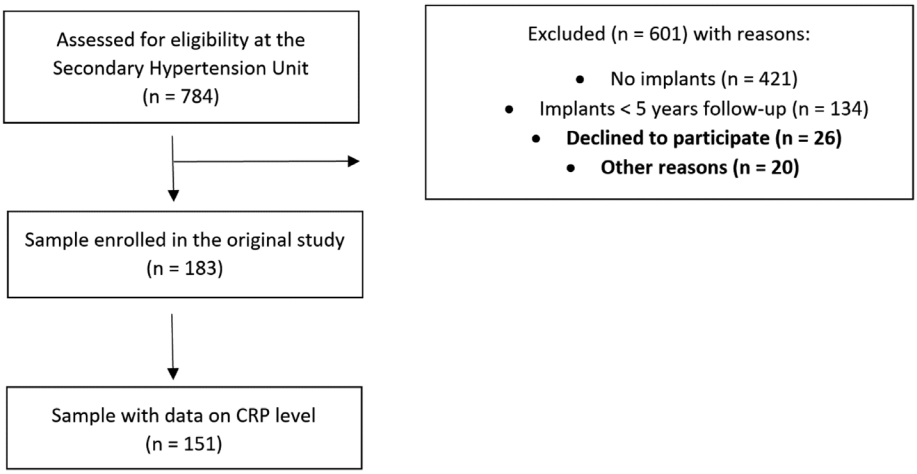

FIGURE 1 Flowchart of recruitment and selection process. CRP, C-reactive protein.

bone loss around an implant, and periodontal and peri-implant status categorized into six subgroups.

Multiple linear regression models were created to ascertain independent variables' effects on average serum CRP levels. Multicollinearity was evaluated through an inspection of correlation coefficients and tolerance/variance inflation factor (VIF) values; P–P plots (probability–probability plots) were used to evaluate if the residuals were normally distributed. Correlation analyses between mean CRP values, the number of antihypertensive medications taken by patients, and cumulative BPE score were further investigated using Spearman's rank-order testing. Statistical significance was set at $p \leq 0.05$. A post hoc power analysis was conducted on the study sample, which has been previously published.[19] This analysis used a one-way analysis of variance (ANOVA) with six groups and an alpha level of 0.05 confirming that a total sample size of 151 patients and an effect size of 0.25 showed a power of 63% in detecting a statistical difference in the high-sensitivity C-reactive protein (hs-CRP) level between groups.

3 | RESULTS

3.1 | Study characteristics

The study sample included 151 participants (Figure 1), with a higher number of females (59%), one-third being current smokers (33%), one in five participants being obese (18% of the whole group), and more than 50% suffering from periodontitis and peri-implant diseases (Appendix Table S1 in online *Journal of Periodontology*). When compared according to the peri-implant and/or periodontal case definitions, obvious differences were detected across the multiple study groups (Table 1). In the peri-implant diseases and periodontitis groups, smokers were more prevalent; furthermore, higher values of glucose and diastolic blood pressure were found. No other major differences were seen. The average PPD around dental implants was highest in patients with peri-implantitis and lowest in those without periodontal and peri-implant diseases. Cumulative BPE scores were greatest in the three groups that included diagnoses of periodontitis. Serum CRP levels were statistically different between groups ($p < 0.05$) (Figure 2). Unadjusted between-group comparisons confirmed that only patients suffering from periodontitis, with or without peri-implant diseases, had statistically higher values than healthy controls. When cumulative BPE scores were compared across all six groups, participants with periodontitis (with or without peri-implant diseases) presented the greatest scores compared to the healthy group (Group A) (15 for Group D, $p = 0.001$, and 16 for Groups E and F, $p < 0.001$) (Figure 3).

Multiple linear regression analysis showed statistically significant associations between increased hs-CRP levels and Group F ($p = 0.028$). Furthermore, an association was found with cumulative BPE scores ($p = 0.002$) (Table 2). This finding was confirmed when nonparametric Spearman correlation was used to compare CRP and cumulative BPE scores ($R = 0.38$, $p < 0.001$).

When CRP levels were compared across groups based on the number of antihypertensive medications, a statistically significant overall effect was observed ($p < 0.001$) (Appendix Figure S1 in online *Journal of Periodontology*). Participants taking ≥3 medications had higher CRP levels compared to those taking none or ≤2 medications ($p < 0.001$). Furthermore, a significant positive correlation was found between the number of antihypertensive medications taken by patients and cumulative BPE scores ($p = 0.049$). When comparing participants taking lipid-lowering medications, no statistically significant

TABLE 1 Descriptive table of participants' characteristics based on peri-implant and periodontal case definition groups.

Variables, *n* (%) or mean (SD)	Group A PH/PiH (*n* = 17)	Group B PH/PiM (*n* = 29)	Group C PH/PI (*n* = 12)	Group D P/PiH (*n* = 6)	Group E P/PiM (*n* = 57)	Group F P/PI (*n* = 30)	*p* value
Sex (male)	14 (22.58)	8 (12.90)	4 (6.45)	1 (1.61)	22 (35.48)	13 (20.97)	**0.006**
Age (years)	65.24 (11.56)	64.00 (10.13)	63.17 (9.03)	60.50 (5.96)	70.70 (8.45)	67.57 (10.72)	**0.006**
BMI (kg/m^2)	28.63 (3.42)	25.47 (3.60)	26.43 (2.60)	24.94 (2.82)	26.07 (3.45)	25.58 (2.87)	**0.048**
Smoking status (smoker)	3 (18)	3 (10)	4 (33)	3 (50)	25 (44)	12 (40)	**0.023**
Glucose (mg/dL)	92.24 (8.90)	103.21 (26.83)	87.42 (8.45)	92.33 (13.02)	91.51 (13.12)	84.73 (8.94)	**0.023**
hs-CRP[a] (mg/L)	1.00 (1.20)	1.20 (2.85)	1.10 (2.38)	3.20 (1.80)	3.10 (2.35)	2.70 (2.53)	**0.001**
Systolic BP[b] (mm Hg)	126.65 (11.49)	127.38 (11.24)	125.33 (13.57)	125.00 (14.87)	128.67 (12.99)	129.70 (11.74)	0.973
Diastolic BP[b] (mm Hg)	81.24 (7.55)	74.72 (9.23)	77.00 (10.50)	69.50 (4.64)	72.07 (6.83)	78.20 (8.31)	**<0.001**
HDL (mg/dL)	59.47 (16.35)	52.11 (14.40)	58.91 (21.81)	68.00 (27.24)	61.96 (18.04)	59.41 (16.50)	0.165
LDL (mg/dL)	127.18 (23.75)	118.79 (34.13)	92.91 (34.63)	104.17 (47.15)	105.07 (32.23)	101.59 (30.92)	0.181
PPD around dental implant (mm)	2.69 (0.85)	3.91 (0.97)	4.90 (1.10)	3.11 (0.47)	3.57 (0.86)	4.24 (1.62)	**<0.001**
Cumulative BPE score	8.59 (2.62)	9.31 (1.70)	10.83 (4.20)	15.17 (2.64)	16.67 (3.03)	16.07 (3.30)	**<0.001**
Number of dental implants[a]	2.00 (2.00)	3.00 (4.00)	4.00 (4.00)	1.00 (3.00)	2.00 (2.00)	2.00 (5.00)	0.106
Mean bone loss around implant (mm)	0.26 (0.50)	1.17 (0.94)	3.46 (1.25)	0.58 (0.66)	1.38 (0.59)	3.67 (1.28)	**<0.001**

Note: *p* values in bold are statistically significant; Kruskal–Wallis statistical tests.

Abbreviations: BMI, body mass index; BP, blood pressure; BPE, Basic Periodontal Examination; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; P, periodontitis; PH, periodontal health; PI, peri-implantitis; PiH, peri-implant health; PiM, peri-implant mucositis; PPD, probing pocket depth.

[a]Median and interquartile range.

[b]24-hour data collection.

TABLE 2 Multiple linear regression results for high-sensitivity C-reactive protein (hs-CRP).

hs-CRP	β	95% CI for β		SE β	*p* value
		Lower	Upper		
Group D	0.593	−0.700	1.886	0.077	0.366
Group E	0.090	−0.657	0.836	0.029	0.813
Group F	1.106	0.124	2.087	0.496	0.028
Cumulative BPE score	0.121	0.045	0.196	0.038	0.002
Mean bone loss around implant	−0.352	−0.584	−0.120	0.117	0.003
Mean PPD	0.236	0.013	0.459	0.190	0.038

Note: Variables with a statistically significant association on univariate analysis were included in linear regression. Model included adjustments for age, sex, smoking, glucose, 24-hour systolic blood pressure, 24-hour diastolic blood pressure, and body mass index. Reference category for peri-implant and periodontal case definition groups is Group A. Coefficient of determination (R^2) = 0.27; adjusted R^2 = 0.206.

Abbreviations: BPE, Basic Periodontal Examination; CI, confidence interval; PPD, probing pocket depth; SE β, standard error of coefficient; β, unstandardized regression coefficient.

differences in CRP levels were noted (Appendix Figure S2 in online *Journal of Periodontology*).

4 | DISCUSSION

This study confirmed an association between periodontal and peri-implant tissues inflammation and systemic inflammation in patients with hypertension. Further, the combination of periodontitis and peri-implant diseases resulted in greater systemic inflammation, while peri-implant diseases alone resulted only in mild increases of CRP.

When we used continuous measures of gingival/mucosal inflammation (cumulative BPE), only participants with a greater extent of peri-implant/

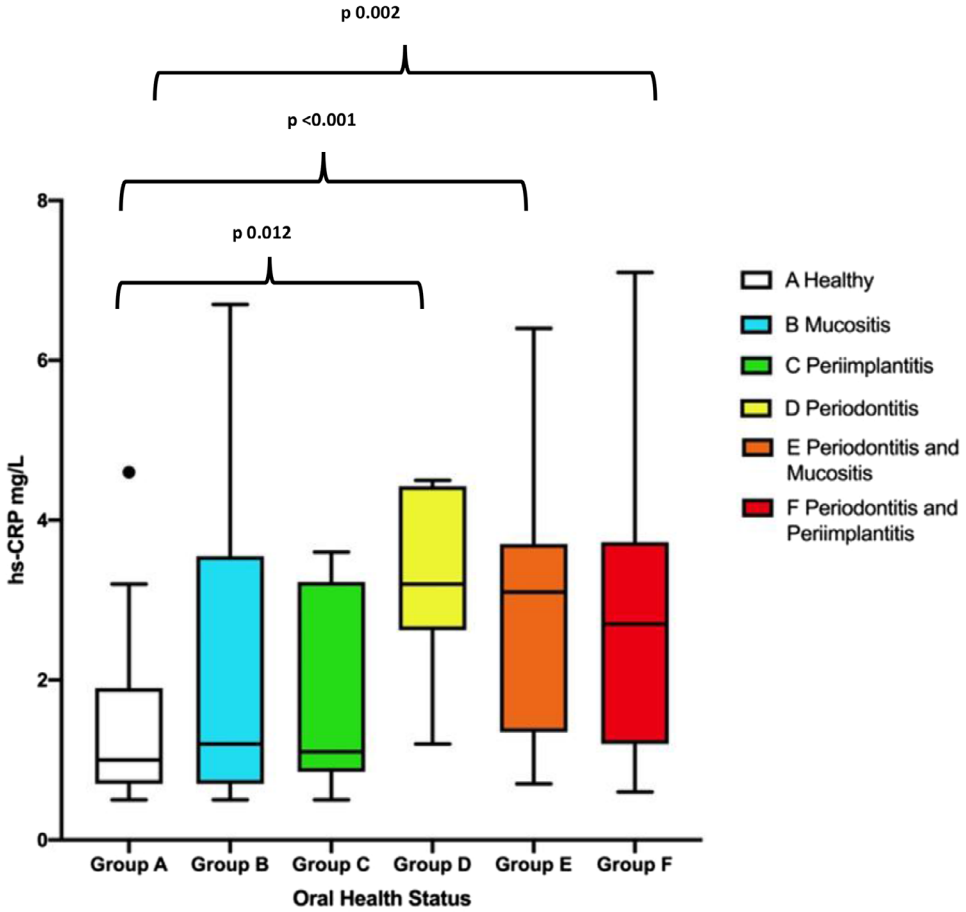

FIGURE 2 Box and whiskers plot of hs-CRP level across condition groups with fence evaluation of intergroup differences. hs-CRP, high-sensitivity C-reactive protein.

periodontal inflammation had higher systemic inflammation, independent of age, sex, adiposity, and smoking differences. This raises the question whether a threshold of local tissue inflammation is necessary to elicit a systemic inflammatory response in contrast with the a priori hypothesis that peri-implant inflammatory lesions (greater than those around teeth) would trigger a greater host response. Human immuno-/histochemical analyses confirmed that peri-implantitis lesions have a more pronounced apical extension of the inflammatory cell infiltrate,[25] they exhibit greater connective tissue vascularity,[16] and they exhibit proportionally greater neutrophils and macrophages when compared to periodontal tissues.[25]

Comparing the results of this study with the current evidence linking periodontitis and systemic inflammation, median CRP levels were higher than those previously reported (3.20 vs. 1.45 mg/L).[26] This difference could be explained in view of the different CRP assays, study sample sizes, and population inclusion criteria. The only observational study investigating the association between peri-implantitis and serum inflammatory biomarkers reported a trend for doubled levels of serum CRP when comparing cases and controls.[27] Our data differ from the reported data because of some important differences. Firstly, the cross-sectional design of our study can influence disparity in group characteristics such as the size, and this could affect the nature of the differences detected. Secondly, the severity and the number of dental implants affected by peri-implantitis might determine the changes in CRP. We cannot exclude a positive association between the amount of peri-implant tissue disruption and serum CRP concentration as observed in periodontitis. Lastly, the biochemical assay used might introduce a further element of variability.

The potential impact of hypertension on our observations should also not be underestimated. Periodontitis has been linked to elevated systolic blood pressure, and CRP seems to be involved in mediating this association.[28] Therefore, we cannot exclude that the presence of hypertension could have reduced the impact of peri-implant diseases on systemic inflammation. In an otherwise healthy population this effect might not be diluted.

Evidence suggests that lipid-lowering medications also have anti-inflammatory properties and may impact serum

JOURNAL OF Periodontology

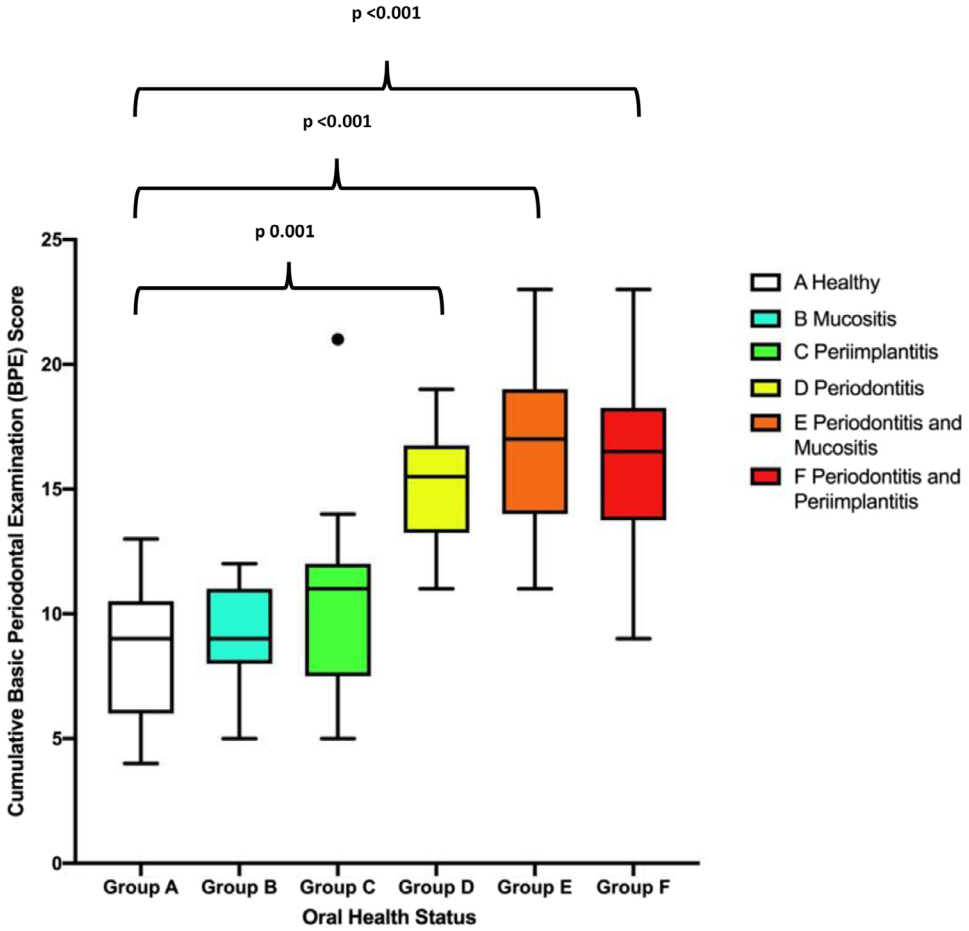

FIGURE 3 Box and whiskers plot of cumulative BPE score across condition groups with fence evaluation of intergroup differences. BPE, Basic Periodontal Examination.

CRP,[29] independent of LDL.[30] In our sample, we found no statistically significant difference in CRP between those taking lipid-lowering medications and those not taking them, possibly excluding a confounding effect of statins. This analysis confirmed that CRP differed in participants taking ≥3 antihypertensives compared to participants taking no medication or 1–2 antihypertensives. While the effects of antihypertensives on CRP and systemic inflammation are unclear, there is some evidence suggesting that CRP levels are affected by the use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.[31] The activation of the sympathetic nervous system may result in a systemic inflammatory response, and the beta-blockers might have an impact on this pathway.[32] However, further research is needed to elucidate the mechanism underlying this association.

Our sample was derived from a larger trial investigating the prevalence of peri-implant diseases in patients with MetS.[19] Only participants who had data on CRP levels (151 out of a total of 183) were included in this analysis. Almost half of the population was not only hypertensive but also diagnosed with MetS, and the distribution per group of this comorbidity could have had an impact on the results due to the presence of greater adipose tissue pro-inflammatory phenotype.

Furthermore, the presence of peri-implantitis in a population with an increased systemic level of hs-CRP could be an important prognostic factor for a deterioration of the inflammatory status compared to the same diagnosis in a group of systemically healthy individuals, which would reflect an increased risk for systemic inflammation.

Increasing evidence points toward the significance of chronic infections as triggers of chronic inflammation and associated cardiometabolic changes.[33,34] CRP provides prognostic information on cardiovascular risks with values of <1, 1–3, and >3 mg/L, indicating lower, average, or higher relative cardiovascular risks, respectively.[29] Using a >3 mg/L threshold, but within the context of other traditional cardiovascular risk factors, we could postulate the potential impact of periodontal/peri-implant diseases on future risk of cardiovascular complications.[29] In our sample, the diagnosis of periodontitis alone, with peri-implant mucositis or peri-implantitis, was associated with

substantially greater odds of having hs-CRP > 3 mg/L. This is consistent with the current evidence reporting higher CRP concentration in patients with periodontitis and a significant reduction following periodontal treatment.[35] Further research is warranted to confirm this association for peri-implant diseases.

A number of mechanisms could explain the effect of periodontitis and peri-implantitis on systemic inflammation, including dumping of local inflammatory biomarkers (e.g., IL-6) and triggering a systemic hepatic response; bacterial end products being disseminated through mucosal breaches; immune-level responses; oral microbiome affecting the gum microbiome and causing metabolites to leak; or, alternatively, a combination of these theories.[36,37]

While CRP has historically been the inflammatory biomarker of proven sensitivity to delineate the acute-phase response following periodontal therapy,[38] emerging evidence stipulates CRP could be a surrogate biomarker for upstream IL-1β activity, a known correlator with biologically failing implants.[39] Future research efforts should focus "upstream" of CRP toward IL-1 and IL-6 for quantifying and qualifying systemic inflammation.[40] As suggested by large randomized controlled trials, the IL-1 inflammatory pathway might play a role in the pathogenesis of inflammatory conditions, such as atherosclerosis. Identifying potential sources of inflammatory activation could therefore lead to a better management of the so-called residual inflammatory cardiovascular risk.

This study, however, has important limitations. Firstly, it is a secondary analysis of a cross-sectional study which was not only designed to test the impact of peri-implant diseases on systemic inflammation. Secondly, the cross-sectional nature would not allow us to define a temporal association between the presence of peri-implant/periodontal inflammation and markers of systemic inflammation. Lack of a formal sample size estimation, sample selection bias, absence of periodontal clinical variables, information of the individual numbers of implants for each participant, and the selection of only implants loaded for more than 5 years complete the list of limitations. Additionally, our data are relative to a population with hypertension; this could pose a question on the external validity of the data. However, the analysis included information on the most common confounders associated with CRP and cardiovascular risk. Furthermore, a robust methodology to analyze the dataset and consistent findings across the different subgroups support our preliminary conclusions, and we urge the reader to interpret our findings as hypothesis generation rather than definitive evidence. A larger, matched sample of participants with tighter control of confounding factors would (a) better identify and quantify any association, (b) determine if a threshold exists for local tissue inflammation before a systemic biochemical response is identifiable, and (c) show which factors impact on the association between peri-implant disease and host response. Lastly, an appropriately powered interventional study with a randomized design would be required to ascertain the nature of the association between peri-implant diseases and systemic inflammation.

5 | CONCLUSIONS

Peri-implant diseases may be associated with systemic inflammation in a measure linked to the severity and extent of the active mucosal inflammation. The combination of peri-implant and periodontal diseases impacts on the individual's systemic inflammatory burden as assessed by serum CRP levels. Further observational and interventional evidence is needed to ascertain the nature of this association.

AUTHOR CONTRIBUTIONS

Vipul Patel and Jeanie Suvan contributed to conception and design of the study and drafted and critically revised the manuscript. Marco Orlandi, Nicola Pranno, and Francesco D'Aiuto contributed to conception, design, and data interpretation and performed all statistical analyses and drafted and critically revised the manuscript. Piero Papi contributed to conception and data acquisition and critically revised the manuscript. Bianca Di Murro, Giorgio Pompa, Antonella Polimeni, and Claudio Letizia contributed to data acquisition and critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

ORCID

Marco Orlandi https://orcid.org/0000-0002-1173-3029
Piero Papi https://orcid.org/0000-0003-2564-530X
Francesco D'Aiuto https://orcid.org/0000-0001-8654-935X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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