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ORIGINAL ARTICLE

Association between subclinical atherosclerosis and oral inflammation: A cross-sectional study

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Abstract

Background: The aim of this cross-sectional study was to investigate the association between carotid intima-media thickness (c-IMT) values and periodontal and peri-implant diseases in a sample of patients with hypertension.

Methods: A total of 151 participants with presence of at least one dental implant in function for >5 years were recruited. Anthropometric measurements, 24-h ambulatory blood pressure monitoring, ultrasound assessment of carotid arteries (c-IMT and presence of plaque) were recorded and venous blood samples obtained. An oral examination was performed by calibrated examiners to ascertain prevalence and severity of periodontal and peri-implant diseases. Binomial logistic regression was performed to investigate the potential association between various measures of exposure of dental diseases and predictors of cardiovascular risk (c-IMT > 0.9 mm and presence of plaque or their combination).

Results: Diagnosis of periodontitis (OR 6.71, 95% CI: 2.68-16.76, $P < 0.001$), cumulative mucosal/gingival inflammation (Periodontal Screening and Recording score) (OR 1.25, 95% CI:1.12-1.41, $P < 0.001$), and mucositis (OR 3.34, 95% CI:1.13-9.85, $P < 0.05$) were associated with c-IMT > 0.9 mm and/or plaque presence independent of age, sex, smoking, 24 h systolic blood pressure and body mass index differences. No statistically significant results were noted for peri-implantitis. Linear regression models confirmed a positive association of cumulative mucosal/gingival inflammation ($\beta = 0.011$, SE 0.002, $P < 0.001$), diagnosis of periodontitis ($\beta = 0.114$, SE 0.020, $P < 0.001$), and peri-implant diseases ($\beta = 0.011$, SE 0.002, $P < 0.001$) with increased c-IMT values.

Conclusions: This study confirms a positive association between mucosal/gingival inflammation and subclinical atherosclerosis assessed by c-IMT values and the presence of carotid plaque in patients with hypertension, independent of traditional cardiovascular risk factors. Future studies are needed to further characterize this relationship.

KEYWORDS
atherosclerosis, cardiovascular diseases, hypertension, peri-implantitis, periodontitis

1 | INTRODUCTION

Hypertension is the most prevalent among cardiovascular diseases (CVDs), affecting approximately 30% to 45% of the worldwide population.[1] It is a major cause of mortality and disability and an ever-growing public health concern.[2,3] Its management is a key step in the prevention of cardiovascular (CV) events, such as myocardial infarction and stroke.[4]

It is common to observe raised blood pressure (BP) values (≥130/85 mmHg) clustered with other traditional CV risk factors (dyslipidemia, obesity, and insulin resistance). Indeed, raised BP is one of the diagnostic criteria of metabolic syndrome (MetS) affecting almost 40% of the world-wide population, with the highest prevalence in individuals over 50 years of age.[5,6]

Among other surrogate measures of CVDs, ultrasound assessment of the carotid intima-media thickness (c-IMT) has been proposed as a non-invasive tool to evaluate structural arterial atherosclerosis, and it is a good predictor of future CV events.[7,8] Further, c-IMT is closely linked to other cardiovascular risk factors, such as diabetes, hypercholesterolemia, and hypertension.[9,10] A c-IMT value >0.9 mm or the presence of stenotic carotid plaque have shown a strong predictive value for future CV events, independent of other traditional risk factors.[11]

Periodontitis is a chronic inflammation triggered by a dysbiotic dental biofilm and the main cause of soft and hard tissue loss around teeth.[12] It is amongst the most common inflammatory diseases of mankind and affects 45% to 50% of the worldwide population.[13,14]

Dental implants are titanium devices, used to replace missing teeth with high survival rates (well over 90%), which explains why their use is steadily increasing.[15] Dental implants are however not free from complications, often linked to progressive inflammation of the mucosal tissues where these are seated (mucositis), which could result in rapid bone loss (peri-implantitis). Periodontal and peri-implant diseases share similarities in their etiology and pathological mechanisms.[16,17]

Consistent evidence suggests that periodontitis is linked not only to a local inflammatory response but also to a systemic host-immune response and to an increased bacterial burden which could impact the progression of atherogenesis, explaining the increased risk of vascular complications found in patients with periodontitis.[18–24] The association between periodontitis and CVDs has been supported by consistent epidemiologic and experimental evidence and recently confirmed in the consensus report of the European Federation of Periodontology and the World Heart Federation.[25]

Little evidence is available, however, on the potential impact of peri-implant dental diseases on systemic markers of health or disease. The aim of this cross-sectional study was to investigate the association between c-IMT and presence of carotid plaque and periodontal and peri-implant diseases in a sample of patients with hypertension.

2 | MATERIALS AND METHODS

2.1 | Study design

Data for this study were retrieved from a cross-sectional study[26] conducted at the departments of Oral and Maxillo-Facial Sciences and Translational and Precision Medicine, at Sapienza University of Rome.

2.2 | Study population

From April 2018 to September 2018, all patients currently in treatment at the Tertiary Centre of Secondary Hypertension Unit, Policlinico Umberto I, Sapienza University of Rome, for primary and/or secondary hypertension were consecutively evaluated and included in this study if they (1) were aged ≥18 years old, and (2) had at least one dental implant in function for >5 years. Arterial hypertension was defined as systolic BP (SBP) values ≥130 mmHg and/or diastolic BP (DBP) values ≥80 mmHg recorded over 24 h with ambulatory blood pressure monitoring (ABPM).[1] Secondary forms of hypertension, such as primary aldosteronism, renovascular diseases, Cushing's syndrome, and pheochromocytoma, were excluded. Each participant gave informed consent and the study received ethical approval by the institutional review board of Sapienza University of Rome (Ref. 4948/2018). The study results are reported according to the STROBE guidelines (www.strobe-statement.org).

2.3 | Medical examination

Anthropometric measurements and venous blood samples were obtained from all participants in the early morning after an overnight fast. An experienced physician (CL) masked to the dental status performed the anthropometric

measurements. Body mass index (BMI) was recorded for each patient (kg/m^2) and waist circumference (WC) was measured placing the measuring tape horizontally around the patient's abdomen and aligning the bottom edge of the tape with the belly button. We used a measuring tape with a spring handle in order to control the pressure exerted on the patient's abdomen. Data about smoking habit, as well as current medications (number and type) and past medical history, were collected by trained staff.

2.4 | Vascular assessments

A 24-h ABPM and ultrasound assessment of carotid arteries was recorded for markers of hypertensive- and metabolic-related vascular damage.[27] The 24-h ABPM was performed using an automatic BP monitor[*]. For each patient, the BP values were obtained every 15 min during the day and every 30 min during the nighttime period. The parameters collected included the mean 24-h SBP/DBP values and their standard deviations (SDs), mean daily and nighttime SBP/DBP values and their SDs, and the nighttime BP dipping values.

An ultrasound scan was performed by an experienced physician (CL) masked to the dental status to image the common carotid artery, the carotid bulb, and the near and far wall segments of the internal carotid artery bilaterally. Images were obtained in longitudinal sections with a single lateral angle of insonation, optimizing the image for the far wall. C-IMT was defined as the distance between the ultrasound interfaces of the lumen-intima and media-adventitia.[27] Six manual measurements were performed, with automatic border detection, at equal distances along 1 cm on the far wall of the common carotid. Carotid stenotic plaque was defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with c-IMT >1.5 mm protruding into the lumen that is distinct from the adjacent boundaries.

2.5 | Biomarkers

Serum concentrations of fasting plasma glucose (FPG), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), high-sensitive C-reactive protein (CRP), creatinine, and blood uric acid level were measured. Urine samples were collected for each patient over 24-h to evaluate the 24-h microalbuminuria and patients were also asked to collect a fasting spot urinary sample on the morning of the delivery of the collected urine samples to detect microalbuminuria.

All patients were screened for MetS according to the NCEP ATP III criteria.[28] Case definition of MetS was based on presenting with 3 or more of the following criteria: (1) WC ≥ 102 cm (male) or ≥88 cm (female); (2) FPG value of ≥110 mg/dl; (3) serum TG concentration of ≥150 mg/dl; (4) serum HDL cholesterol concentration of <40 mg/dl (male) or <50 mg/dl (female); and (5) SBP/DBP ≥ 130/85 mmHg, obtained by 24-h ABPM.

2.6 | Periodontal and peri-implant examination

A full oral/dental examination was carried out by a calibrated examiner (BDM) as previously described.[26] The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions criteria were used for a case definition of periodontitis including the adapted criteria for peri-implant diseases in observational studies.[29,30] A patient was defined a "periodontitis case" in accordance with the definition provided by Tonetti et al.[30] Briefly, peri-implant health was defined as the absence of clinical signs of mucosal inflammation, bleeding and/or suppuration on gentle probing, without radiographic bone loss. Peri-implant mucositis was characterized by the presence of mucosal bleeding and/or suppuration on gentle probing, without radiographic bone loss. Lastly, peri-implantitis was defined as the presence of mucosal bleeding and/or suppuration on gentle probing, with radiographic bone levels ≥3 mm apical of the most coronal portion of the intra-osseous part of the dental implant. A Periodontal Screening and Recording (PSR) index[31] was collected in each of the sextants using a millimetric periodontal probe[†] with a light force (approximately 0.2 N). Peri-implant clinical assessments included probing pocket depth (PPD) as a continuous measure in millimeters (mm), and plaque index and bleeding on probing recorded as dichotomic outcomes (present/absent). Furthermore, mesial and distal implant crestal bone levels were measured on digital periapical radiographs obtained by using an imaging plate scanner[‡] and taken by means of the parallel cone technique using a Rinn alignment system[§]. Image analysis software[**] was used to estimate mean marginal bone loss levels by an independent examiner, not involved in other aspects of the study, considering a mean error of ± 0.5 mm.

[*] Spacelabs 90207, SpaceLabs, Issaquah, WA, USA

[†] PCP-UNC 15, Hu-Friedy, Chicago, IL, USA
[‡] PSPIX^2, Acteon Group, Norwich, UK
[§] XCP Centratore, Rinn, York, PA, USA
[**] Version 3.7.0 Digimizer Medical Software, Brolkstraat, Belgium

2.7 | Statistical analysis

Data were evaluated using standard statistical analysis software[††]. A database was created using a dedicated program[‡‡] and corrected for errors/inconsistencies. Descriptive statistics included mean ± SD values for continuous variables and number (percentage) for categorical variables. The Shapiro-Wilk test was used to determine whether continuous data conformed to a normal distribution. Group comparison was assessed by Mann-Whitney *U* test for continuous variables and by chi-square test of homogeneity and Fisher's exact test for categorical variables.

Study outcomes included the presence of c-IMT > 0.9 mm and of any carotid atherosclerotic plaque. These were chosen on basis of their predictive value for future increased cardiovascular risk.[1]

Measures of exposure included a variety of continuous and categorical variables collected at the oral examination. A cumulative mucosal inflammatory index (the sum of all PSR values per patient) was calculated as previously described.[32] Average PPD and bone levels were calculated as patient-level variables. C-IMT > 0.9 mm or presence of plaque or the combination of these two variables were modelled against the following independent variables: sex (male/female), diagnosis of periodontitis (yes/no), smoking (yes/no), presence of peri-implant diseases (healthy implant/mucositis/peri-implantitis), cumulative PSR, mean marginal bone loss, BMI, WC, CRP, glucose, total cholesterol, HDL, LDL, TG, creatinine, blood uric acid level, 24-h SBP, 24-h DBP, microalbuminuria with a spot measurement, and microalbuminuria detection in 24 h.

Binomial logistic regression models were then created (Model 1: c-IMT > 0.9 mm or c-IMT ≤ 0.9 mm with the presence of carotid atherosclerotic plaque versus c-IMT ≤ 0.9 mm and absence of atherosclerotic plaques; Model 2: c-IMT > 0.9 mm versus c-IMT ≤ 0.9 mm; Model 3: presence of carotid atherosclerotic plaque versus absence of carotid atherosclerotic plaque). Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure.[33] The results of binomial regression models were presented as odds ratio (OR) and 95% confidence intervals (CIs). Sensitivity analyses were performed in the subgroup of participants without periodontitis (i.e., only peri-implant mucositis/peri-implantitis) in order to ascertain the impact of case definition of periodontitis on the association between all exposure variables and various study outcomes.

Multiple linear regression (backward stepwise) analysis was performed to ascertain the effects of independent variables on average c-IMT as the continuous outcome. Correlation analyses between mean c-IMT values and cumulative PSR were further investigated using Spearman's rank-order testing. Bonferroni correction was used when multiple comparisons were performed. Statistical significance was set at $P \leq 0.05$.

3 | RESULTS

A total of 151 patients were enrolled in this study, having 474 dental implants placed, with a mean of 3.13 implants per patient. The mean functional time was 7.34 ± 2.23 years (range: 5 to 22 years).

As for periodontal and peri-implant status, 61.6% were classified as periodontitis cases, whilst 57% of the total sample presented with mucositis and 27.8% of the whole sample with peri-implantitis. Participants with c-IMT > 0.9 mm or with presence of carotid atherosclerotic plaque showed higher levels of serum CRP ($P < 0.001$), microalbuminuria spot ($P < 0.001$), 24 h microalbuminuria ($P < 0.001$), 24 h SBP ($P = 0.029$) and, cumulative PSR ($P < 0.001$) compared to the rest of the sample. Further, increased prevalence of periodontitis ($P < 0.001$) and peri-implant diseases ($P = 0.008$) were confirmed in this group (Table 1 and see Table S1 in the online *Journal of Periodontology*). A statistically significant higher number of patients treated with beta-blocker, calcium channel blocker, diuretics, or anticoagulant/antiplatelet drugs presented c-IMT values > 0.90 mm or presence of carotid atherosclerotic plaque (Table 2 and see Table S2 in the online *Journal of Periodontology*).

Statistically significant associations were observed for c-IMT > 0.90 mm with cumulative PSR (OR = 1.25, 95% CI: 1.12-1.41) and presence of periodontitis (OR = 6.71, 95% CI: 2.56-17.61) (Table 3). The results were confirmed in (Model 2) (Table 3). Further, in Model 3, statistically significant associations were observed for the presence of carotid atherosclerotic plaque only with cumulative PSR values (OR = 1.19, 95% CI: 1.07-1.32) (Table 3). Results were confirmed when performing analyses in the subgroup of participants without case definition of periodontitis.

The linear regression analysis confirmed a positive association of c-IMT with cumulative PSR values ($\beta = 0.011$, SE 0.002, $P < 0.001$), presence of periodontitis ($\beta = 0.102$, SE 0.020, $P < 0.001$), and presence of peri-implant diseases (combined diagnosis of peri-mucositis and peri-implantitis) ($\beta = 0.086$, SE 0.028,

[††] Version 20.0, Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA

[‡‡] Excel, Microsoft, Redmond, WA, USA

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TABLE 1 Baseline characteristics of participants according to c-IMT values and presence of carotid plaque ($n = 151$)

Variable (mean ± SD)(n,%)	c-IMT > 0.90 mm/plaque (mean/median; N = 103)	c-IMT ≤ 0.90 mm/no plaques (mean/median; N = 48)	*P* value
Age, years	69.69 ± 9.29/71.00	61.16 ± 9.38/60.50	<0.001
Sex, male (n; %)	41 (39.8%)	21 (43.8%)	0.723
Smoking, current (n; %)	35 (34.0%)	15 (31.2%)	0.853
CRP, mg/l	2.85 ± 1.40/3.10	1.73 ± 1.50/1.00	<0.001
BMI, kg/m^2	25.78 ± 3.16/25.67	27.31 ± 3.79/27.00	0.023
Waist circumference, cm	97.09 ± 9.45/96.00	99.84 ± 13.24/102.00	0.084
Glucose, mg/dl	93.36 ± 18.76/92.00	91.81 ± 10.55/91.00	0.871
Total cholesterol, mg/dl	190.50 ± 43.00/195.00	199.19 ± 34.05/190.50	0.473
Triglycerides, mg/dl	123.02 ± 68.17/107.00	148.54 ± 68.39/134.50	0.009
HDL, mg/dl	59.68 ± 18.19/54.00	58.77 ± 18.12/53.00	0.521
LDL, mg/dl	107.58 ± 32.92/117.00	109.33 ± 36.04/107.00	0.525
Creatinine, mg/dl	0.96 ± 0.27/0.93	0.87 ± 0.22/0.80	0.263
Uric acid, mg/dl	5.78 ± 1.21/5.50	5.60 ± 1.73/5.00	0.95
Microalbuminuria spot, mg/dl	19.32 ± 1.21/1.90	5.56 ± 1.21/0.85	<0.001
24 h microalbuminuria, mg/dl	24.79 ± 50.34/3.90	8.9 ± 4.40/2.45	<0.001
24 h heart rate, bpm	70.03 ± 5.91/69.00	74.49 ± 8.44/73.00	0.008
24 h systolic blood pressure, mmHg	128.76 ± 12.53/131.00	126.49 ± 10.57/123.00	0.029
24 h diastolic blood pressure, mmHg	73.10 ± 8,88/72.00	79.21 ± 6.69/78.00	<0.001
Metabolic syndrome, (n; %)	36 (34.9%)	22 (45.85%)	0.213
Cumulative PSR	14.88 ± 4.14/15.00	11.35 ± 4.51/11.00	<0.001
Periodontitis (n; %)	78 (75.7%)	15 (31.2%)	<0.001
Peri-implant diseases (n; %)			0.008
Healthy implants	10 (9.7%)	13 (27.1%)	
Mucositis	66 (64.1%)	20 (41.7%)	
Peri-implantitis	27 (26.2%)	15 (31.2%)	

Note: Group comparison was assessed by Mann-Whitney *U* test for continuous variables and by Chi-square test of homogeneity and Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant.

Abbreviations: BMI, body mass index; c-IMT, carotid intima-media thickness; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSR, Periodontal Screening and Recording index.

TABLE 2 Types of medications taken by participants according to carotid intima-media thickness (c-IMT) values and presence of carotid plaque ($n = 151$)

	c-IMT > 0.90 mm/plaque (*N* = 103)	c-IMT ≤ 0.90 mm/no plaques (*N* = 48)	*P* value
Beta-blocker	38 (36.9%)	5 (10.4%)	0.001
Calcium channel blockers	56 (54.4%)	15 (31.2%)	0.009
Ace inhibitors	15 (14.6%)	4 (8.3%)	0.430
Diuretic	14 (13.6%)	0 (0%)	0.005
Anticoagulant/Antiplatelet	75 (86.2%)	11 (23.4%)	<0.001
Lipid-lowering	39 (37.9%)	21 (43.8%)	0.592

Note: Group comparison was assessed by Chi-square test of homogeneity and Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant.

TABLE 3 Binomial logistic regression models presented as odds ratios and 95% confidence intervals of c-IMT > 0.90 or presence of plaque or their combination according to the periodontal and peri-implant status

	Model 1	Model 2	Model 3
Cumulative PSR	1.25 (1.12-1.41)**	1.32 (1.18-1.47) ***	1.19 (1.07-1.32) *
Presence of periodontitis	6.71 (2.56-17.61)**	0.12 (0.05-0.29) ***	0.24 (0.10-0.61)
Mucositis	2.10 (0.67-6.62)	1.69 (0.55-5.126)	0.83 (0.25-2.82)
Peri-implantitis	0.91 (0.25-3.27)	1.34 (0.39-4.60)	0.45 (0.12-1.70)
Periodontitis*Mucositis	0.09 (0.004-1.94)	0.36 (0.002-0.77)	0.45 (0.019-10.89)
Periodontitis*Peri-implantitis	0.27 (0.01-5.11)	0.15 (0.01-2.76)	0.30 (0.015-5.77

Note: Model 1: c-IMT > 0.90 mm or c-IMT ≤ 0.90 mm with the presence of carotid atherosclerotic plaque versus c-IMT ≤ 0.90 mm and absence of atherosclerotic plaques; Model 2: c-IMT > 0.90 mm versus c-IMT ≤ 0.90 mm; Model 3: presence of carotid atherosclerotic plaque versus absence of carotid atherosclerotic plaque. Variables with statistically significant association on univariate analysis were included in the logistic regression. All models included adjustment for age, sex, smoking, 24 h systolic blood pressure, and BMI. The reference category for mucositis and peri-implantitis is healthy implants. Assumption of collinearity was confirmed and rejected (Cumulative PSR, Tolerance = 0.42, VIF 2.36; Presence of periodontitis, Tolerance = 0.43, VIF = 2.34; Peri-implant disease, Tolerance 0.94, VIF = 1.07).

Abbreviations: BMI, body mass index; c-IMT, carotid intima-media thickness; PSR, Periodontal Screening and Recording index; VIF, variance inflation factor.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

TABLE 4 Multiple backward stepwise linear regression models (with $P = 0.05$ to enter and $P = 0.10$ to leave) of c-IMT according to periodontal and peri-implant status

	β coefficient	95.0% CI	*P* value
Cumulative PSR	0.011	0.006-0.015	<0.001
Presence of periodontitis	0.102	0.063-0.141	<0.001
Peri-implant diseases	0.086	0.030-0.141	0.036

Note: Variables with statistically significant association on univariate analysis were included in the backward stepwise linear regression.
Variables with high multicollinearity (such as cumulative PSR, presence of periodontitis, and peri-implant diseases) were not included. Assumption of collinearity was confirmed and rejected (Cumulative PSR, Tolerance = 0.97, VIF 1.034; Presence of periodontitis, Tolerance = 0.90, VIF = 1.12; Peri-implant disease, Tolerance 0.93, VIF = 1.08) in the same models.
Abbreviations: CI, confidence interval; c-IMT, carotid intima-media thickness; PSR, Periodontal Screening and Recording index; VIF, variance inflation factor.

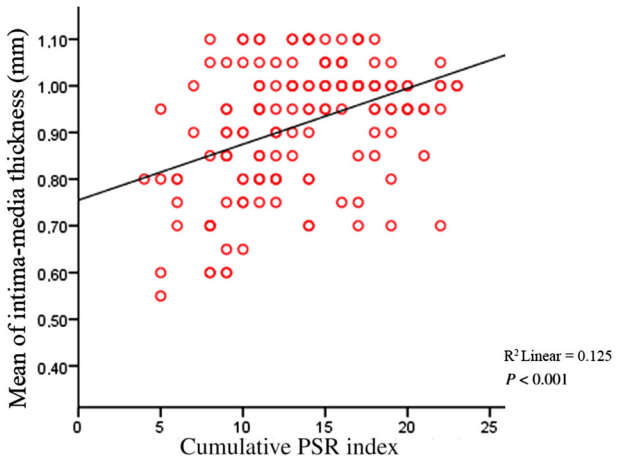

FIGURE 1 Scatter plot of carotid intima-media thickness (mm) values by cumulative Periodontal Screening and Recording (PSR) index using Spearman's rank-order testing

$P < 0.036$) (Table 4). Lastly, a moderate but statistically significant positive linear correlation between c-IMT and PSR was observed (R = 0.35; $P < 0.001$, Figure 1).

4 | DISCUSSION

This study is among the first reports outlining an association between not only periodontal but also peri-implant mucosal inflammation and markers of subclinical atherosclerosis, evaluated using c-IMT and the presence of plaque as surrogate vascular imaging outcomes. A linear link between the degree of oral soft tissue inflammation and vascular measures was observed. These results were independent of common traditional CVD risk factors.

The association between peri-implant diseases and CVD has been scarcely investigated to date. A recent systematic review confirmed that the available evidence on the association is inconclusive and limited.[34] By contrast, the evidence linking periodontitis and hypertension is consistently growing: based on the results of a recent systematic review and meta-analysis, and of a large case-control study, participants with moderate and severe periodontitis showed an increase of 20% to 50% in the odds of hypertension.[35,36] The same relationship has been confirmed in randomized clinical trials (RCTs), demonstrating a possible reduction of SBP and DBP values after successful periodontal therapy.[37] Nevertheless, larger and

well-designed intervention studies are needed to understand the potential benefit of periodontal and peri-implant inflammation control as a novel non-pharmacological intervention to lower BP values and produce systemic health benefits.

By contrast, there are several drug interventions that have an impact on c-IMT progression, such as BP- and lipid-lowering medications. First, statin treatment alters significantly the progression of IMT over a 10-year period when compared with patients not taking them.[38] Similar beneficial effects have been confirmed when antiplatelet[39] and antihypertensive medications[40] are prescribed. In our sample, there were no statistically significant differences in the distribution of medications among patients with IMT > 0.9 mm/plaque presence or IMT < 0.9 mm/plaque absence, with the exception of anticoagulants, diuretics, and beta-blockers. There is little evidence on the potential influence of some of these medications on gingival diseases including periodontitis, with the exception of drug-induced gingival overgrowth caused by calcium-channel blockers (i.e., nifedipine), and the association between increased gingival bleeding and antiplatelet drugs.[41] Use of statins has been linked to a reduced rate of tooth loss.[42] Therefore, we cannot rule out that some imbalance in the medications used in the study could have impacted our results and interpretation, and hence further research on this topic is advocated.

A linear association between mucosal/gingival inflammation and c-IMT values was observed in this study. This is in line with previous evidence from cross-sectional studies[43] confirming that in patients with periodontitis a direct relationship was found between deeper PPD (gum pockets) and c-IMT values. Our sensitivity analyses further confirmed that peri-implant mucosal inflammation could be a contributor to the vascular disease burden of an individual, although this might be of lesser magnitude than that represented by periodontitis.

Different systematic reviews of observational studies[24,44] highlighted how patients with periodontitis exhibit higher c-IMT values, although the heterogeneity of definitions adopted for periodontitis and c-IMT measurements could have influenced the results of the included studies and, more importantly, their interpretation. Patients with periodontitis on average present with greater c-IMT values (0.08 mm) when compared to controls. This association is further corroborated by evidence from intervention and longitudinal studies demonstrating a beneficial effect from improvement in c-IMT values for the management of periodontal inflammation (reviewed by Orlandi and colleagues).[23] A recent large-scale meta-analysis of RCTs involving data from more than 100,000 patients reported that reducing c-IMT progression of 10 μm/y was associated with a relative risk of 0.91 (95% CI: 0.87-0.94) for mortality related to CVD events.[45] A number of plausible mechanisms have been proposed linking periodontal inflammation and vascular health.[21] Increased levels of systemic inflammatory mediators (CRP, IL-1, IL-6, TNF-α) can directly affect the endothelium, promoting low-grade systemic inflammation and tissue damage mediated by the hyperactivation of T and B lymphocytes and the increase in oxidative stress, the migration of leukocytes, and platelet aggregation (reviewed by Herrera and colleagues).[21] Upregulation of thrombotic and hemostatic factors have been linked to periodontitis whilst limited evidence exists for peri-implant diseases.[21]

Alternatively, peri-implant diseases and periodontitis induce extraoral bacterial dissemination (*Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Treponema denticola*) in atheroma plaques (reviewed by Sanz and colleagues).[25] Periodontal pathogens can induce vascular damage and endothelial disfunction: *P. gingivalis*, which secretes gingipain proteases that compromise the integrity of the endothelial junction and elevate its permeability, is interestingly also the most abundant bacterial species in the coronary arteries.[46]

The microbiological profile of peri-implantitis is more heterogeneous and complex than that of periodontitis, including not only periodontal pathogens (*P. gingivalis, P. intermedia, F. nucleatum, T. denticola*) but also *Staphylococcus aureus* and other non-cultivable gram-negative species and anaerobic gram-positive rod associated species.[47,48] There is evidence that the peri-implant sulcus is more vulnerable to pathogens and that the local inflammatory response in the peri-implant mucosa is at least twice as large as that in periodontal lesions[49]; hence, it could represent an even greater inflammatory/infectious trigger (Figure 2).

Some limitations should be acknowledged, however, in this study. The nature of the cross-sectional design and the small sample size included in this study preclude drawing any cause-effect inferences between exposure (periodontal and peri-implant diseases) and outcome (increased subclinical atherosclerosis). Furthermore, sample selection could lead to some bias in peri-implant disease prevalence due to the absence of specific implant data (brand, surface treatment, guided bone regeneration procedures, specialist or generic practitioner placing the implants).

Another limitation is the lack of further detailed clinical dental and oral measures which might have led to inaccuracies and imprecise assessment of the severity of periodontitis and peri-implant diseases. Nevertheless, using internationally recognized case definitions of periodontitis[30] and hypertension,[1] evaluation of BP levels using a 24-h ABPM device and inclusion of CVD risk factors strengthen our findings. Moreover, the results of this study should be clearly interpreted as hypothesis

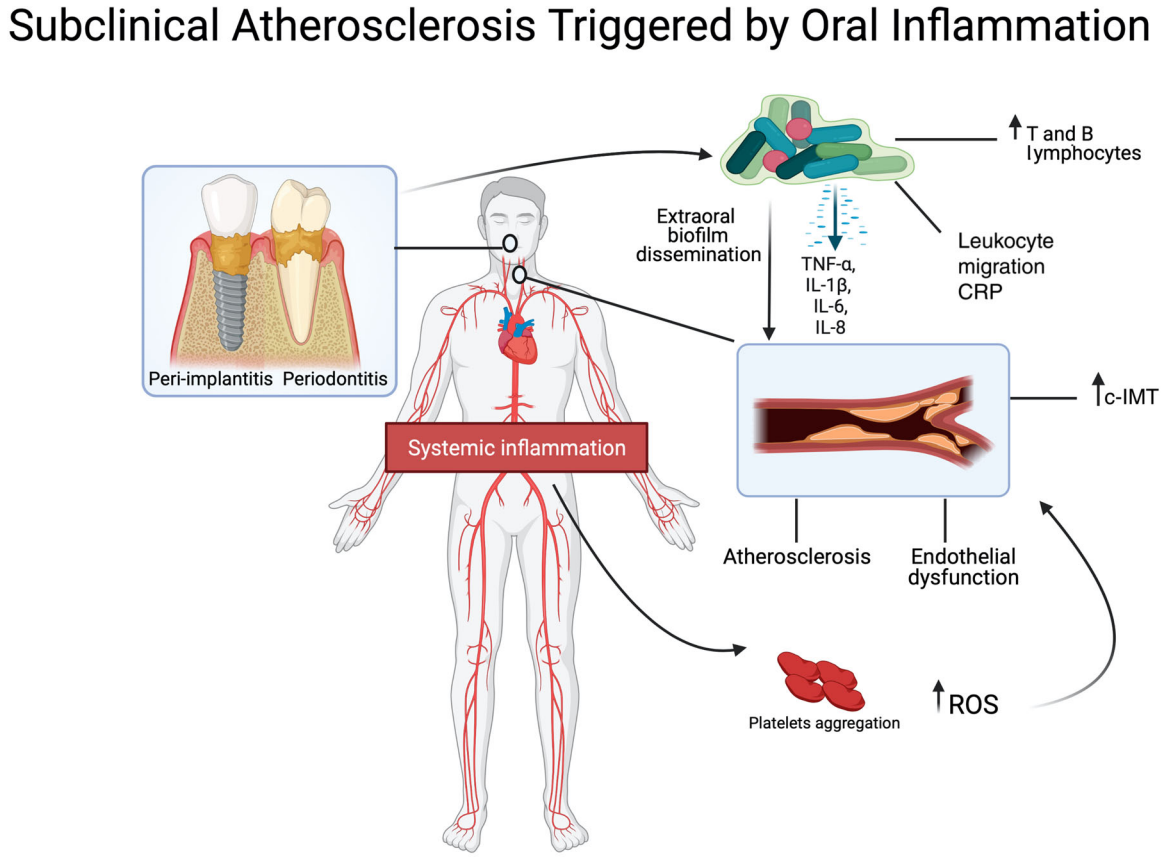

FIGURE 2 Mechanisms linking periodontal/peri-implant inflammation and subclinical atherosclerosis (created with BioRender.com). Periodontal and peri-implant inflammation caused by periodontal bacteria induce an acute-phase inflammatory response, with increased levels of systemic inflammatory mediators (CRP, IL-1, IL-6, TNF-α), the hyperactivation of T and B lymphocytes and increased oxidative stress, leukocyte migration, and platelet aggregation. Further, peri-implant diseases and periodontitis can induce extraoral bacterial dissemination (*Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Treponema denticola*) and cause atheromas and endothelial dysfunction. CRP, C-reactive protein; c-IMT, carotid intima-media thickness; ROS, reactive oxygen species

generating, regarding the possible role of peri-implant and periodontal diseases on the onset and progression of subclinical atherosclerosis.

Future efforts should include larger samples and longitudinal studies to further characterize the nature of the relationship between subclinical atherosclerosis and periodontal/peri-implant inflammation, but ultimately interventional studies are needed to evaluate the effects of periodontal and peri-implant disease therapy on the progression rate of c-IMT. If the association between these common mucosal inflammatory diseases is proven to be causal, then the implications for the health of the public could be significant, as the number of dental implants placed per year is estimated at 12–18 million worldwide.[50] Physicians should be aware of the potential impact of peri-implant and periodontal inflammation on the presentation and possibly the progression of CVDs with regards to the implementation of protective measures and public health policies contributing to the general good health.

AUTHOR CONTRIBUTIONS

PP and FDA contributed to the conception, design, and data interpretation, and drafted and critically revised the manuscript. NP, MO, and EMA contributed to the design and data interpretation, performed all statistical analyses, and critically revised the manuscript. BDM, GP, AP, CL, LP, and AC 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

All authors declare no conflict of interest.

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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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