Association between Subclinical Atherosclerosis and Oral Inflammation. A cross-sectional study

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Conflict of interest declaration
The authors declare they have no conflict of interest related to this study.

Abstract
Aims: 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 at least one dental implant in function for >5 years were recruited. Anthropometric measurements, 24-hours ambulatory blood pressure monitoring, ultrasound assessment of carotid arteries and venous blood samples were obtained. Prevalence and severity of periodontal and peri-implant diseases were assessed by oral assessment. Binomial logistic regression was used to investigate the potential association between periodontal/peri-implant inflammation and the following outcomes: a) c-IMT >0.9 mm and b) presence of plaque or their combination.
Results: Diagnosis of periodontitis (OR 6.71, $p<0.001$), mucositis (OR 3.34, $p<0.05$) and cumulative mucosal/gingival inflammation (PSR score) (OR 1.25, $p<0.001$) were associated with greater odds of carotid atherosclerosis. Inconclusive findings were noted for peri-implantitis. Linear regression models confirmed a positive association of PSR scores ($\beta=0.011$, SE 0.002, $p<0.001$), 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 in patients with hypertension, indipendently of traditional cardiovascular risk factors.

Riassunto
Introduzione: Lo scopo di questo studio cross-sectional è quello di valutare l'associazione tra i valori di spessore dell'intima-media carotidea (IMT) e le patologie parodontali e peri-implantari in una popolazione ipertesa.

Metodi: Sono stati arruolati 151 partecipanti con almeno un impianto dentale in funzione da >5 anni. Per ogni paziente, sono stati ottenute le misurazioni antropometriche, il monitoraggio pressorio 24ore e le analisi del sangue, è stata inoltre effettuato l'esame ultrasonografico carotideo. Una visita parodontale ha valutato la severità e la prevalenza delle patologie peri-implantari e parodontali. La regressione logica binomiale è stata utilizzata per valutare l'associazione tra l'infiammazione orale e IMT>0.9 mm, placca carotidea o loro combinazione.

Risultati: La diagnosi di parodontite (OR 6.71, *p*<0.001), mucosite (OR 3.34, p<0.05) e i valori di PSR, indice cumulativo di infiammazione orale (OR 1.25, p<0.001) sono risultati associati con un aumento del rischio per l'aterosclerosi carotidea. La regressione lineare ha confermato una correlazione tra valori di PSR (β=0.011, SE 0.002, p<0.001), parodontite (β=0.114, SE 0.020, *p*<0.001) e patologie peri-implantari (β=0.011, SE 0.002, *p*<0.001) con valori aumentati di IMT.

Conclusioni: Questo studio conferma una associazione tra l'infiammazione orale e l'aterosclerosi subclinica in un campione di popolazione ipertesa, indipendentemente dai tradizionali fattori di rischio cardiovascolari.

Introduction

Hypertension is the most prevalent among cardiovascular diseases (CVDs), affecting approximately 30-45% of the worldwide population[1,2]. It is a major cause of mortality and disability and an ever-growing public health concern[3,4]. Its management is a key step in the prevention of cardiovascular (CV) events, such as myocardial infarction and stroke[5,6].

It is common to observe raised blood pressure values (≥ 130/85 mmHg) clustered with other traditional CVD risk factors (dyslipidaemia, obesity and insulin resistance). Indeed, raised blood pressure 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[7,8].

Among other surrogate measures of CVD, the 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 as a good predictor of future CV events[9,10]. Further, c-IMT is closely linked to other cardiovascular risk factors, such as diabetes, hypercholesterolemia and hypertension[11,12]. A c-IMT value greater than 0.9 mm or the presence of a stenotic carotid plaque have shown a strong predictive value for future CV events, independent of other traditional risk factors[13].

Periodontitis is amongst the most common inflammatory diseases of mankind. It is a chronic inflammation triggered by a dysbiotic dental biofilm and the main cause of soft and hard tissues' loss around teeth[14]. Evidence confirms that periodontitis affects 45%-50% of the worldwide population[15,16].

Dental implants are titanium devices, used to replace missing teeth with high survival rates (well over 90%), which confirms why their use is steadily increasing[17]. 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 aetiology and pathological mechanisms[18,19].

Consistent evidence suggests that periodontitis is linked not only to a local inflammatory response but also a systemic host-immune response and increased bacterial burden which could impact on the progression of atherogenesis, explaining the increased risk of vascular complications found in patients with periodontitis[20-26].

The association between periodontitis and CVD has been supported by consistent epidemiologic and experimental evidences and recently confirmed in the Consensus report of the European Federation of Periodontology (EFP) and the World Heart Federation (WHF)[27].

Little evidence however is available 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 periodontal and peri-implant diseases in a sample of patients with hypertension and MetS.

Material and Methods

Study population

From April 2018 to September 2018, all referrals 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 were consecutively evaluated and included in this study if a) aged ≥ 18 years old, b) presenting with a diagnosis of hypertension and c) the presence of at least one dental implant in function for >5 years. Arterial hypertension was defined as systolic blood pressure (SBP) values ≥130 mmHg and/or diastolic (DBP) values ≥80 mmHg recorded over the 24h 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 institution review board of "Sapienza" University of Rome (Ref. 4948/2018). The study results are reported according to the STROBE guidelines (www.strobe-statement.org).

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 and the sonographic assessment. 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 bottom. 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), past medical history, were collected by trained staff.

Vascular assessments

A 24-hours ABPM and ultrasound assessment of carotid arteries were recorded as markers of hypertensive- and metabolic-related vascular damage[29]. The 24-hours ABPM was performed using the Spacelabs 90207 (SpaceLabs®, Washington, USA). For each registration, the blood pressure (BP) values were obtained every 15 minutes during the day and every 30 minutes during the night time period. The parameters collected included: mean 24-hours SBP/DBP and its standard deviation (SD), mean daily and night-time SBP/DBP and their SD, the dipping values.

An ultrasound scan was used 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[29]. 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 greater than 1.5 mm protruding into the lumen that is distinct from the adjacent boundaries.

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 (hs-CRP), creatinine and blood uric acid level were measured. Urine samples were collected for each patient over the 24-hours 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[30]. 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) fasting plasma glucose value ≥ 110 mg/dL; (3) serum triglycerides concentration ≥ 150 mg/dL; (4) serum HDL - cholesterol concentration < 40 mg/dL (male) or < 50 mg/dL (female) and (5) SBP/DBP ≥ 130/85 mmHg, obtained by 24-hours ABPM.

Periodontal and peri-implant examination

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 epidemiological studies [31,32]. 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 patient was defined a "periodontitis case" in accordance with the definition provided by Tonetti et al.[32].

A Periodontal Screening and Recording (PSR) index[33] was collected in each of the sextants using a millimetric periodontal probe (PCP-Unc 15, Hu-Friedy®, Chicago, Illinois, USA) with a light force (approximately 0.2 N) by a trained calibrated examiner (BDM).

To achieve intra-examiner reliability, the examiner was calibrated to show an agreement of 90% within 1 mm by duplicate measurements of probing depths on randomly selected teeth (10) and dental implants (10). Peri-implant clinical assessments included probing pocket depth (PPD) as continuous measure in millimetres (mm), Plaque Index (PI) and Bleeding on Probing (Bop) 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 (VistaScan, Durr Dental, Germany) and taken by means of the

parallel cone technique using a Rinn alignment system (XCP Centratore, Rinn, York, PA, USA). An image analysis software (version 3.7.0 Digimizer, Medical Software Brolkstraat, Belgium) was used to estimate mean marginal bone loss (MBL) levels by an independent examiner, not involved in other aspects of the study, considering a mean error of ± 0.5 mm was considered.

Statistical analysis

Data were evaluated using standard statistical analysis software (version 20.0, Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA). A database was created using Excel (Microsoft, Redmond, WA, USA) 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 or not the 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 as of their predictive value to 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 each patient) was calculated as previously described[34]. Average PPD and bone levels were calculated as patient-level variables. C-IMT >0.9 or presence of plaque or the combination between these two variables were modelled against the following independent variables: gender (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, waist circumference, CRP, glucose, total cholesterol, HDL, LDL, Triglycerides, creatinine, blood uric acid level, 24-hour SBP, 24-hour DBP, microalbuminuria with a spot measurement and microalbuminuria detection in 24h.

Binomial logistic regression models were then created [c-IMT > 0.9mm or c-IMT ≤ 0.9mm with the presence of carotid atherosclerotic plaque versus c-IMT ≤ 0.9mm and absence of atherosclerotic plaques (Model 1); c-IMT > 0.9mm versus c-IMT ≤ 0.9mm (Model 2); presence of carotid atherosclerotic plaque versus absence of carotid atherosclerotic plaque (Model 3)]. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure. The results of binomial were presented as odds ratio (OR) and 95% confidence intervals.

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

Results

The study sample included 151 participants presenting with a prevalence of periodontitis of 61.6 % 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 had increased prevalence of periodontitis ($p<0.001$) and peri-implant diseases ($p=0.008$).

Statistically significant associations between c-IMT > 0.90mm and cumulative PSR (OR=1.25, 95% CI:1.12-1.41), presence of periodontitis (OR=6.71, 95% CI: 2.68-16.76) and of mucositis (OR=3.34, 95% CI: 1.13-9.85) were observed. The results were confirmed in the multivariate analyses (Model 2). Further, in Model 3 statistically significant associations between the presence of carotid atherosclerotic plaque and cumulative PSR values (OR=1.19, 95% CI: 1.07-1.32) and of periodontitis (OR=3.43, 95% CI: 1.47-8.04) were observed but not for mucositis or peri-implantitis (Table 3).

A positive linear association of c-IMT with cumulative PSR values (β=0.011, SE 0.002, $p<0.001$), presence of periodontitis (β=0.114, SE 0.020, $p<0.001$) and of peri-implant diseases (combined diagnosis of peri-mucositis and peri-implantitis) (β=0.011, SE 0.002, $p<0.001$) were found (Table 4). Lastly, a moderate but statistically significant positive linear correlation between c-IMT and PSR was observed ($R= 0.35$; $p < 0.001$, Fig 1).

Conclusions

This study outlines an association of periodontal and peri-implant mucosal inflammation with subclinical atherosclerosis, evaluated using c-IMT as a surrogate vascular imaging outcome. 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.

An association between peri-implant dental 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[35]. On

the contrary, the evidence linking periodontitis and hypertension is consistently growing: based on the results of a recent systematic review and meta-analysis and large case-control study participants with moderate and severe periodontitis showed increased (20-50%) odds of hypertension[36,37]. The same relationship has been confirmed in randomized clinical trials (RCTs), demonstrating a possible reduction of SBP and DBP values after successful periodontal therapy. Nevertheless, larger and well-designed intervention studies are needed to understand the potential benefit of periodontal and peri-implant inflammation control as novel non-pharmacological intervention to lower blood pressure values and produce systemic health benefits.

In contrast there are several drug interventions that impact on c-IMT progression, such as blood pressure- and lipids- lowering medications. Firstly, statin treatment alters significantly the progression of IMT over a 10-year period when comparing 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 on our results and interpretation 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 form cross-sectional studies[43] confirming that in patients with periodontitis a direct relationship between deeper PPD (gum pockets) and c-IMT values was found.

Different systematic reviews of observational studies[26,44] 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 studies included 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 in managing periodontal inflammation with an improvement on c-IMT values (reviewed by Orlandi and co-workers)[25]. A recent large-scale meta-analysis of RCTs involving data from more than 100,000 patients, reported that reducing cIMT 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[23]. Increased levels of systemic inflammatory mediators (CRP, IL-1, IL-6, TNF-α) can affect directly 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, leukocytes migration and platelet aggregation (reviewed in Herrera et al.)[23]. Upregulation of thrombotic and haemostatic factors have been linked to periodontitis whilst limited evidence exist for peri-implant diseases[23].

Alternatively, peri-implant diseases and periodontitis induce extraoral bacterial dissemination (*Porphyromonas gingivalis, Prevotella Intermedia, Fusobacterium nucleatum, Treponema Denticola*) in atheromas (reviewed in Sanz and co-workers)[27]. Periodontal pathogens can induce vascular damage and endothelial disfunction: gingipain proteases of *Porphyromonas gingivalis* compromise the integrity of the endothelial junction and elevate its permeability and, interestingly, is 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 (*Porphyromonas gingivalis, Prevotella Intermedia, Fusobacterium nucleatum, Treponema Denticola*) but also *S. 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.

Some limitations should be acknowledged in this study. The nature of a cross-sectional design and the small sample size included in this study precluded drawing any cause-effect inferences between exposure (periodontal and peri-implant diseases) and outcome (increased subclinical atherosclerosis). 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[32] and hypertension[1], evaluation of blood pressure levels using a 24-hours ABPM device and inclusion of CVD risk factors strengthen our findings. Moreover, the results of this study should be clearly interpreted as hypothesis generating on the possible role of peri-implant and periodontal diseases on the onset and progression of subclinical atherosclerosis (Fig. 2).
Future efforts should include larger samples, 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 diseases 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.

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Tables

Table 1. Baseline characteristics of participants according to periodontal and peri-implant status (n = 151). 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. A p value <0.05 was considered as statistically significant.

Variables (*mean ± SD) (n; %)*	**No Periodontitis N=58**	**Periodontitis N=93**	**Healthy implant N=23**	**Mucositis N=86**	**Peri-implantitis N=42**
Age, years	64.37 ± 10.35	68.78 ± 9.59	64.00 ± 10.48	68.56 ± 9.50	65.89 ± 10.72
Gender, Males	26 (44.8%)	36 (38.7%)	15 (65.2%)	30 (34.9%)	17 (40.5%)
Smoking, current	10 (17.2.0%)	40 (43.0%)	6 (26.1%)	28 (32.6%)	16 (33.1%)
Presence of plaque	20(34.5%)	66(71.0%)	10(43.5%)	54(62.8%)	22(52.4%)
C_IMT, mm	0.84 ± 0.15	0.97 ± 0.10	0.83 ± 0.18	0.94 ± 0.12	0.93 ± 0.12
CRP, mg/l	1.92 ± 1.51	2.87 ± 1.40	1.95 ± 1.35	2.65 ± 1.55	2.54 ± 1.45
BMI, kg/m^2	26.68 ± 3.69	25.98 ± 3.24	27.67 ± 3.61	25.99 ± 3.54	25.91 ± 2.87
Waist Circumference, cm	98.35 ± 12.43	97.66 ± 9.67	102.35 ± 12.96	96.28 ± 9.39	98.74 ± 11.51
Glucose, mg/dL	97.65 ± 21.34	89.98 ± 12.29	92.26 ± 9.80	96.43 ± 19.70	85.74± 9.18
Total Cholesterol, mg/dL	200.35 ± 35.46	188.69 ± 43.01	207.65 ± 38.01	192.43 ± 42.82	185.82 ± 35.55
Triglycerides, mg/dL	145.82 ± 70.89	121.50 ± 66.55	117.91 ± 38.16	127.19 ± 63.91	146.11 ± 89.88
HDL, mg/dL	59.68 ± 18.19	58.77 ± 18.12	61.70 ± 19.44	58.83 ± 17.86	59.24 ± 18.19
LDL, mg/dL	116.65 ± 33.76	102.86 ± 32.87	121.17 ± 31.97	109.04 ± 33.95	98.21 ± 32.22
Creatinine, mg/dL	0.90 ± 0.29	0.95 ± 0.24	0.88 ± 0.20	0.94 ± 0.31	0.93 ± 0.16
Uric Acid, mg/dL	5.62 ± 1.33	5.79 ± 1.43	5.27 ± 1.05	5.65 ± 1.24	6.16 ± 1.73
Microalbuminuria spot, mg/dL	14.98 ± 36.32	15.25 ± 35.18	2.73 ± 4.24	23.66 ± 44.04	4.52 ± 15.02
24 h Microalbuminuria, mg/dL	20.58 ± 46.42	19.62 ± 45.04	3.61 ± 3.07	30.84 ± 55.91	6.77 ± 22.11
24 h Heart rate, bpm	72.19 ± 7.73	70.89 ± 6.60	70.65 ± 7.31	70.86 ± 6.81	72.92 ± 7.36
24 h SBP, mmHg	128.76 ± 12.53	126.49 ± 10.57	126.22 ± 12.12	128.01 ± 12.02	129.13 ± 11.98
24 h DBP, mmHg	77.29 ± 9.61	73.51 ± 7.84	78.17 ± 8.61	72.63 ± 7.84	77.95 ± 9.24
Cumulative PSR	9.39 ± 2.70	16.52 ± 3.06	10.30 ± 3.91	14.30 ± 4.37	14.89 ± 4.34

Table 2. Binomial logistic regression models presented as Odds ratios (OR) and 95% confidence intervals (CI) of IMT>0.9 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 (2.68-16.76)*****	**8.97 (3.81-21.14)** ***	**3.43 (1.47-8.04) ****
Mucositis	**3.34 (1.13-9.85)***	**3.05 (1.08-8.64)** *	1.24 (0.41-3.75)
Peri-implantitis	1.85 (0.58-5.95)	2.90 (0.94-8.96)	0.79 (0.24-2.63)

Model 1: IMT > 0.90mm or IMT ≤ 0.90mm with the presence of carotid atherosclerotic plaque OR IMT ≤ 0.90mm and absence of atherosclerotic plaques; **Model 2:** IMT > 0.90mm OR IMT ≤ 0.90mm; **Model 3:** presence of carotid atherosclerotic plaque OR absence of carotid atherosclerotic plaque. All models included adjustment for age, gender, smoking, 24 h Systolic blood pressure and BMI. The reference category for Mucositis and Peri-implantitis is: Healthy implants
Statistically significant: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 3. Multiple backward stepwise linear regression models (with p = 0.10 to enter and p = 0.05 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	0.114	0.036-0.157	<0.001
Peri-implant diseases	0.035	0.004-0.066	0.028

Model: reduced model that best explains the data.

Figures

Figure 1. Scatter plot of c-IMT (mm) values by cumulative PSR using Spearman's rank-order testing

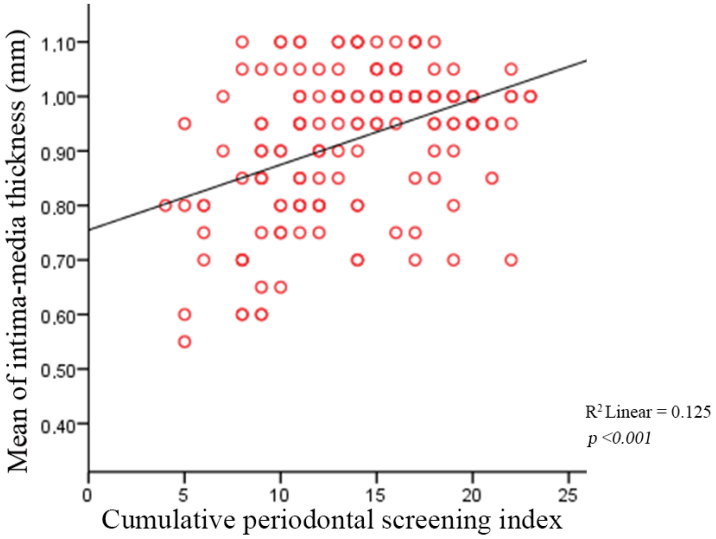

Figure 2. Mechanisms linking periodontal/peri-implant inflammation and subclinical atherosclerosis (created with BioRender.com). Periodontal and peri-implant inflammation caused by periodontal bacteria induce an acute-phase inflammatory response, with increased levels of systemic inflammatory mediators (CRP, IL-1, IL-6, TNF-α), the hyperactivation of T and B lymphocytes and the increase in oxidative stress, leukocytes migration and platelet aggregation. Furthermore, peri-implant diseases and periodontitis can induce extraoral bacterial dissemination (Porphyromonas gingivalis, Prevotella Intermedia, Fusobacterium nucleatum, Treponema Denticola) and cause atheromas and endothelial dysfunction.