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Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study

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ABSTRACT

Purpose: The aim of this study was to compare the inflammatory and lipid profile of patients with and without peri-implantitis.
Methods: A cross-sectional biochemical study was carried out in which blood samples were collected from 16 patients with peri-implantitis and from 31 subjects with healthy implants. Clinical peri-implant parameters were obtained from all subjects. Levels of tumor necrosis factor-alpha and interleukin-10 (IL-10) were measured in serum. Lipid fractions, glucose and creatinine levels, and complete blood count were also assessed.
Results: After controlling for a history of periodontitis, statistically significant differences between peri-implantitis patients and controls were found for total cholesterol (estimated adjusted mean difference, 76.4 mg/dL; 95% confidence interval [CI], 39.6, 113.2 mg/dL; $P<0.001$), low-density lipoprotein (LDL) cholesterol (estimated adjusted mean difference, 57.7 mg/dL; 95% CI, 23.8, 91.6 mg/dL; $P<0.001$), white blood cells (WBC) (estimated adjusted mean difference, $2.8×10^3$/μL; 95% CI, 1.6, $4.0×10^3$/μL; $P<0.001$) and IL-10 (estimated adjusted mean difference, −10.4 pg/mL; 95% CI, −15.8, −5.0 pg/mL; $P<0.001$). The peri-implant probing pocket depth (PPD) was modestly positively correlated with total cholesterol (r=0.512; $P<0.001$), LDL cholesterol (r=0.463; $P=0.001$), and WBC (r=0.519; $P<0.001$). A moderate negative correlation was observed between IL-10 and PPD (r=0.609; $P<0.001$).
Conclusions: Otherwise healthy individuals with peri-implantitis showed increased low-grade systemic inflammation and dyslipidemia.

Keywords: Cardiovascular diseases; Dyslipidemias; Inflammation; Leukocytes; Peri-implantitis

INTRODUCTION

Peri-implantitis is a common immune-mediated inflammatory condition of bacterial origin, which is characterized by peri-implant soft tissue inflammation and bone loss around implants [1]. Recent epidemiological studies reported a high prevalence of this disease

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

worldwide, affecting between 24% and 45% of individuals with implants [2-5]. When compared to periodontitis, peri-implant lesions might be considered as "more invasive," as an increased immune response and osteoclastogenesis are present; furthermore, as a result of the lack of epithelial lining between the peri-implant lesion and the apical portion of the peri-implant pocket, infection can reach the alveolar bone [6].

Recent animal studies have shown elevation of peripheral levels of pro-inflammatory biomarkers (e.g., total protein, albumin, and white blood cells [WBC]) after ligature-induced experimental peri-implantitis [7,8]. It is worth mentioning that the surgical treatment of experimental peri-implantitis by means of open flap debridement led to a reduction of these systemic inflammatory parameters, which reached similar values to baseline [7,8]. It could be hypothesized that similarly to periodontitis, the inflamed and ulcerated peri-implant pocket epithelium allows the entrance of locally produced inflammatory mediators (e.g., leukocytes and cytokines) into the bloodstream, evoking a systemic immune and acute inflammatory response that subsequently could interact with lipid metabolism, thereby elevating blood levels of total cholesterol and low-density lipoprotein (LDL) cholesterol, which in turn may increase the risk of atherosclerotic disease. This is supported by previous experimental studies where long-term oral infection with lipopolysaccharide from *Porphyromonas gingivalis* in B6 Apoehl mice was associated with elevated very-low LDL, LDL, and total cholesterol levels, as well as reduced high-density lipoprotein levels due to an increase in liver-produced pro-inflammatory mediators, such as interleukin-6 (IL-6) [9]. There is also evidence that infection and inflammation may contribute to a pro-atherogenic lipid profile by overproduction of oxidized LDL [10]. Based on this, patients with peri-implantitis could present a similar systemic state to that seen in periodontitis patients. To our knowledge, there is a lack of clinical studies evaluating whether patients diagnosed with peri-implantitis have an exacerbated systemic pro-inflammatory state with dyslipidemia.

The aim of the present investigation was 2-fold: firstly, to investigate the relationship between peri-implantitis and systemic inflammation; and secondly, to analyze whether this systemic inflammatory state in peri-implantitis is associated with dyslipidemia.

MATERIALS AND METHODS

A cross-sectional biochemical study was carried out following the STROBE guidelines [11]. The research was performed in accordance with the Declaration of Helsinki of the World Medical Association (2008) and was approved by the Ethics Committee of the Servizo Galego de Saúde and Xunta de Galicia (2016/399 and 2017/508). Written informed consent was obtained from each patient after a full explanation of the oral examination and blood sample collection.

Study population

Otherwise healthy individuals diagnosed with peri-implantitis were identified among the population referred for dental care to the School of Dentistry at the University of Santiago de Compostela between January 2018 and January 2019. Subjects with peri-implant health who were also in apparent good general health were identified from the University Clinical Hospital of Santiago de Compostela between October 2016 and April 2017.

Peri-implantitis group

Peri-implantitis subjects were defined based on the 2018 Consensus Classification of Periodontal Diseases (presence of bleeding on probing [BoP] and/or suppuration, probing pocket depth [PPD] ≥6 mm and/or ≥3 mm of radiographic bone loss) [12]. The inclusion criteria were as follows: (I) ≥18 years of age; (II) presence of at least 1 implant diagnosed with peri-implantitis; (III) absence of implant mobility; (IV) absence of systemic pathology; (V) not taking any local and/or systemic host modulators such as anti-inflammatory drugs, lipid-lowering medications, immunosuppressants, or antibiotics in the last 6 months; and (VI) no active clinical signs of periodontitis.

Individuals diagnosed with peri-implantitis were identified among the population referred for dental care to the School of Dentistry at the University of Santiago de Compostela between January 2018 and January 2019. From the 22 subjects initially screened, 6 were excluded because they had systemic diseases (cardiovascular diseases, n=4; diabetes, n=1; rheumatoid arthritis, n=1). Hence, the case group consisted of 16 patients with peri-implantitis.

Peri-implant health group

Subjects with healthy implants were classified as controls according to the 2018 Consensus Classification of Periodontal Diseases (absence of erythema, BoP and/or suppuration, increased PPD, and bone loss) [12]. The inclusion criteria were as follows: (I) ≥18 years of age; (II) presence of healthy implants; (III) absence of systemic pathology; (IV) not taking any local and/or systemic host modulators such as anti-inflammatory drugs, lipid-lowering medications, immunosuppressants, or antibiotics in the last 6 months; and (V) no active clinical signs of periodontitis.

Control individuals were identified from the University Clinical Hospital of Santiago de Compostela between October 2016 and April 2017. From the 48 participants initially screened, 17 were excluded due to the presence of systemic diseases (diabetes, n=5; cardiovascular diseases, n=4), antibiotic use (n=1), diagnosis of peri-implantitis (n=2) or peri-implant-mucositis (n=4), or refusal to give a blood sample (n=1). The final sample of the control group consisted of 31 individuals.

Clinical and radiographic examination

Clinical peri-implant examinations were performed in all participants by previously trained and calibrated periodontists (examiners #1 and #2). Briefly, the calibration was completed before the start of the study at the Periodontology Unit, Faculty of Odontology (University of Santiago de Compostela) using 10 non-study patients suffering from peri-implantitis. Intra-examiner reliability and inter-examiner reliability were assessed using the intraclass correlation coefficient (ICC) for PPD of peri-implant pockets. The intra-examiner ICC values were 0.88 and 0.85 for examiners #1 and #2, respectively. The inter-examiner values were 0.84. Thus, the reliability of the measurements was satisfactory.

PPD (in mm) and BoP (% of sites that bleed upon probing) were measured in all implants present in the mouth. Measurements were recorded at 6 sites per implant (mesiobuccal, distobuccal, midbuccal, mesiolingual, distolingual, and midlingual) using a calibrated University of North Carolina periodontal probe (UNC 15; Hu-Friedy, Chicago, IL, USA). The number of implants in each group was also recorded.

An intraoral radiograph was obtained from each implant to evaluate crestal bone level (in mm). The X-ray was taken following the long cone parallelism technique with the help of positioning splints manufactured for this purpose individually for each patient. Digital periapical radiographs were taken and viewed on a calibrated computer screen using a software program (Digora™, KaVo Dental, Biberach an der Riss, Germany). Marginal bone loss was defined as the distance from the widest supracrestal part of the implant to the alveolar crest.

History of periodontitis and smoking status

For both peri-implantitis patients and controls, history of periodontitis and tobacco consumption was recorded. We considered participants as having a previous history of periodontitis if they had received periodontal treatment at least once in their lives and if, at the time their peri-implant status was examined and blood samples were collected, no clinical signs of periodontitis were detected (absence of periodontal sites with PPD ≥4 mm with or without BoP and full-mouth BoP <10%). Current smokers were defined as those who smoked >10 cigarettes/day.

Serum samples collection and laboratory tests

Blood samples were obtained in the morning after the peri-implant examination was done. Briefly, 2 mL of venous blood was collected from the antecubital fossa by venipuncture using a 20-gauge needle with a 2-mL syringe. Blood samples were allowed to clot at room temperature and, after 1 hour, serum was separated from blood by centrifugation (15 minutes at 3000×g) and 0.5 mL of extracted serum was immediately transferred to 1.5-mL aliquots. Each aliquot was stored at −80°C until required for analysis. Serum levels of tumor necrosis factor-alpha (TNF-α) were determined using an immunodiagnostic IMMULITE® 1000 System (Siemens Healthcare Diagnostics, Munich, Germany). Serum levels of IL-10 were quantified using the enzyme-linked immunosorbent assay technique following manufacturer instructions (BioLegend, San Diego, CA, USA). Lipid fractions, glucose, and creatinine (all measured in serum), as well as the complete blood count, were determined by routine biochemical methods.

All determinations were performed in independent laboratories blinded to clinical data.

Statistical analysis

No formal sample size calculation was performed since this was a pilot study and there are no data in the literature regarding this topic. However, a *post hoc* power analysis based on the results obtained from the present study and using our primary outcome (i.e., WBC concentrations) confirmed a 90% power to detect a $2.0×10^3/\mu L$ difference in WBC between study groups, with a standard deviation (SD) of $0.4×10^3/\mu L$ (Macro !NSize for PASW Statistics, http://www.metodo.uab.cat/macros.htm).

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used to carry out all statistical analyses. To identify variables that followed a normal distribution, the Kolmogorov-Smirnov test was applied. Mean values ± SD and median (P_{25}, P_{75}) were calculated for normally and non-normally distributed continuous variables, respectively. The statistical tests used to compare continuous data were the independent *t*-test or the Mann-Whitney *U* test. Categorical variables were reported as percentages and compared using the χ^2 test. General linear models for analysis of covariance were created to compare mean values of significant biomarkers between cases and controls adjusted for potential confounders (covariates).

A mixed model analysis was used to account for the different number of implants in each patient (the different implants were considered as repeated measures), and the dependent variable was each biomarker. In addition, non-parametric correlation analysis between peri-implant clinical parameters and circulating biomarkers was performed using the Spearman rank correlation coefficient. All tests were performed at a significance level of α=0.05.

RESULTS

The peri-implantitis patients and controls were similar in terms of age and sex (P=0.995 and P=0.917, respectively). Although a higher percentage of current smokers were detected in the case group than in the control group, this difference was not statistically significant (P=0.472). Nevertheless, more than 3-quarters of the cases (13 of 16) presented a previous history of periodontitis in comparison to none of controls (0/31) (P<0.001). As expected, the values of clinical peri-implant parameters such as PPD and BoP were significantly higher in peri-implantitis patients (both P<0.001) (Table 1). These results did not differ when linear mixed analysis was performed, accounting for the number of implants per patient (Table 1). The total number of implants was 20 and 36 in the case and control groups, respectively. The mean number of implants per patient was similar between groups (1.2±0.7 vs. 1.1±0.4, P=0.985).

Raw (unadjusted) data for lipid fractions, metabolic parameters, complete blood count, and inflammatory biomarkers are displayed in Table 2. Patients with peri-implantitis exhibited higher circulating levels of cholesterol (P<0.001), LDL cholesterol (P=0.001), WBC (P<0.001), monocytes (P<0.001), and TNF-α (P=0.033) than healthy controls. In contrast, serum levels of IL-10 were lower in subjects with peri-implantitis than in controls (P<0.001). These results did not differ when linear mixed analysis was performed, accounting for the number of implants per patient (Table 2). Only the neutrophil concentration showed a statistically significant difference between groups (P=0.034).

After adjustment for a history of periodontitis, statistically significant differences between the peri-implantitis patients and controls remained for total cholesterol (estimated adjusted mean difference, 76.4 mg/dL; 95% confidence interval [CI], 39.6, 113.2 mg/dL; P<0.001), LDL cholesterol (estimated adjusted mean difference, 57.7 mg/dL; 95% CI, 23.8, 91.6; P<0.001), WBC (estimated adjusted mean difference, $2.8\times10^3/\mu L$; 95% CI, 1.6, $4.0\times10^3/\mu L$; P<0.001) and IL-10 (estimated adjusted mean difference, −10.4 pg/mL; 95% CI, −15.8, −5.0 pg/mL; P<0.001), but not for TNF-α (estimated adjusted mean difference, 7.6 pg/mL; 95% CI, −60.2, 75.5 pg/mL, P=0.821) and monocytes (estimated adjusted mean difference, $0.2\times10^3/\mu L$; 95% CI, −0.2, $0.6\times10^3/\mu L$; P=0.252).

Table 1. Study sample characteristics (n=47)

Parameter	Peri-implantitis (n=16)	Controls (n=31)	P value[a]	P value[b]
Age (yr)	57.4±10.0	57.4±9.1	0.995	-
Males	8 (50.0)	15 (48.4)	0.917	-
Current smokers	5 (31.2)	6 (19.4)	0.472	-
Previous history of periodontitis	13 (81.2)	0 (0.0)	**<0.001**	-
PPD (mm)	6.0±1.7	3.9±0.2	**<0.001**	**<0.001**
BoP (%)	89.9±21.0	0.0±0.0	**<0.001**	**<0.001**

Values are presented as mean±standard deviation or number (%). Significant results are reported in bold.
PPD: probing pocket depth, BoP: bleeding on probing.
[a]P values for univariate analysis; [b]P values for linear mixed model analysis.

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Table 2. Biochemical characteristics (n=47)

Parameter	Peri-implantitis (n=16)	Controls (n=31)	P value[a]	P value[b]
Total cholesterol (mg/dL)	212.0 (175.0, 231.0)	156.0 (143.0, 172.0)	**<0.001**	**<0.001**
Triglycerides (mg/dL)	80.0 (61.0, 127.0)	66.0 (44.0, 111.0)	0.205	0.119
HDL cholesterol (mg/dL)	61.0 (55.0, 90.0)	55.0 (44.0, 73.0)	0.138	0.112
LDL cholesterol (mg/dL)	120.0 (101.0, 134.0)	91.0 (80.0, 101.0)	**0.001**	**<0.001**
Total/HDL cholesterol ratio	3.0 (2.4, 3.7)	2.8 (2.1, 3.4)	0.111	0.077
LDL/HDL cholesterol ratio	2.0±1.0	1.6±0.4	0.154	0.063
Creatinine (mg/dL)	0.6 (0.5, 0.7)	0.7 (0.6, 0.9)	0.320	0.435
Glucose (mg/dL)	83.0 (73.0, 90.0)	81.0 (73.0, 88.0)	0.669	0.420
RBC (10^6/µL)	4.5 (4.2, 4.9)	4.6 (4.2, 5.0)	0.543	0.599
Platelets (10^3/µL)	231.2±57.6	222.7±52.3	0.612	0.605
WBC (10^3/µL)	5.8 (4.3, 6.6)	3.7 (3.3, 3.9)	**<0.001**	**<0.001**
Lymphocytes (10^3/µL)	1.9±0.7	1.7±0.6	0.474	0.465
Monocytes (10^3/µL)	0.4 (0.3, 0.5)	0.3 (0.2, 0.3)	**<0.001**	**0.001**
Neutrophils (10^3/µL)	3.0±1.2	2.4±0.7	0.085	**0.034**
Eosinophils (10^3/µL)	0.08 (0.05, 0.21)	0.15 (0.07, 0.21)	0.290	0.289
Basophils (10^3/µL)	0.04 (0.01, 0.05)	0.04 (0.02, 0.05)	0.821	0.276
TNF-α (pg/mL) (n=46)	93.2 (56.7, 166.0)	65.6 (44.9, 85.7)	**0.033**	**0.003**
IL-10 (pg/mL)	1.9 (1.9, 2.0)	13.7 (9.5, 15.8)	**<0.001**	**<0.001**

Values are presented as number (range) or mean±standard deviation. Significant results are reported in bold.
HDL: high-density lipoprotein, LDL: low-density lipoprotein, RBC: red blood cells, WBC: white blood cells, TNF-α: tumor necrosis factor alpha, IL-10: interleukin-10.
[a]P values for univariate analysis; [b]P values for linear mixed model analysis.

While modest positive correlations were found between PPD and total cholesterol (r=0.512; P<0.001) (Figure 1A), LDL cholesterol (r=0.463; P=0.001) (Figure 1B) and WBC (r=0.519; P<0.001) (Figure 1D), a moderate negative correlation was found between IL-10 and PPD (r=0.609; P<0.001) (Figure 1C) in all participants. Similar, but slightly higher, estimates were observed for BoP and total cholesterol (r=0.602; P<0.001), LDL cholesterol (r=0.483; P=0.001), WBC (r=0.630; P<0.001), and IL-10 (r=−0.758; P<0.001).

DISCUSSION

To the best of our knowledge, this is the first study assessing the inflammatory profile of patients with peri-implantitis. The findings of this pilot study showed an enhanced systemic inflammatory state characterized by elevated levels of WBC as well as the presence of dyslipidemia in patients with peri-implantitis compared to individuals with healthy implants. We found moderate linear correlations of the depth of the peri-implant pockets and peri-implant bleeding with markers of inflammation (WBC and IL-10) and blood lipids (total cholesterol and LDL cholesterol).

In peri-implantitis, the presence of subgingival pathogens elicits a local inflammatory response, which is characterized by larger proportions of polymorphonuclear leukocytes and macrophages. Furthermore, this inflammatory response is amplified due to the production of pro-inflammatory cytokines and prostaglandins. The release of these substances into the bloodstream stimulates further recruitment of pro-inflammatory mediators and leukocytes at the local site. It should be highlighted that it has been demonstrated that this local inflammatory response is more pronounced in peri-implant tissues than in periodontal tissues [6]. The ulcerated gingival epithelium of severely periodontally affected patients allows these locally produced inflammatory mediators to enter the bloodstream and induce an acute-phase reaction in the liver, thereby contributing to the overall systemic inflammatory burden [13]. If we take into account the pathophysiological similarities of
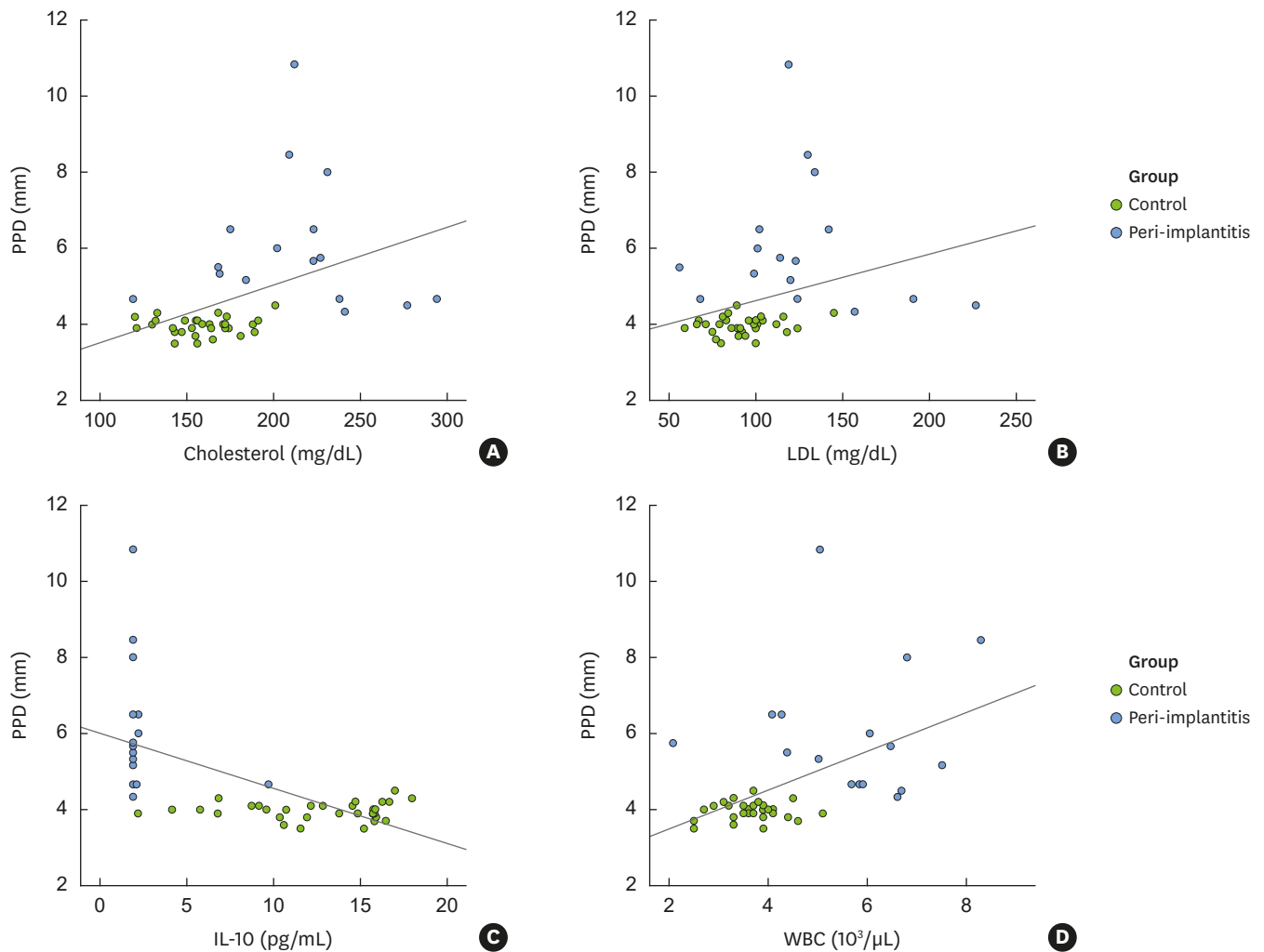
Figure 1. Scatter plots showing correlations between PPD (mm) and: (A) total cholesterol (mg/dL); (B) LDL cholesterol (mg/dL); (C) IL-10 (pg/mL); (D) WBC (10^3/µL). PPD: probing pocket depth, LDL: low-density lipoprotein, IL-10: interleukin-10, WBC: white blood cells.

both diseases, a persistent peri-implant inflammatory state might also have an impact on systemic inflammation. In the present study, patients with peri-implantitis had an increase in leukocytes (WBC), reflecting a possible chronic systemic inflammatory stimulus, which might have been caused by the persistent peri-implant disease, as has been shown recently in periodontitis [14]. A linear correlation was also found between clinical peri-implant inflammatory parameters and WBC levels. Along similar lines, recent animal studies have shown an increased systemic inflammatory response after ligature-induced experimental peri-implantitis that was characterized by high levels of total protein, albumin, and WBC, which reverted to baseline after surgical peri-implant treatment [7,8]. The systemic inflammatory state of peri-implantitis patients was confirmed by lower circulating levels of IL-10, a cytokine with important anti-inflammatory properties [15]. It has been suggested that decreased levels of IL-10 may favor a more inflammatory milieu since IL-10 has potent deactivating properties in macrophages and T-cells, and thus can act as a downregulator of cell-mediated immune responses, such as those potentially seen in peri-implantitis [15].

Another relevant finding from this study is that the peri-implantitis patients exhibited dyslipidemia, as characterized by higher blood LDL cholesterol levels. This observation confirms previous results reporting higher LDL cholesterol and total cholesterol levels among periodontitis patients when compared to healthy controls [16-18]. A relationship between infections and lipid metabolism has been widely documented in the past decades. Chronic infectious diseases are now thought to have an impact on lipid plasma levels [19-21]. This dyslipidemia is thought to be part of a host response aimed at decreasing the toxicity of harmful microbiological agents [22]. The present investigation found an association between peri-implantitis and abnormal lipid levels, which may be mediated by the constant activation of the inflammatory process determined by the presence of periodontal pathogens in peri-implant pockets.

Based on the present results, one might speculate that peri-implantitis could be associated with atherosclerotic disease. The acute-phase response during peri-implant infection/inflammation protects the host from further infection. Changes in acute-phase proteins (e.g., C-reactive protein [CRP]) neutralize invading microorganisms such as periodontal bacteria, minimize the extent of tissue damage, participate in the local immune response and tissue regeneration, and replenish proteins used in the inflammatory process [22,23]. These changes, if present for a prolonged period of time, can lead to detrimental consequences to the host, such as the development of low-grade chronic systemic inflammation. In this sense, changes in acute-phase reactant synthesis are mediated by cytokines produced in response to a variety of stimuli in multiple cell types, including macrophages, monocytes, lymphocytes, and endothelial cells [24,25]. Cytokines responsible for the coordination of both immune and inflammatory responses such as ILs or TNF-α might induce alterations in lipid and lipoprotein metabolism that contribute to atherogenesis [22]. Due to the high prevalence of peri-implantitis and atherosclerotic vascular diseases such as coronary heart disease and stroke, future epidemiological studies should investigate whether individuals with peri-implantitis are at a high risk of having cardiovascular events.

Some shortcomings need to be acknowledged in relation to our investigation. Firstly, this was a pilot study and, therefore, the results are preliminary and hypothesis-generating. However, *post hoc* power calculation was performed, showing that our study had a power of 90% to detect clinically meaningful differences between peri-implantitis patients and controls in terms of WBC concentrations. Secondly, due to the cross-sectional nature of the study, causality cannot be demonstrated; hence, we cannot rule out the possibility that other factors could also be involved in the upregulation of peripheral inflammatory mediators and dyslipidemia seen in peri-implantitis patients. Although all participants were in apparent good general health, some of them could have suffered from undiagnosed medical conditions such as pre-hypertension, pre-diabetes, or obesity. In this sense, a recent study demonstrated that an extremely high body mass index ($\geq$40 kg/m^2) was associated with worse peri-implant conditions, increased systemic pro-inflammatory state and dyslipidemia [26]. In the present investigation, an important factor that might have influenced the results was the previous history of periodontitis, as most of the peri-implant cases presented with successfully treated periodontal disease. Even after adjustment for this confounding factor, significance remained for levels of WBC, IL-10, cholesterol, and LDL. In addition, when the clinical peri-implant assessment was done and blood samples were collected, none of the patients had active signs of periodontitis, which therefore might not have had a strong impact at a systemic level. Another limitation is that commonly used serum biomarkers reflecting systemic pro-inflammatory processes such as CRP or IL-6 were not measured in

this study. Nevertheless, WBC has been widely used in the literature as a surrogate marker of systemic inflammation [27]. We also included a well-known cytokine with anti-inflammatory action (IL-10) [15]. Our results showed not only that concentrations of WBC were elevated in peri-implantitis patients, but also that IL-10 serum levels were reduced when compared to subjects with healthy implants, thus supporting our initial hypothesis.

It can be concluded that otherwise healthy patients diagnosed with peri-implantitis presented with a low-grade inflammatory state (increased circulating levels of WBC) accompanied by dyslipidemia (increased blood levels of cholesterol and LDL). Further studies are warranted to confirm our preliminary results using large population-based cohorts. Experimental studies are also needed to investigate the potential biological mechanisms behind this link. Lastly, carrying out intervention studies will be of paramount interest to test whether non-surgical and surgical peri-implant therapy could have a beneficial systemic effect in terms of reducing the overall inflammatory burden in patients affected by peri-implantitis.

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