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ORIGINAL ARTICLE

The systemic impact of non-surgical treatment of peri-implantitis with or without adjunctive systemic metronidazole: Secondary analysis of a randomized clinical trial

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Abstract

Objectives: The aim of this study was to evaluate the systemic effect of non-surgical peri-implantitis treatment (NSPIT) with or without the administration of systemic metronidazole.

Methods: In this secondary analysis from a previously published clinical trial (NCT03564301), peri-implantitis patients were randomized into two groups: test, receiving NSPIT plus 500 mg of oral systemic metronidazole three times a day for 7 days ($n = 10$); and control group, receiving NSPIT plus placebo ($n = 11$). Serum samples were obtained at baseline, 3 and 6 months after therapy to determine levels of inflammatory biomarkers, lipid fractions and complete blood counts.

Results: Both treatment modalities produced improvements in clinical and radiographic parameters. After 6 months from NSPIT, a substantial reduction in C-reactive protein (6.9 mg/dL; 95% CI: 3.7 to 9.9, $p < .001$) and low-density lipoprotein cholesterol (21.8 mg/dL; 95% CI: −6.9 to 50.5, $p = .013$) as well as a modest increase in neutrophils counts (0.4×10^3/μL; 95% CI: −0.4 to 1.1, $p = .010$) was observed in the control group while the test group showed a significant reduction of TNF-α (110.1; 95% CI: 38.9 to 181.4, $p = .004$).

Conclusions: NSPIT showed a short-term beneficial systemic effect regardless of adjunctive use of systemic metronidazole.

KEYWORDS
antibiotic, cardiovascular disease, C-reactive protein, inflammation, peri-implantitis, treatment

1 | INTRODUCTION

Peri-implantitis is a chronic inflammatory infectious disease which affects the surrounding tissues of dental implants. It is estimated that at least one-quarter of people with implants will develop peri-implantitis at some point of their lives, what makes this oral condition highly prevalent in the adult population worldwide (Derks et al., 2016; Kordbacheh Changi et al., 2019; Matarazzo et al., 2018; Rodrigo et al., 2018). During

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the last decade, several systematic reviews have shown that a wide range of pro-inflammatory mediators [i.e., interleukin 1 beta (IL-1β), IL-6 or tumor necrosis factor alpha (TNF-α) among others] can be detected in peri-implant crevicular fluids of patients with peri-implantitis mainly due to a strong inflammatory host response produced within the peri-implant tissues against bacterial challenge (Candel-Marti et al., 2011; Ghassib et al., 2019; Javed et al., 2011).

Similarly to periodontitis, it is plausible that the aforementioned locally produced inflammatory cytokines could gain access to the bloodstream through the ulcerated peri-implant epithelium leading to an acute-phase response in the liver with increased production of acute phase reactants such as C-reactive protein (CRP). If this acute inflammatory process is not resolved might eventually lead to a low-grade chronic systemic inflammatory state which can often be seen in some of the most prevalent and disabling non-communicable chronic conditions such as atherosclerotic vascular diseases, diabetes, rheumatic diseases, chronic kidney dysfunction or even Alzheimer's disease (Furman et al., 2019). Recently, a case–control study showed that subjects with cardiovascular disease (CVD) had a higher prevalence of moderate-to-severe peri-implantitis than those without infected dental implants (≈50% vs. ≈30%) (Wang, Ou, et al., 2021).

Moreover, recent clinical and experimental evidence have demonstrated a potential link between peri-implantitis and systemic inflammation (Blanco et al., 2021; Chaushu et al., 2020, 2021; Ustaoglu & Erdal, 2020; Wang, Sugai, et al., 2021). In two cross-sectional studies, patients with peri-implantitis showed higher levels of some markers of systemic inflammation such as TNF-α and leucocytes when compared to subjects with healthy implants (Blanco et al., 2021; Chaushu et al., 2020, 2021; Ustaoglu & Erdal, 2020). In addition, a dyslipidemic state was also observed in peri-implantitis individuals (elevated blood levels of total and low-density lipoprotein cholesterol as well as triglycerides) in these observational reports (Blanco et al., 2021; Ustaoglu & Erdal, 2020; Wang, Sugai, et al., 2021). In CVD patients, peri-implantitis was also associated with elevated levels of pro-inflammatory cytokines (Wang, Sugai, et al., 2021). All these preliminary clinical findings were supported by previous animal studies where circulating concentrations of leukocytes and other inflammatory mediators were increased after experimental peri-implantitis was induced by ligatures placement (Chaushu et al., 2020, 2021). It has to be highlighted that in these experiments, treatment of peri-implant lesions reverted levels of inflammatory markers to normal values (Chaushu et al., 2020, 2021).

Recently, our group published the results of a randomized clinical trial (RCT) suggesting that the use of systemic metronidazole could result in additional improvement of clinical, radiographic and microbiological parameters when used as adjunct to non-surgical treatment in patients with peri-implantitis (Blanco et al., 2022). On the other hand, several reports evaluated the potential systemic adjunctive benefit of administration of systemic antibiotics in the non-surgical periodontal therapy with conflicting results (Cosgarea et al., 2020; Giannopoulou et al., 2016; López et al., 2012). However, to our knowledge, no human intervention study has tested whether non-surgical peri-implantitis treatment (NSPIT) in conjunction with the use of systemic antibiotics could have a systemic anti-inflammatory effect in subjects diagnosed with peri-implantitis.

Therefore, the primary aim of this secondary analysis was to assess the effect of the use of systemic metronidazole in the NSPIT on serum inflammatory markers (CRP, IL-6, IL-10 and TNF-α) over a period of 6 months when compared to NSPIT alone. Secondly, the study investigated changes in lipid fractions and differential blood counts after NSPIT. Clinical and radiographic outcomes were also evaluated to validate the level of efficacy of NSPIT.

2 | MATERIALS AND METHODS

2.1 | Experimental design and study population

We have analyzed the changes in host-derived systemic biomarkers in the context of a 12-month single-center, parallel-arm, triple-blind, placebo-controlled RCT which evaluated the adjunctive effect of systemic metronidazole administration to non-surgical treatment of peri-implantitis (ClinicalTrials.gov NCT03564301) (Blanco et al., 2022). Recruitment and study flowchart are shown in Figure 1.

The aim was to include at least 20 consecutive patients with peri-implantitis recruited into the aforementioned trial for additional analyses of systemic biomarkers. Follow-up for this purpose was set at 6 months as in the majority of studies published in the field of Periodontal Medicine this is a commonly used time frame to assess changes in systemic biomarkers after non-surgical treatment. Participants were recruited among referral to the Periodontology Unit of the University of Santiago de Compostela (Spain) between January 2018 and July 2019. The trial included patients diagnosed with peri-implantitis presenting with at least one implant with bleeding on probing (BoP) and/or suppuration, probing pocket depth (PPD) ≥6 mm and ≥3 mm of detectable bone loss after initial remodeling (Berglundh et al., 2018; Renvert et al., 2018). Exclusion criteria included: (i) underage, (ii) previous history of allergy to metronidazole, (iii) implant mobility, (iv) pregnant or lactating females, (v) had received any pharmacological therapy within the 3 months before the start of the trial, or (vi) severe systemic illnesses or malignancies.

Ethical approval was obtained from the Research Ethics Committee of Santiago de Compostela/Lugo (2017/508) and the investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki on experimentation involving human beings (Order SCO/256/2007). Informed consent was obtained from all individual participants included in the study. The present study was performed and reported according to the CONSORT guidelines for reporting parallel-group randomized clinical trials.

2.2 | Randomization, allocation concealment and masking

Randomization and masking procedures were published elsewhere (Blanco et al., 2022). In brief, following a baseline visit, each patient

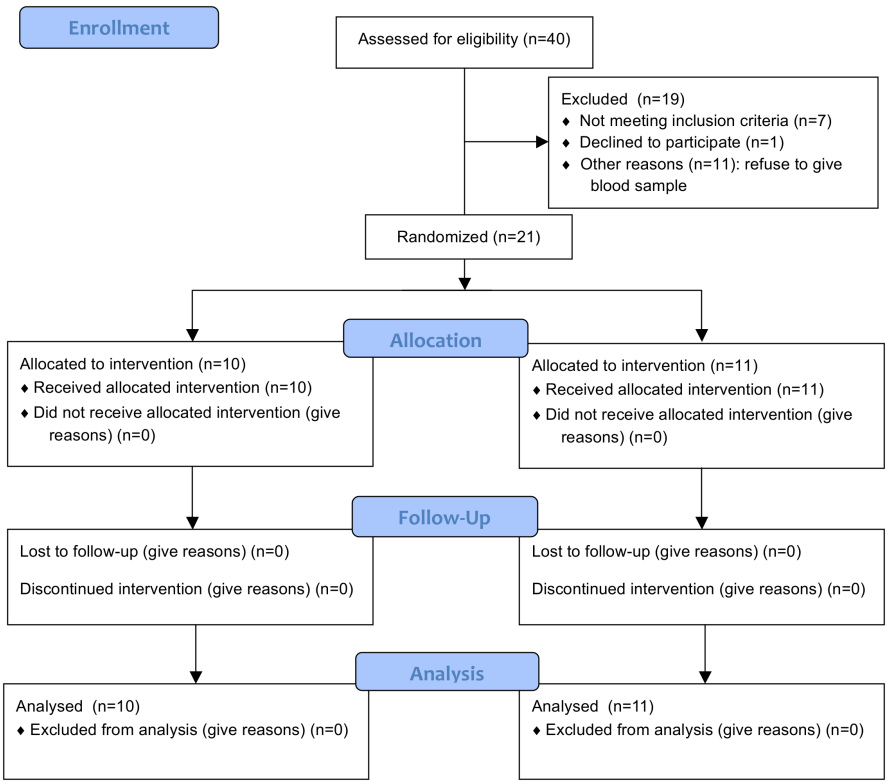

FIGURE 1 Flow chart of the recruitment and study protocol.

recruited into the trial was randomly allocated (using a computer-generated table) to receive either NSPIT + metronidazole ($n = 10$) or NSPIT + placebo ($n = 11$). Restricted randomization was performed (minimization), stratifying for smoking habits and history of periodontitis. Allocation to treatment was concealed in an opaque envelope. The patient, examiner, therapist and statistician were masked to the group allocation.

2.3 | Clinical outcomes

Clinical parameters were assessed using a UNC-15 periodontal probe (Hu-Friedy®, Chicago, IL, USA) by one calibrated examiner (JD) at six sites per implant (Blanco et al., 2022). These parameters were recorded at baseline, 3 and 6 months. In cases where the prosthesis did not allow adequate access to the implant, it was removed for clinical assessment at each appointment. PPD was calculated as the distance from the gingival peri-implant margin to the bottom of the peri-implant pocket (in millimeters). Peri-implant recession was measured as distance from the free gingival margin (more coronal portion of the free gingiva) to the more apical portion of the crown (in millimeters). BoP was assessed dichotomously also in six sites per implant (expressed in %).

2.4 | Radiographic outcomes

Intraoral phosphor plate long-cone parallel technique radiographs were taken with the aid of custom-made holders to evaluate peri-implant marginal radiographic bone levels at baseline, 3 and 6 months. The same custom-made holders for each specific implant were used in all visits. Those radiographs were analyzed using a digital radiographic software (ImageJ 1.47 V Wayne Rasband, National Institutes of Health and Laboratory of Optical and Computational Instrumentation, University of Wisconsin, Wisconsin, USA). All examinations were performed by an independent and calibrated examiner (AP) to the nearest 0.1 mm using IMAGE J software (Blanco et al., 2022). The scale was set and calibrated by the height of the dental implant, which yielded a pixel/mm ratio. The implant shoulder was used as a fixed reference point. To assess linear changes at interproximal alveolar crestal bone height, the distance from the implant shoulder to the most coronal bone to implant contact (RBL) was determined both at the mesial and distal aspect of each implant and expressed in millimeters.

2.5 | Non-surgical peri-implant therapy (NSPIT)

Pre-treatment visits were scheduled to help the study subjects achieve and maintain adequate self-performed plaque control. Supragingival debridement and elimination/reduction of plaque-retentive factors, including modification of existing prosthesis were performed (de Tapia et al., 2019), and oral hygiene instructions were provided. After optimal plaque control was achieved (full-mouth plaque score < 20%), patients received one session of non-surgical debridement as described previously (Blanco et al., 2022) by an experienced periodontist. Prosthesis were removed during treatment, if possible, and relocated at the end of the treatment session. Before starting the instrumentation, the patient rinsed with 0.12% chlorhexidine digluconate (Perio-aid, Dentaid, Spain).

Non-surgical treatment under local anesthesia consisting of supra- and submucosal mechanical debridement using ultrasound with a stainless steel periodontal tip (EMS®, Electro Medical Systems, Nyon, Switzerland) were performed in one treatment session with no time restriction. Ultrasonic debridement was performed with concomitant irrigation of chlorhexidine of 0.12% (Perio-aid, Dentaid, Spain). After that, a stainless steel curette Columbia 4R/4 L (LM Instruments Oy, Pargas, Finland) was used to remove the granulation tissue and minor mucosal curettage. Then, peri-implant pockets were irrigated with 0.12% chlorhexidine digluconate (Perio-aid, Dentaid, Spain). A regimen consisting of oral systemic metronidazole 500 mg for 7 days (three times/day) was prescribed in patients from the test group immediately after the treatment session while place pills were administered in the control group.

Follow-up visits were scheduled at 3 and 6 months after NSPIT. During these appointments, the examiner recorded any changes in medical history and adverse events. Clinical measurements, radiographs, and blood samples were taken at each of those visits. At the end of each appointment, oral hygiene instructions and motivation were provided together with a session of supragingival debridement. Sites with residual peri-implant pockets (sites with PPD ≥ 5 mm) also received submucosal debridement with same ultrasonic device described above.

2.6 | Biochemical analysis

Serial blood samples were collected before and 3 and 6 months after completion of therapy. Briefly, 2 mL of venous blood was collected from the antecubital fossa by venepuncture using a 20-gauge needle with a 2 mL syringe. Blood samples were allowed to clot at room temperature and, after 1 h, serum was separated from blood by centrifugation (15 min 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 CRP concentrations were measured with a latex immunoassay namely MULTIGENT CRP Vario assay using the ARCHITECT *c*Systems (Abbott Laboratories, IL, USA). Serum levels of TNF-α were determined using an immunodiagnostic IMMULITE® 1000 Systems (Siemens Healthcare Diagnostics, Munich, Germany). Serum levels of IL-6 and IL-10 were quantified with enzyme-linked immunosorbent assay technique following manufacturer instructions (BioLegend, San Diego, CA, USA). Blood lipids and complete blood count were determined by routine biochemistry.

To minimize variability, all assays were performed at the end of the study, in duplicates and with the same kits at all timepoints by staff masked to study and treatment allocation.

2.7 | Statistical analysis

This is a secondary analysis of an RCT, hence, no formal sample size calculation was made. All data are presented as mean and standard deviation unless otherwise specified. Differences between two treatment groups at baseline were evaluated by Student *t* test and Fisher's exact test for continuous and categorical variables, respectively. An intention-to-treat, last value carried forward data analysis was performed in a conventional manner using two-way mixed analysis of variance (ANOVA) with post hoc comparison made by Bonferroni test and adjusted for potential confounders. Pearson´s correlation coefficient analysis was applied to assess correlations between changes in clinical/radiographic and systemic markers. All comparisons have been done at patient level. All statistical analyses were done using an appropriate statistical software (IBM SPSS Statistics version 24.0 for Windows, IBM Corporation, Armonk, NY, USA). The α value was set at 0.05.

3 | RESULTS

3.1 | Sample characteristics

No statistically significant differences were observed in subject characteristics by treatment group at baseline (Table 1). However, groups were notably unbalanced for gender, smoking habit, history of periodontitis and presence of systemic comorbidities. All subjects completed the trial and attended at each visit. Adverse events were similar between study groups being the most frequent gastrointestinal disorder (two participants, one per group), headaches (four participants, two per group), metallic taste (two participants, one per group), and oral tissue alterations (one participant from the test group). No major changes in patient's medical history were reported in either group over the study period.

3.2 | Effect of NSPIT on clinical and radiographic outcomes

NSPIT resulted in a marked improvement in clinical and radiographic parameters over the 6 months after therapy irrespectively of the treatment modality delivered (Table 2).

TABLE 1 Baseline characteristics of trial participants.

Parameter	Test ($n = 10$)	Control ($n = 11$)
Age (years)	59.6 (11.7)	58.6 (10.2)
Males, *n* (%)	6 (60.0)	2 (18.2)
Current smokers, *n* (%)	1 (10.0)	4 (36.4)
Presence of systemic condition, *n* (%)	4 (40.0)	1 (9.1)
Previous history of periodontitis, *n* (%)	6 (60.0)	10 (90.9)
Number of implants/patient	1.6 (1.1)	1.9 (1.4)
Prosthesis removed, *n* (%)	5 (50)	5 (45.5)
Re-instrumentation of residual pockets, *n* (%)	6 (60)	6 (54.5)

TABLE 2 Changes in clinical and radiographic outcomes over time in each study group.

Group	Parameter	Baseline	3 months	6 months	Intragroup all groups (*p*-value)	Intragroup baseline versus 3 months (*p*-value)	Intragroup 3 months versus 6 months (*p*-value)	Intragroup baseline versus 6 months (*p*-value)	Time*treatment interaction (intergroup *p*-value)
Test ($n=10$)	PPD (mm)	6.5 (1.8)	4.6 (1.1)	4.3 (1.3)	**.014**	**.020**	1.000	**.009**	
Control ($n=11$)		5.7 (1.1)	4.7 (1.3)	4.5 (1.0)	.363	.761	1.000	.491	
	Intergroup (*p*-value)	.078	.497	.545					.471
Test ($n=10$)	maxPPD (mm)	8.5 (1.4)	6.2 (1.7)	5.6 (1.7)	**.003**	**.039**	.249	**.002**	
Control ($n=11$)		8.1 (1.8)	6.0 (2.1)	5.2 (1.2)	**.022**	**.049**	1.000	**.016**	
	Intergroup (*p*-value)	.263	.394	.698					.626
Test ($n=10$)	RBL (mm)	6.1 (1.6)	5.7 (1.6)	4.7 (1.6)	**.000**	.561	**.000**	**.004**	
Control ($n=11$)		5.4 (2.0)	5.0 (2.3)	4.7 (2.3)	.419	.566	1.000	.587	
	Intergroup (*p*-value)	.221	.268	.655					**.021**
Test ($n=10$)	Recession (mm)	0.5 (0.9)	0.8 (0.7)	0.7 (0.7)	.588	1.000	1.000	.961	
Control ($n=11$)		0.2 (0.3)	0.8 (0.7)	0.6 (0.6)	**.036**	**.040**	.555	.719	
	Intergroup (*p*-value)	.244	.788	.299					.454
Test ($n=10$)	BoP (%)	83	42	40	**.001**	**.001**	1.000	.064	
Control ($n=11$)		92	65	50	**.040**	.511	.629	.050	
	Intergroup (*p*-value)	.822	.108	.856					.181

Note: Statistically significant results are denoted in bold. *p*-values are adjusted for gender, smoking habit, presence of systemic diseases and previous history of periodontitis.

Abbreviations: BoP, bleeding on probing; PPD, probing pocket depth; RBL, radiographic bone level.

Substantial reductions in PPD (mean decrease of 1.9 mm, 95% CI: 0.7 to 3.2 in the test group and mean decrease of 1.0 mm, 95% CI: −0.1 to 2.2 in the control group, $p = .497$ for intergroup comparison), maximum PPD (mean decrease of 2.3 mm, 95% CI: 0.1 to 4.6 in the test group and mean decrease of 2.1 mm, 95% CI: 0.0 to 4.2 in the control group, $p = .263$ for intergroup comparison), radiographic bone gain (mean increase of 0.4 mm, 95% CI: −0.1 to 1.0 in the test group and mean increase of 0.4 mm, 95% CI: −0.2 to 0.8 in the control group, $p = .268$ for intergroup comparison), and bleeding scores (mean decrease of 41%, 95% CI: 18 to 63 in the test group and mean decrease of 27%, 95% CI: 6 to 48 in the control group, $p = .108$ for intergroup comparison) were achieved in both groups 3 months after NSPIT. At 6 months, these improvements were more evident in the test group (for ΔPPD: 2.2 mm, 95% CI: 1.0 to 3.4, $p = .009$; for ΔmaxPPD: 3.4 mm, 95% CI: 1.3 to 5.5, $p = .002$; for ΔRBL: 1.4 mm, 95% CI: 0.7 to 2.2, $p = .004$; and for ΔBoP: 42%, 95% CI: 16 to 68, $p = .064$) than in the controls (for ΔPPD: 1.2 mm, 95% CI: 0.1 to 2.4, $p = .491$; for ΔmaxPPD: 2.4 mm, 95% CI: 0.4 to 4.3, $p = .016$; for ΔRBL: 0.7 mm, 95% CI: 0.0 to 0.4, $p = .587$; and for ΔBoP: 34%, 95% CI: 1 to 58, $p = .050$). However, time*treatment interaction for intergroup comparisons was only statistically significant for radiographic bone gain ($p = .021$). As expected, an increase in peri-implant recession was noted after therapy in both groups which reached statistical significance at 3 months in the control group (mean increase of 0.6 mm, 95% CI: 0.1 to 1.1, $p = .040$). No statistically significant differences were observed for any clinical parameter when participants who underwent re-instrumentation of residual peri-implant pockets were compared to those who have not.

3.3 | Effect of NSPIT on systemic outcomes

Comparisons for biomarkers are shown in Table 3. Time*treatment interaction was statistically significant for CRP ($p = .046$) and IL-6 ($p = .018$). Statistically significant differences between groups were noted for IL-6 (mean difference = 42.6 pg/mL; 95% CI: −122 to 167.2, $p = .012$) and TNF-α concentrations (mean difference = 0.7 pg/mL; 95% CI: −17.6 to 19.1, $p = .031$) at 3 months and for IL-6 (mean difference = 4.5 pg/mL; 95% CI: −11.9 to 20.9, $p = .019$) at 6 months after therapy.

Intragroup comparisons showed reductions in the control group for CRP at 6 months compared to baseline values (mean decrease of 6.9 mg/dL; 95% CI: 3.7–9.9, $p < .001$). With regards to the test group, a substantial decrease in TNF-α was found at 3 and 6 months after NSPIT (mean reduction at 3 months of 102.6; 95% CI: 24.2–181.1, $p = .006$ and mean reduction at 6 months of 110.1; 95% CI: 38.9–181.4, $p = .004$) compared to baseline. A trend towards an increase in peripheral IL-10 levels was also observed, albeit differences were not statistically significant.

Only a modest increase in platelets was observed in the test group between 3 and 6 months after NSPIT (mean increase of $29.2 \times 10^3/\mu L$; 95% CI: 9.1–49.4, $p = .040$) and in neutrophil counts in the test group between baseline and 6 months (mean increase = 0.4; 95% CI: −0.4 to 1.1, $p = .010$). Intergroup differences were observed for triglycerides levels at 6 months (mean difference = 13.6 mg/dL; 95% CI: −45.2 to 72.3, $p = .047$) and intragroup reductions in the control group for LDL cholesterol at 3 (mean decrease = 8.6 mg/dL; 95% CI: −18.7 to 35.9, $p = .012$) and 6 months (mean decrease = 21.8 mg/dL; 95% CI: −6.9 to 50.5, $p = .013$) compared to baseline. No substantial intra and intergroup changes were noted in other lipid fractions and the remaining hematological parameters. No statistically significant differences were observed for any clinical parameter when participants who received re-instrumentation of residual peri-implant pockets were compared to those who have not.

3.4 | Correlation analysis

A moderate positive correlation was found for reduction in TNF-α concentrations between baseline and 6 months and radiographic bone gain at 6 months (Figure 2) as well as baseline PPD (Figure 3). No other clinical or radiographic parameters were correlated with changes in systemic biomarkers.

4 | DISCUSSION

To our knowledge, this is the first human investigation evaluating the systemic impact of non-surgical treatment of peri-implantitis. Findings from this secondary analysis of an RCT suggest that NSPIT has a systemic anti-inflammatory effect (reduction in circulating levels of CRP, IL-6 and TNF-α) after 6 months of follow-up.

A potential association between peri-implantitis and systemic inflammatory state has recently been described (Blanco et al., 2021; Ustaoglu & Erdal, 2020). In these human studies, patients with peri-implantitis showed greater concentrations of WBCs and TNF-α than those subjects with healthy implants. These findings are in accordance with animal experiments where after induction of peri-implantitis by means of ligature placement, an increase in some inflammatory parameters such as total protein, albumin and WBCs was noticed (Chaushu et al., 2020, 2021). In the present study, we observed that after 6 months of NSPIT, levels of well-characterized inflammatory mediators (CRP, IL-6 TNF-α) were statistically significant reduced when compared to baseline values. In line with these results, previous animal studies demonstrated that treatment of experimentally induced peri-implantitis using a surgical conservative approach consisting of open flap debridement was able to revert concentrations of inflammatory biomarkers to baseline levels (Chaushu et al., 2020, 2021). Likewise the findings observed in the present clinical trial, plenty of investigations support a mid-term reduction of systemic inflammation (measured by CRP, IL-6, TNF-α and other inflammatory markers) after non-surgical periodontal therapy in patients with and without comorbidities (D'Aiuto et al., 2019; Iwamoto et al., 2003; Kamil et al., 2011; Marcaccini et al., 2009).

TABLE 3 Changes in biochemical outcomes over time in each study group.

Group	Biomarker (reference values)	Baseline	3 months	6 months	Intragroup all groups (*p*-value)	Intragroup baseline versus 3 months (*p*-value)	Intragroup 3 months versus 6 months (*p*-value)	Intragroup baseline versus 6 months (*p*-value)	Time*treatment interaction (*p*-value)
Inflammatory mediators									
Test ($n=10$)	CRP (mg/L) (<0.5 mg/L)	7.6 (1.6)	4.2 (2.7)	4.0 (2.1)	.683	1.000	1.000	1.000	
Control ($n=11$)		9.9 (4.5)	6.1 (4.1)	3.1 (1.5)	**.000**	.307	.104	**.000**	
	Intergroup (*p*-value)	**.038**	.077	.695					**.046**
Test ($n=10$)	IL-6 (pg/mL) (<7 pg/mL)	5.3 (3.7)	4.8 (3.5)	2.6 (1.0)	.183	.649	.259	1.000	
Control ($n=11$)		4.6 (4.1)	3.9 (4.4)	2.2 (1.2)	**.004**	.286	**.016**	.058	
	Intergroup (*p*-value)	.054	**.012**	**.019**					**.018**
Test ($n=10$)	IL-10 (pg/mL) (<10 pg/mL)	2.5 (1.1)	2.3 (1.1)	2.3 (1.1)	.753	1.000	1.000	1.000	
Control ($n=11$)		1.9 (0.1)	2.0 (0.3)	3.5 (1.9)	.451	1.000	1.000	.792	
	Intergroup (*p*-value)	.922	.218	.585					.614
Test ($n=10$)	TNF-α (pg/mL) (<8 pg/mL)	117.5 (75.1)	14.9 (15.5)	7.4 (3.0)	**.007**	**.006**	.883	**.004**	
Control ($n=11$)		84.5 (66.5)	15.6 (19.2)	5.8 (1.6)	**.001**	.699	**.014**	.144	
	Intergroup (*p*-value)	.109	**.031**	.926					.091
Lipid fractions									
Test ($n=10$)	TC (mg/dL) (<255 mg/dL)	217.2 (44.1)	206.1 (28.9)	197.2 (25.1)	.978	1.000	1.000	1.000	
Control ($n=11$)		207.2 (47.9)	197.8 (35.8)	183.9 (34.7)	.057	.173	.393	.051	
	Intergroup (*p*-value)	.993	.499	.161					.422
Test ($n=10$)	Triglycerides (mg/dL) (<150 mg/dL)	91.6 (71.2)	121.5 (104.8)	106.7 (63.4)	.388	.551	.713	1.000	
Control ($n=11$)		106.3 (48.4)	112.2 (55.2)	93.2 (57.3)	.885	1.000	1.000	1.000	
	Intergroup (*p*-value)	.311	.651	**.047**					.732
Test ($n=10$)	HDL-C (mg/dL) (>40 mg/dL)	69.7 (23.4)	65.0 (16.4)	63.4 (20.9)	.219	.229	.732	1.000	
Control ($n=11$)		64.0 (19.9)	62.2 (13.4)	66.4 (19.5)	.963	1.000	1.000	1.000	
	Intergroup (*p*-value)	.097	.093	.088					.433
Test ($n=10$)	LDL-C (mg/dL) (<150 mg/dL)	131.2 (48.6)	121.6 (30.7)	114.1 (34.2)	.583	.903	1.000	1.000	
Control ($n=11$)		121.8 (33.7)	113.2 (23.8)	100.0 (28.7)	**.010**	**.012**	.640	**.013**	
	Intergroup (*p*-value)	.401	.675	.466					.085
Differential blood counts									
Test ($n=10$)	RBC (10^6/μL) (4.5–5.5 × 10^6/μL)	4.5 (0.4)	4.5 (0.4)	4.6 (0.5)	.057	.075	.125	1.000	
Control ($n=11$)		4.5 (0.3)	4.5 (0.4)	4.6 (0.2)	.346	.411	1.000	1.000	
	Intergroup (*p*-value)	.987	.348	.857					.083
Test ($n=10$)	Platelets (10^3/μL) (135.0–369.0 × 10^3/μL)	262.2 (44.1)	240.4 (33.8)	269.6 (31.0)	**.026**	.064	**.040**	1.000	
Control ($n=11$)		223.2 (65.1)	233.0 (62.5)	234.9 (68.2)	.238	.309	1.000	.430	

(Continues)

TABLE 3 (Continued)

Group	Biomarker (reference values)	Baseline	3 months	6 months	Intragroup all groups (*p*-value)	Intragroup baseline versus 3 months (*p*-value)	Intragroup 3 months versus 6 months (*p*-value)	Intragroup baseline versus 6 months (*p*-value)	Time*treatment interaction (*p*-value)
	Intergroup (*p*-value)	**.010**	.064	**.027**					.063
Test ($n=10$)	WBC ($10^3/\mu L$) ($4.09–10.5\times10^3/\mu L$)	5.9 (1.1)	5.8 (1.3)	6.0 (1.6)	.858	1.000	1.000	1.000	
Control ($n=11$)		5.3 (1.6)	5.7 (0.8)	5.9 (1.3)	.287	.863	1.000	.321	
	Intergroup (*p*-value)	.960	.337	.470					.530
Test ($n=10$)	Lymphocytes ($10^3/\mu L$) ($0.7–4.67\times10^3/\mu L$)	2.2 (0.5)	2.1 (0.8)	1.9 (0.7)	.849	1.000	1.000	1.000	
Control ($n=11$)		1.9 (0.7)	2.1 (0.6)	1.9 (0.3)	.271	1.000	.296	.600	
	Intergroup (*p*-value)	.284	.184	.884					.489
Test ($n=10$)	Monocytes ($10^3/\mu L$) ($0.108–0.86\times10^3/\mu L$)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	.847	1.000	1.000	1.000	
Control ($n=11$)		0.6 (0.6)	0.5 (0.1)	0.5 (0.1)	.608	1.000	1.000	1.000	
	Intergroup (*p*-value)	.819	.251	.785					.734
Test ($n=10$)	Neutrophils ($10^3/\mu L$) ($1.7–7.33\times10^3/\mu L$)	3.1 (1.0)	3.0 (1.3)	3.4 (1.2)	.759	1.000	1.000	1.000	
Control ($n=11$)		2.7 (1.3)	3.0 (0.6)	3.3 (1.2)	**.008**	1.000	.135	**.010**	
	Intergroup (*p*-value)	.608	.946	.443					.089
Test ($n=10$)	Eosinophils ($10^3/\mu L$) ($0.02–0.6\times10^3/\mu L$)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	.168	1.000	.166	.344	
Control ($n=11$)		0.1 (0.1)	0.1 (0.0)	0.1 (0.1)	.111	1.000	.107	.188	
	Intergroup (*p*-value)	.151	.052	.840					.082
Test ($n=10$)	Basophils ($10^3/\mu L$) ($0.004–0.12\times10^3/\mu L$)	0.1 (0.0)	0.1 (0.1)	0.0 (0.0)		1.000	1.000	1.000	
Control ($n=11$)		0.1 (0.1)	0.1 (0.1)	0.1 (0.0)		1.000	1.000	1.000	
	Intergroup (*p*-value)	.972	.987	.899					.466

Note: Statistically significant results are denoted in bold. *p*-Values are adjusted for gender, smoking habit, presence of systemic diseases and previous history of periodontitis.

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein; IL-10, interleukin 10; IL-6, interleukin 6; LDL-C, low-density lipoprotein; RBC, red blood cells; TC, total cholesterol; TNF-α, tumor necrosis factor alpha; WBC, white blood cells.

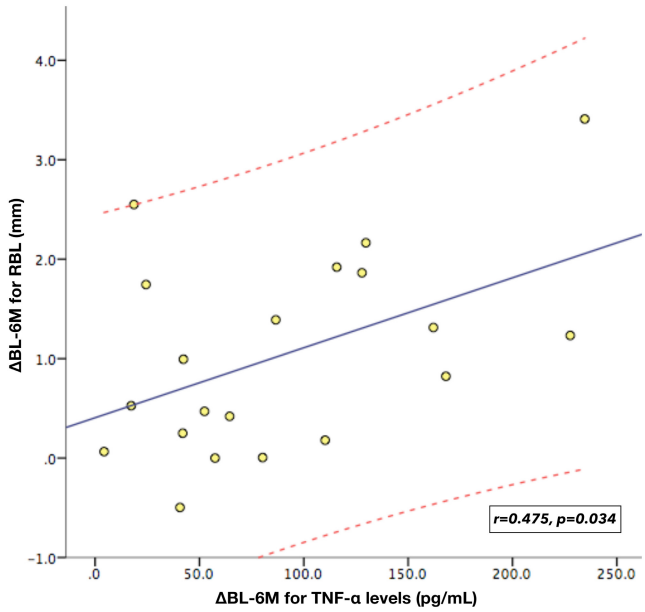

FIGURE 2 Scatter plot showing a positive correlation between radiographic bone fill (mm) and decrease in serum levels of TNF-α (pg/mL) after 6 months of non-surgical peri-implantitis treatment.

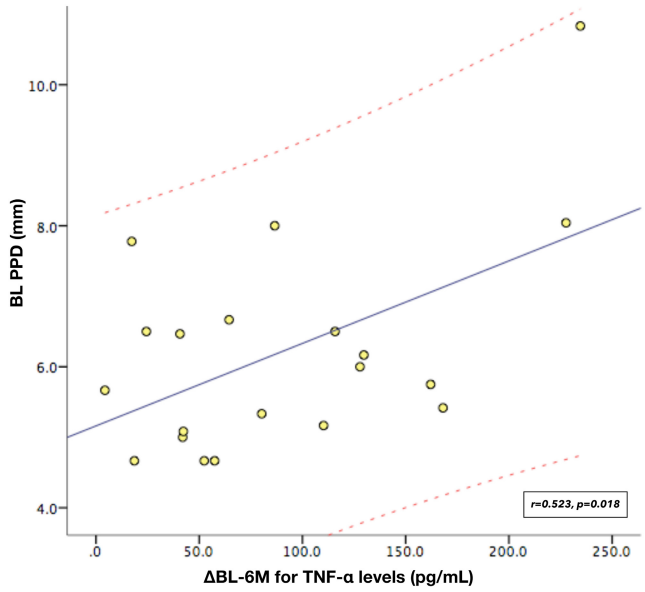

FIGURE 3 Scatter plot showing a positive correlation between baseline probing peri-implant pocket depth (mm) and decrease in serum levels of TNF-α (pg/mL) after 6 months of non-surgical peri-implantitis treatment.

Results from this secondary analysis RCT can shed some light on the systemic impact of peri-implantitis ("Peri-implant Medicine"), which is one of the top research priorities as stated recently by the International Academy of Periodontology at its first research meeting (Bartold et al., 2019). Carcuac and colleagues have demonstrated that the infiltrated connective tissue in sites with peri-implantitis is four to six times larger than in those affected by periodontitis (Carcuac et al., 2013). Based on this, it can be speculated that one implant affected with peri-implantitis equals to four to six teeth with periodontitis in terms of inflamed tissue. Moreover, this inflammatory infiltrate is not only larger but also reaches the surrounding bone, as a deep local infection and inflammation. Therefore, the systemic effect of peri-implantitis could be even greater than periodontitis. In this sense, recent evidence showed that peri-implantitis is associated with a state of low-grade systemic chronic inflammation (Blanco et al., 2021; Ustaoglu & Erdal, 2020). This chronic state of systemic inflammation is often characterized by immune response activation, disruption of physiological cellular functions as well as alteration in tissues and organs which in turn could increase the risk of onset or progression of some of the most disabling and fatal human non-communicable chronic diseases (Furman et al., 2019). For example, it has been shown that increased levels of peripheral CRP and IL-6 are strong predictors of future cardiovascular events (Ridker et al., 1997; Ridker, Hennekens, et al., 2000; Ridker, Rifai, et al., 2000). Moreover, results from a seminal multinational randomized controlled clinical trial including 10,000 participants with established cardiac disease have proved that the use of a monoclonal antibody that blocks the activity of IL-1β significantly reduced recurrent major adverse cardiovascular events by 15%–17% (Ridker et al., 2017) with the benefit directly related to the magnitude of reduction in downstream IL-6 and CRP (Ridker et al., 2018; Ridker, Libby, et al., 2018). Another example of the relationship between anti-inflammatory treatment and improvements in general health is the positive effect of TNF inhibition therapy on insulin resistance in patients with rheumatoid arthritis (Burska et al., 2015). In line with this evidence, in the present clinical trial, we observed a positive, although modest, correlation between reduction in the radiographic intrabony peri-implant defect depth and decrease in the circulating levels of TNF-α. The anti-inflammatory effect of NSPIT that has been observed in our study is confirmed by a modest reduction in neutrophil counts which are key players in the chronic inflammatory response and tissue damage (Rawat & Shrivastava, 2022). Results from our trial also found an increase in platelets after NSPIT. It is believed that platelets might assist in bacterial clearance by presenting bacteria to neutrophils for inducing phagocytic elimination (Margraf & Zarbock, 2019). Therefore, taking all this into account, identifying potential sources of chronic systemic inflammation such as peri-implantitis which is an infectious disease that can be treated with non-pharmacological interventions might be of interest in patients with a hyperinflammatory phenotype that are potentially at high risk of having other comorbidities or systemic complications such as cardiovascular diseases (Wang, Ou, et al., 2021; Wang, Sugai, et al., 2021). On the other hand, it has to be highlighted that in our study, we found that LDL-cholesterol levels were reduced in both groups after 6 months of therapy although only in the control group this decrease reached statistically significance. The effect of NSPIT on LDL reduction as seen in this study is similar in magnitude to that achieved by some of the most commonly used lipid-lowering drugs (Tokgözoğlu & Libby, 2022). Further trials

with larger samples sizes should explore the potential impact of NSPIT on lipids.

The efficacy of non-surgical treatment of peri-implant lesions has been a matter of debate as in many cases surgical approaches are recommended to control peri-implant infections. In the last years, a number of RCTs have investigated the adjunctive effect of systemic antibiotics in NSPIT with contradictory results (Blanco et al., 2022; De Waal et al., 2021; Polymeri et al., 2022; Shibli et al., 2019; Stein et al., 2017). In this investigation, a clear improvement in both pocket depth and bleeding reduction as well as radiographic bone fill was observed at 6 months after therapy, irrespectively of the use of systemic metronidazole. This results differ with the ones obtained in the original RCT were the test group outperformed the control group (Blanco et al., 2022). Possible explanations to this discrepancy is the lower number of participants in each group as well as the shorter follow-up (6 vs. 12 months) compared to the clinical trial by Blanco et and co-workers (Blanco et al., 2022). In addition, baseline characteristics both at patient level such as gender, smoking habit, presence of systemic conditions and previous history of periodontitis as well as clinical and radiographic parameters, for example, initial PPD or RBL differed between groups and this might have an impact on the outcomes assessed in the present secondary analysis. In fact, initial PPD was correlated with reduction in levels of TNF-α at 6 months. The positive local effect of NSPIT was reflected at a systemic level, as serum concentrations of CRP and TNF-α were reduced over the study period. Furthermore, a correlation was found between radiographic bone gain and reduction in TNF-α levels. On the other hand, the potential adjunctive systemic benefit of systemic antimicrobials to the non-surgical treatment of periodontitis has been investigated in several reports (Cosgarea et al., 2020; Giannopoulou et al., 2016; López et al., 2012). In line with our results, an RCT carried out by López and co-workers observed that in patients with periodontitis and metabolic syndrome, levels of systemic inflammation (as measured by CRP) were reduced irrespective of whether systemic antibiotics were used in conjunction with scaling and root planning (López et al., 2012). Another RCT, did not find differences between the use or not of systemic antibiotics as adjuncts to non-surgical periodontal treatment in aggressive periodontitis patients when host-derived systemic biomarkers were assessed (Giannopoulou et al., 2016). On contrary, a secondary analysis of an RCT showed significant improvements in markers of systemic inflammation when amoxicillin and metronidazole were used together with subgingival debridement to treat periodontitis when compared to non-surgical therapy alone (Cosgarea et al., 2020). However, no differences in systemic outcomes were noted between short and longer antibiotic protocols (3 vs. 7 days) (Cosgarea et al., 2020).

This investigation has several limitations to be acknowledged by the authors. Firstly, this is a secondary analysis of a previously published RCT (Blanco et al., 2022) and therefore, no formal sample size was calculated a priori. Hence, future trials with proper sample sizes are needed to replicate our preliminary findings with longer follow-ups and perhaps including patients who also receive surgical treatment. Secondly, the population included in our analysis was heterogeneous since some of the participants were smokers or had concomitant comorbidities such as high blood pressure or hypercholesteremia and even baseline clinical and radiographic characteristics were not comparable between groups. All these factors might have an impact on the systemic inflammatory state. The next trials on this topic should include otherwise healthy subjects to rule out potential confounding effects. Lastly, although a standard assay was used to measure CRP instead of the high sensitivity test that detects mild changes in circulating CRP, we found significant changes from baseline to 6 months after treatment.

5 | CONCLUSION

In this secondary analysis of an RCT, a systemic anti-inflammatory impact with reduction in peripheral levels of CRP, IL-6 and TNF-α was observed after 6 months of non-surgical treatment of peri-implantitis regardless of the use of systemic metronidazole. Large-scale RCTs are needed to confirm these preliminary results. Mechanistic studies are also warranted to elucidate potential biological pathways underlying the systemic effects of peri-implantitis and its treatment.

AUTHOR CONTRIBUTIONS

Antonio Liñares: Conceptualization; funding acquisition; writing – original draft; methodology; writing – review and editing; supervision; resources; project administration. **Jose Dopico:** Investigation; writing – review and editing; methodology. **Carlota Blanco:** Investigation; writing – review and editing; methodology. **Alex Pico:** Investigation; methodology; writing – review and editing. **Tomás Sobrino:** Software; formal analysis; data curation; writing – review and editing; methodology. **Juan Blanco:** Conceptualization; funding acquisition; writing – review and editing; methodology; project administration; supervision; resources. **Yago Leira:** Conceptualization; writing – original draft; writing – review and editing; methodology; software; formal analysis; project administration; data curation; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of Santiago de Compostela/Lugo approved this study (ID: 2017/508).

CONSENT TO PARTICIPATE

Written informed consent to participate in the present study was obtained from all individual participants included in the study.

CONSENT FOR PUBLICATION

Written informed consent for publication was provided by all participants.

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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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