Check for updates

Received: 9 November 2017 | Revised: 24 December 2018 | Accepted: 2 January 2019

DOI: 10.1111/clr.13405

ORIGINAL RESEARCH

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Triclosan-containing fluoride toothpaste on clinical parameters and osteo-inflammatory mediators when applied in a stent during experimental peri-implant mucositis in smokers

Suzana Peres Pimentel[1] | Fernanda Vieira Ribeiro[1] | Renato Correa Casarin[1,2] | Fabiano Ribeiro Cirano[1] | Vanessa Haguihara Luchesi[1] | Vanessa Gallego Arias Pecorari[1] | Marcio Zaffalon Casati[1]

[1]Dental Research Division, School of Dentistry, Paulista University, São Paulo, Brazil

[2]Department of Prosthodontics and Periodontics, School of Dentistry at Piracicaba, University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil

Correspondence
Marcio Zaffalon Casati, Departamento de Odontologia, Universidade Paulista – UNIP, São Paulo, Brazil.
Email: mzcasati@gmail.com

Funding information
São Paulo Research Foundation (FAPESP), São Paulo, SP, Brazil –, Grant/Award Number: Processes 11/51037-6; São Paulo Research Foundation, Grant/Award Number: 11 and 51037-6

Abstract

Objectives: To determine the effect of triclosan-containing fluoride toothpaste on the clinical parameters and the osteo-immunoinflammatory mediators in the peri-implant fluid when applied in a stent during experimental peri-implant mucositis in smokers.

Materials and methods: Twenty-six smokers with an implant-supported crown were enrolled in this double-blind, randomized, crossover study. During the two 3-week periods without mechanical toothbrushing (washout period: 30 days), patients were randomly assigned to triclosan/fluoride (n:13) or fluoride toothpaste (n:13), three times/day. Clinical and immunoenzymatic assays were performed at baseline, 3, 7, 14 and 21 days.

Results: Both groups showed increase in the Plaque Index throughout the study ($p = 0.001$), without inter-group differences at 21 days ($p > 0.05$). No intra- or inter-group differences were observed for IFN-γ, IL10, IL-1β, IL8, IL-17, IL-6, TNF-α, MMP-2, MMP-9, TGF-β, OC, OPN, ICTP, OPG and RANKL ($p > 0.05$). However, the RANKL/OPG ratio was significantly higher in fluoride toothpaste-treated sites when compared to triclosan/fluoride-treated sites at the end of period without mechanical toothbrushing, on the 21st day ($p = 0.041$).

Conclusion: Triclosan-containing toothpaste favorably modulated osteo-immunoinflammatory mediators during the experimental peri-implant mucositis in smokers, decreasing the ratio of RANKL/OPG.

KEYWORDS
cigarette smokers, dental implants, mucositis, toothpaste, triclosan

1 | INTRODUCTION

Cigarette smoking not only increases the risk of developing periodontitis, but has also been related to a higher prevalence of diseases around implants, negatively influencing the peri-implant bone loss and promoting edentulism (Arora, Schwarz, Sivaneswaran, & Banks, 2010; Atieh, Alsabeeha, Faggion, & Duncan, 2013; Mombelli, Müller, & Cionca, 2012; Saaby, Karring, Schou, & Isidor, 2016; Turri, Rossetti, Canullo, Grusovin, & Dahlin, 2016). Smoking negatively modifies the pattern of host response (Ataoglu et al., 2002; Konermann et al.,

© 2019 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

2016; Peruzzo et al., 2016; Ryder, 2007) and promotes suppression in the osteo-immunoinflammatory mediator profile around dental implants even in non-manifesting inflammation sites (Negri et al., 2016).

Although implant therapy has been recognized as a predictable alternative to dental rehabilitation, peri-implant lesions have been reported to be a frequent clinical problem (Costa et al., 2012; Papathanasiou, Finkelman, Hanley, & Parashis, 2016). While the management of peri-implant mucositis is considered a prerequisite for the prevention of peri-implantitis (Salvi & Zitzmann, 2014), the avoidance of mucositis should be the aim of all clinicians, mainly considering the stronger inflammatory response in soft tissues around implants when compared to that of their gingival counterparts (Salvi et al., 2012) and taking into account the absence of a standard therapeutic protocol in the management of mucositis around implants (Costa et al., 2012; Heitz-Mayfield & Mombelli, 2014).

Triclosan is a substance that, when incorporated into toothpaste, has been described as an efficient approach in the control of periodontal diseases (Escribano et al., 2016; Pera et al., 2012; Rosling et al., 1997; Seymour et al., 2017). Moreover, the regular use of a triclosan-containing dentifrice was effective at decreasing the clinical signs of inflammation of peri-implant mucositis (Ramberg, Lindhe, Botticelli, & Botticelli, 2009) and to improve dental implant maintenance by reducing dental plaque and peri-implant bleeding (Sreenivasan et al., 2011). Although these previous trials have not studied experimental mucositis, as performed in the current investigation, it could be hypothesized that the promising outcomes observed when using triclosan would be supported, in part, by its anti-inflammatory effects (Barros et al., 2010).

Considering the potential of triclosan as a modulator of host response and taking into account the negative impact of smoking in the peri-implant bone loss and implant failure (Heitz-Mayfield, 2008; Saaby et al., 2016), it would be relevant to investigate whether the use of a triclosan dentifrice could prevent peri-implant mucositis in smoking patients. The priori hypothesis of this trial was to determine whether a triclosan-containing toothpaste could affect clinical parameters and local pattern of osteo-immunoinflammatory mediators in the peri-implant crevicular fluid (PICF) during the progression of experimental peri-implant mucositis in smokers.

2 | MATERIAL AND METHODS

2.1 | Study design

This study was designed as double-blind, randomized, crossover study to evaluate the influence of a triclosan-containing toothpaste in the profile of osteo-immunoinflammatory mediators in the PICF of smokers and in the clinical measurements during the progression of experimental peri-implant mucositis. This investigation was approved by the ethics committee of Paulista University (Protocol 97.117). The ClinicalTrials.gov identifier is NCT03241407.

2.2 | Population screening

Patient recruitment started in July 2013 and was completed by the end of September 2014. Clinical procedures and evaluations were carried out between September 2013 and November 2014. Data entry and statistical analyses were performed in April 2015. All the patients were recruited from the patients referred to Paulista University.

2.3 | Inclusion and exclusion criteria

Patients should be smokers (more than 10 cigarettes/day, for at least 2 years), >30 years old and present at least one single unit implant-supported crown (screw-retained) in the molar/pre-molar region (implant-abutment connection external hexagonal), in function for at least 12 months, with a width of keratinized tissue ≥2 mm. Peri-implant tissue should be healthy [probing depth (PD) <4 mm with no Bleeding on Probing (BoP) and no evidence of radiographic bone loss beyond bone remodeling] (AAP, 2013). Patients should be periodontally healthy and present full-mouth plaque scores (FMPS) (Ainamo & Bay, 1975) and full-mouth bleeding scores (FMBS) (Muhlemann & Son, 1971) ≤20%.

The exclusion criteria were pregnancy, lactation, non-smokers, systemic conditions that could interfere in the progression of peri-implant diseases and bone metabolism (e.g., diabetes and immunologic disorders), use of long-term administration of anti-inflammatory, bisphosphonates and immunosuppressive medications, antibiotic therapies in the previous 6 months, patients that required bone grafts before or alongside the implant surgery, and history of previous regenerative procedures in the area treated with implant.

Patients were thoroughly informed of the nature, potential risks and benefits of their participation in the study, and they each signed an informed consent document.

2.4 | Experimental groups

In the pre-experimental phase, all patients were submitted to a prophylaxis procedure, supragingival scaling and polishing of the entire dentition and instruction in optimal oral hygiene practices to guarantee their ability to perform proper plaque control. Subsequently, patients were re-evaluated to confirm scores at baseline compatible with gingival/mucosal health (FMPS and FMBS ≤20%).

Patients were asked to refrain from toothbrushing at the implant site for a period of 21 days. They wore a silicone stent filled with the toothpaste (triclosan-containing or non-triclosan-containing fluoride toothpaste) 3 times per day for 2 min. The silicone stent involved the implant and adjacent teeth covering 2–3 mm of peri-implant mucosa. During this 3-week period, participants were randomly assigned, by a researcher not involved in the study, to two groups by a computer-generated list using the Excel program of the Microsoft Office package: Triclosan/Fluoride Toothpaste(n = 13) or Fluoride Toothpaste (n = 13). Conventional toothbrushing was performed in the non-stent areas, with the same toothpaste used in the silicone stent. Allocation concealment was conducted with sequentially numbered opaque

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

sealed envelopes, which were only opened by the intervention operator (VHL) at the time of intervention. The patients and examiner did not know what the designated allocation was.

After 3 weeks, a professional prophylaxis was performed, and a washout period of 30 days was established. All patients restarted their optimal mechanical plaque control practices to reach pre-experimental levels of oral cleanliness and gingival/mucosal health. Then, a second experimental 3-week period without mechanical toothbrushing around the implants was established and the experimental groups were exchanged. After that, a new professional prophylaxis was performed. Patients were blinded to the therapies, and the toothpaste (both with same color) were delivered to patients in opaque tubes, ensuring the patients' masking to the therapy.

All evaluations (clinical and immunoenzymatic) were performed at baseline, 3, 7, 14 and 21 days of each period of experimental mucositis induction.

Levels of osteo-immunoinflammatory mediators were considered the primary outcome variable. The number of patients included was based on previous crossover investigations that found differences in the crevicular fluid levels of osteo-immunoinflammatory markers in different clinical status (Hallström et al., 2013; Sarmento et al., 2014). A post hoc power analysis of this study was conducted using the mean and standard deviation of RANKL/OPG outcomes at 21 days, since the ratio of these osteo-inflammatory-related markers is considered relevant to the establishment and severity of peri-implant diseases (Duarte et al., 2009). It was considered an effect size 0.75. It was observed a power value of 0.821 with the present data using the program sample power SPSS 21.[1]

2.5 | Clinical examination

The same examiner (SPP), who was blinded to the groups, performed all clinical measurements. To perform the intra-examiner calibration, 15 non-study individuals presenting dental implants were selected. The examiner measured the PD of all individuals twice within 24 hr. The intra-class correlation was calculated as 95% reproducibility.

Individual stents were prepared to standardize the location of periodontal probe[2] in order to evaluate the following parameters at four sites of the experimental dental implants at baseline, 3-, 7-, 14- and 21-day follow-ups: 1) Plaque Index (PI/%): dichotomous Plaque Index along the mucosal margin around implants, 2) BoP (%):dichotomous index of Bleeding on Probing around implants, 3) position of the peri-implant margin (PPM/mm): distance from the stent to the peri-implant margin; 4) relative clinical attachment level (RCAL/mm): distance from the stent to the bottom of the peri-implant pocket; and 5) peri-implant PD (mm): calculated by deducting PPM from RCAL. The FMPS (Ainamo & Bay, 1975) and FMBS (Muhlemann & Son, 1971) were calculated before the beginning of each period of experimental mucositis.

[1]IBM, Armonk, NY, USA.

[2]North Carolina—Hu-Friedy, Chicago, IL, USA.

2.6 | Osteo-immunoinflammatory profile assessment

PICF was collected from dental implant sites by the same examiner (SPP) by placing filter paper strips[3] into the sulcus of the dental implants (vestibular and lingual), as previously described (Negri et al., 2016). PICF samples were immediately stored at −20°C.

Levels of interferon (IFN)-γ, interleukin (IL)-17, IL-1β, IL-10, IL-6, IL-8, tumor necrosis factor (TNF)-α[4], osteoprotegerin (OPG), osteocalcin (OC), osteopontin (OPN)[5], matrix metalloproteinase (MMP)-2, MMP-9[6], transforming growth factor (TGF)-β[7], soluble receptor activator of nuclear factor-κβ ligand (RANKL)[8] and cross-linked telopeptide of type I collagen (ICTP)[9] in the PICF were determined using the MAGpix™ instrument[10] and Xponent® software[11]. The mean concentration of each mediator was calculated using the individual as a statistical unit and expressed as pg/ml.

2.7 | Data analysis

All analyses were completed using SAS program release 9.1[12]. Data were examined for normality using the Kolmogorov–Smirnov test, and those that achieved normality were analyzed using parametric methods, whereas those that presented non-normal distribution were analyzed using non-parametric tests. FMPS and FMBS measured before the beginning of each period of experimental mucositis in both groups were compared using the Wilcoxon test. For the other clinical parameters (PI, BoP, PPM, RCAL and PD), the two-way ANOVA/Tukey test was used to detect differences between groups and periods. Levels of osteo-immunoinflammatory markers between groups and among follow-ups were compared using the Wilcoxon and Friedman test, respectively. An experimental level of significance was determined at 5%. Multiplicity-adjusted P-values were calculated using the Bonferroni adjustment.

3 | RESULTS

Twenty-six patients were included in the study. No dropout occurred (Figure 1). The study population was characterized as 57.7% male (mean age: 49.62 ± 16.01 years).

[3]Periopaper, Oraflow, Plainview, NY, USA.

[4]Human Th17 HTH17MAG-14 K, Millipore Corporation, Billerica, MA, USA.

[5]Human Bone HBNMAG-51 K, Millipore Corporation, Billerica, MA, USA.

[6]Human MMP Panel 2 HMMP2MAG-55 K, Millipore Corporation, Billerica, MA, USA.

[7]Multi-species TGF-β TGFBMAG-64 K, Millipore Corporation, Billerica, MA, USA.

[8]Human Single Plex Bone HRNKLMAG-31 K, Millipore Corporation, Billerica, MA, USA.

[9]Uscn Life Science Inc., Wuhan, Hubei, PRC.

[10]MiraiBio, Alameda, CA, USA.

[11]sMillipore, Corporation, Billerica, MA, USA.

[12]Cary, NC, USA.

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

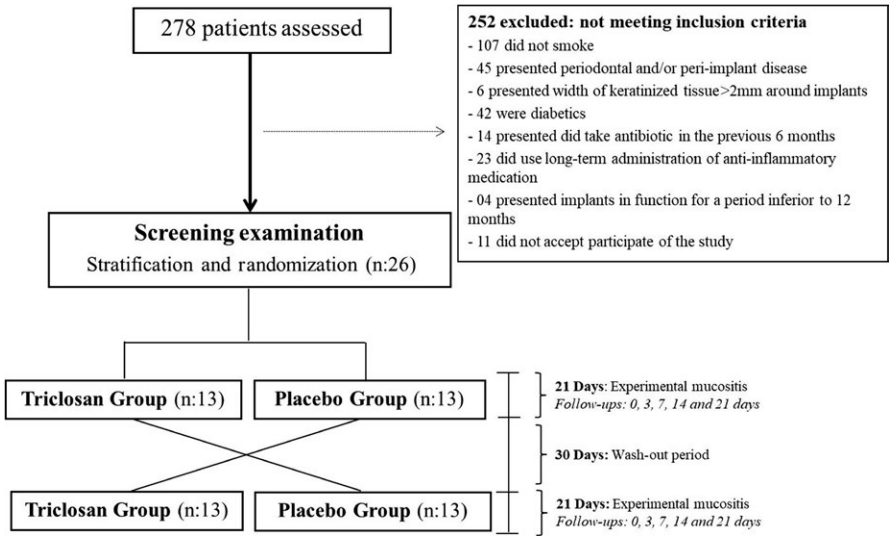

FIGURE 1 Flowchart of the study

TABLE 1 Mean (± *SD*) of PI, BoP, PPM, PD and RCAL at experimental sites at baseline, 3-, 7-, 14- and 21-day follow-ups

		PI (%)	BoP (%)	PD (mm)	RCAL (mm)	PPM (mm)
Triclosan/fluoride toothpaste group	Baseline	6.9 ± 10.4c	0.0 ± 0.0	3.1 ± 1.0	9.0 ± 1.5	5.9 ± 1.3
	3 days	35.7 ± 24.4[a]	3.6 ± 9.6	2.7 ± 0.8	8.7 ± 1.4	6.0 ± 1.4
	7 days	38.3 ± 26.8[a,b]	3.9 ± 9.4	2.9 ± 1.0	8.9 ± 1.6	6.0 ± 1.4
	14 days	60.3 ± 21.9[b,d]	3.2 ± 6.9	3.0 ± 0.9	8.8 ± 1.5	5.8 ± 1.6
	21 days	74.0 ± 19.1[d]	3.2 ± 6.9	2.7 ± 0.7	8.6 ± 1.3	5.8 ± 1.4
Fluoride toothpaste group	Baseline	9.8 ± 13.2	0.0 ± 0.0	3.6 ± 0.5	8.8 ± 0.6	5.2 ± 0.6
	3 days	45.2 ± 34.2[a]	6.0 ± 14.1	3.7 ± 0.6	8.9 ± 0.7	5.3 ± 0.7
	7 days	58.8 ± 16.8[a]	5.0 ± 8.0	3.6 ± 0.5	8.9 ± 0.6	5.3 ± 0.6
	14 days	75.6 ± 16.4[c]	4.5 ± 7.8	3.8 ± 0.6	9.3 ± 0.7	5.4 ± 0.1
	21 days	75.5 ± 17.7[c]	6.9 ± 16.8	3.7 ± 0.9	9.2 ± 1.1	5.5 ± 0.4

[a]Significant intra-group differences by the ANOVA/Tukey when compared to baseline ($p < 0.05$). [b]Significant inter-group differences by the ANOVA/Tukey ($p < 0.05$). [c]Significant intra-group differences by the ANOVA/Tukey when compared to baseline and 3 days ($p < 0.05$). [d]Significant intra-group differences by the ANOVA/Tukey when compared to baseline, 3 and 7 days ($p < 0.05$).

3.1 | Clinical results

No significant differences for the FMPS (11.54 ± 6.34 and 10.37 ± 6.04, for the first and second periods of mucositis induction, respectively; $p > 0.05$) and FMBS (3.18 ± 2.02 and 1.95 ± 0.99, for the first and second periods of mucositis induction, respectively; $p > 0.05$) before the beginning of each phase of experimental mucositis were detected. A significant intra-group increase in the Plaque Index at experimental implant site was detected in both the triclosan/fluoride ($p = 0.009$) and fluoride toothpaste therapies from the third day ($p = 0.008$), enhancing progressively until the 21st day ($p = 0.001$, for both groups; Table 1). Although a lower percentage of plaque has been detected in triclosan-treated sites after 7 ($p = 0.007$) and 14 days ($p = 0.026$) when compared to fluoride toothpaste-treated implants, at the end of the experimental period (21st day), a similar Plaque Index was observed in both groups ($p > 0.05$; Table 1). The means of the BoP, PD, RCAL and PPM at the experimental sites were not statistically different between the groups at any time points, and no intra-group differences were detected throughout the period of mucositis induction for both treatments ($p > 0.05$; Table 1).

3.2 | Osteo-immunoinflammatory levels

No intra- or inter-group differences were observed for IFN-γ, IL10, IL-1β, IL8, IL-17, IL-6, TNF-α, MMP-2, MMP-9, TGF-β, OC, OPN, ICTP, OPG and RANKL ($p > 0.05$; Tables 2 and 3). Nevertheless, the RANKL/OPG ratio was significantly higher in fluoride toothpaste-treated sites when compared to triclosan/fluoride-treated sites at the end of period without mechanical toothbrushing, on the 21st day ($p = 0.041$; Table 3).

4 | DISCUSSION

The clinical observations from this study showed that at both fluoride toothpaste and triclosan/fluoride toothpaste-treated implant sites, an increased Plaque Index was demonstrated from the 3rd day without mechanical toothbrushing, and an increase of plaque

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Mean (± *SD*) of concentrations (pg/μl) of immunoinflammatory mediators at baseline, 3-, 7-, 14- and 21-day follow-ups

		IFN-γ(pg/μl)	IL–10(pg/μl)	IL–17(pg/μl)	IL–1β(pg/μl)	IL–6(pg/μl)	IL–8(pg/μl)	TNF-α(pg/μl)	MMP–2(pg/μl)	MMP–9(pg/μl)
Triclosan/fluoride toothpaste	Baseline	3.0 + 3.6	1.9 + 2.1	9.5 + 21.7	38.4 ± 48.9	1.0 ± 2.0	109.5 + 275.1	2.9 ± 9.4	731.0 ± 806.1	20,631.5 ± 20,103.2
	3	4.0 + 4.1	4.7 + 7.9	4.0 + 3.6	73.2 ± 113.3	2.8 ± 5.5	59.6 + 92.0	1.3 ± 2.2	2,162.9 ± 2,654.7	31,681.5 ± 27,952.1
	7	3.0 + 2.5	2.0 + 2.5	3.2 + 2.3	95.8 ± 111.6	1.0 ± 2.2	98.8 + 236.7	0.8 ± 1.4	762.9 ± 819.9	28,681.5 ± 36,847.0
	14	1.9 + 1.2	0.9 + 0.6	2.4 + 1.6	43.6 ± 54.9	0.1 ± 0.1	10.5 + 8.8	0.2 ± 0.5	1,128.9 ± 1625.1	43,476.1 ± 48,449.3
	21	2.3 + 2.2	1.9 + 2.4	1.9 + 1.4	70.2 ± 104.5	1.9 ± 3.6	48.7 + 145.5	2.4 ± 5.9	1,030.8 ± 945.3	16,961.8 ± 17,064.1
Fluoride toothpaste	Baseline	2.5 + 2.9	1.7 + 2.2	9.2 + 23.9	55.3 + 53.7	0.8 ± 2.4	77.0 + 200.5	0.6 ± 1.2	1,310.6±!580.2	28,097.8 ± 22,041.1
	3	2.3 + 1.4	1.1 + 0.9	2.8 + 1.8	66.9 + 120.1	0.5 ± 0.4	88.3 + 167.2	0.3 ± 0.4	1887.4 ± 1804.5	54,860.4 ± 58,208.1
	7	1.5 + 1.3	0.9 + 1.0	4.6 + 10	137.6 + 323.1	0.3 ± 0.8	52.8 + 181.9	0.3 ± 0.9	510.0 ± 471.8	24,704.3 ± 31,888.4
	14	1.6 + 1.0	1.0 + 0.6	2.0 + 1.4	99.9 + 161.3	0.4 ± 0.6	49.0 + 123.2	0.1 ± 0.3	617.0 ± 571.5	25,240.7 ± 31,729.8
	21	2.1 + 2.1	1.1 + 1.1	2.7 + 2.6	154.7 + 364.8	0.1 ± 0.2	34.6 + 77.5	0.6 + 0.2	819.1 ± 524.7	59,899.2 ± 66,690.4

Note. No intra-or inter-group differences were detected by the Wilcoxon or Friedman tests ($p > 0.05$).

TABLE 3 Mean (±*SD*) of concentrations (pg/μl) of bone-related markers at baseline, 3-, 7-, 14- and 21-day follow-ups

		OPG(pg/μl)	RANKL(pg/μl)	RANKL/OPG (E^1) (pg/μl)	OC(pg/μl)	OPN(pg/μl)	TGF-β(pg/μl)	ICTP(pg/μl)
Triclosan-fluoride toothpaste	Baseline	53.2 ± 62.5	2.9 ± 1.7	1.4 ± 1.6	708.7 ± 898.7	509.2 ± 582.9	5.5 ± 5.6	204.3 ± 194.7
	3	65.2 ± 87.4	2.7 ± 3.9	0.8 ± 0.8	1,177.7 ± 847.9	1,189.3 ± 843.2	11.9 ± 11.6	304.0 ± 184.3
	7	45.0 ± 31.7	2.6 ± 1.4	1.2 ± 1.3	627.5 ± 804.2	497.4 ± 596.2	7.1 ± 10.5	283.3 ± 270.8
	14	35.8 ± 43.7	2.0 ± 2.4	1.3 ± 2.3	1,083.4 ± 799.0	571.2 ± 394.4	4.3 ± 2.5	150.7 ± 104.2
	21	37.6 ± 31.5	1.9 ± 1.4	0.8 ± 0.5	680.7 ± 767.7	474.3 ± 484.5	5.4 ± 3.1	197.4 ± 145.0
Fluoride toothpaste	Baseline	55.3 ± 46.9	2.8 ± 1.7	0.9 ± 1.1	918.4 ± 772.3	445.6 ± 324.8	7.3 ± 8.0	449.9 ± 679.8
	3	68.7 ± 56.6	2.9 ± 2.2	0.6 ± 0.5	1,233.1 ± 1,284.0	853.7 ± 763.6	7.2 ± 3.4	292.8 ± 315.8
	7	43.5 ± 39.5	3.1 ± 3.4	2.6 ± 4.9	691.7 ± 1,014.7	565.1 ± 652.8	2.8 ± 1.8	278.7 ± 257.1
	14	40.0 ± 26.9	2.9 ± 3.1	1.3 ± 1.4	827.9 ± 954.5	524.2 ± 534.9	3.9 ± 1.7	319.1 ± 361.9
	21	34.4 ± 37.9	3.5 ± 3.5	1.8 ± 1.5[a]	1706.5 ± 1,474.2	1,089.8 ± 914.8	8.2 ± 8.7	257.4 ± 258.6

[a]Significant inter-group differences by the Wilcoxon ($p < 0.05$).

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

levels was reported until the 21st day ($p < 0.05$; Table 1), without any difference between groups at the end of experiment ($p > 0.05$; Table 1). Ata-Ali, Flichy-Fernandez, Ata-Ali, Penarrocha-Diago, and Penarrocha-Diago (2013) showed that bacterial plaque induces an inflammatory response that can lead to the development of peri-implant mucositis and although earlier clinical data have mentioned a cause-and-effect association between experimental mucositis induction and the establishment of peri-implant inflammation around implants (Pontoriero et al., 1994; Zitzmann, Berglundh, Marinello, & Lindhe, 2001), in the present study, peri-implant sites assigned to plaque accumulation did not show an significant increase in the BoP during period without mechanical toothbrushing, independent of fluoride toothpaste or triclosan/fluoride toothpaste treatments ($p > 0.05$; Table 1).

The absence of effective clinical evidence of inflammatory response in soft tissues around implants throughout the current study, regardless of plaque accumulation, could be related to the profile of population from this trial restricted to smokers. It is well known that products from tobacco oxidation may change clinical aspects related to both periodontal and peri-implant lesions causing local conditions as vasoconstriction (Kumar & Faizuddin, 2011; Peruzzo et al., 2016; Prakash et al., 2014). Previous researches reported that smoking habit promotes decreased clinical signs of gingivitis (Kumar & Faizuddin, 2011; Peruzzo et al., 2016). Taking into account the influence of smoking around clinical signs of inflammatory conditions, it could be hypothesized that some subclinical inflammation could be present, although not clinically detectable, in the implants of the current study from smokers.

This outcome concerning the clinical inflammatory evaluation of this trial may have masked the probable clinical anti-inflammatory efficacy of triclosan dentifrice in smoking individuals. In truth, previous studies have demonstrated the favorable value of triclosan/fluoride toothpaste in the decline of bleeding around both teeth and implants when compared to fluoride dentifrices in non-smokers (Al Habashneh, Farasin, & Khader, 2017; Ramberg et al., 2009; Sreenivasan et al., 2011). Interestingly, a recent study from our research group evaluating the impact of a triclosan-containing toothpaste during the progression of experimental peri-implant mucositis in non-smokers also revealed that peri-implant sites assigned to daily triclosan/copolymer dentifrice treatments did not show an increase in the BoP throughout the period of plaque accumulation, whereas a more evident, significant inflammatory reaction was perceived from the 14th day of mucositis in the fluoride toothpaste-treated sites (Ribeiro et al., 2018). In line with this, Ramberg et al.(2009) comparing the influence of triclosan versus fluoride toothpaste in non-smoking patients with mucositis—no experimental mucositis—demonstrated that BoP was diminished by triclosan use from 53.8% to 29.1%, whereas in the fluoride toothpaste group, there was an increase from 52.3% to 58.8% after 6 months. It is noteworthy that another clinical data that could be related to an eventual anti-inflammatory propriety of the triclosan toothpaste was that in the triclosan-treated sites there was not an increase in PD as observed in the fluoride toothpaste-treated sites (i.e., less swelling of the mucosa), although no significant difference has been detected ($p > 0.05$; Table 1).

Considering the promising anti-inflammatory role of triclosan around natural teeth and dental implants, it could be assumed that the encouraging anti-inflammatory clinical effects of triclosan have not been noticeably identified in the present study in a population of smoker individuals. Nevertheless, this is the first study to investigate the impact of a chemical protocol on the prevention of soft tissue lesions around implants with biofilm accumulation in the presence of smoking; supplementary trials are required to support the current findings.

Interestingly, additional molecular outcomes from this study suggest a possible anti-inflammatory potential of triclosan in controlling the immunoinflammatory response around implants in smokers, even in the presence of biofilm. The current investigation indicated a tendency toward up-regulation of IL-10 only in triclosan/fluoride toothpaste-managed implant sites throughout the experiment, especially on the 3rd day, although no increase in levels was identified at the end of mucositis induction ($p > 0.05$; Table 2). IL-10 is known to be an anti-inflammatory biomarker that is able to prevent pro-inflammatory mechanisms by inhibiting the production of cytokines such as IL-1, IL-2, IL-6, IL-8, TNF-α and IFN-γ (Pigossi et al., 2012; Scarel-Caminaga et al., 2004). In line, outcomes from a similar study performed in non-smokers (Ribeiro et al., 2018) demonstrated that IL-10 levels were higher on the 21st day in sites treated with triclosan/fluoride toothpaste compared to fluoride toothpaste-treated implant sites and that IL-10 concentrations were decreased in fluoride toothpaste-treated implant sites throughout the study when compared to baseline values, highlighting the hopeful impact of triclosan in modulating this anti-inflammatory biomarker.

When considering pro-inflammatory mediators, our results suggested a tendency toward amplification of IL-1β levels throughout the development of experimental peri-implant mucositis only in the fluoride toothpaste group with higher concentrations on the 21st day compared to baseline ($p > 0.05$; Table 2). IL-1β is involved with periodontal tissue breakdown and presents a key role in the advance of peri-implant lesions (Ataoglu et al., 2002; Petković et al., 2010). Earlier studies revealed augmented levels of IL-1 β in peri-implantitis (Aboyoussef, Carter, Jandinski, & Panagakos, 1998; Murata et al., 2002) and mucositis sites when compared with healthy control implants (Ataoglu et al., 2002; Ebersole & Taubman, 1994). In agreement, non-smokers also demonstrated an increase in the IL-1β levels during the development of experimental mucositis only in fluoride toothpaste-treated sites, showing higher concentrations on the 21st day when compared to baseline (Ribeiro et al., 2018).

Additional outcomes concerning pro-inflammatory mediators in the current trial showed a tendency toward reduction in IL-8 concentrations during the period without mechanical toothbrushing only in the triclosan/fluoride toothpaste group, with remarkable reduced values on the 14th day compared to baseline follow-up ($p > 0.05$; Table 1). The over-expression of IL-8, an important chemoattractant cytokine and activator of neutrophils in inflammatory conditions, was observed in both periodontal and peri-implant tissues affected

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

by inflammatory lesions compared to healthy ones (Finoti et al., 2017; Venza et al., 2010). In accordance with the outcomes from the present study showing the effectiveness of a triclosan dentifrice in modulating local mediators involved in peri-implant lesions, the encouraging properties of triclosan causing the inhibition of pro-inflammatory biomarker production, such as IFN-γ, IL-6, PGE2 and IL-1β, have also been reinforced by prior data (Barros et al., 2010; Mustafa, Bakhiet, Wondimu, & Modeer, 2000; Riley & Lamont, 2013), even though no evidence exists regarding the effect of triclosan on pro-inflammatory mediators in the local peri-implant fluid in a smoking population, as examined in this study.

Although mucositis around implants is defined by its restriction to inflammation of the soft tissues without marginal bone loss, the peri-implant analysis of osteoclastogenesis/blastogenesis-related factors in this investigation revealed that RANKL/OPG ratio was significantly higher in fluoride toothpaste-treated sites when compared to sites receiving triclosan following 21 days without mechanical toothbrushing ($p < 0.05$; Table 3).

In this study, the augmented levels of RANKL/OPG ratio observed in implant sites that did not receive triclosan dentifrice suggest the protective influence of this agent during the development of peri-implant mucositis, supporting a possible inhibition of the establishment of peri-implantitis. In line, data from our earlier investigation using the same design as this study, but performed in non-smokers, showed that OPG was significantly increased from the 14th until the 21st day compared to baseline and 7 days only in triclosan-treated implants (Ribeiro et al., 2018). Other molecules, such as bone morphogenetic protein (BMP)2 and BMP6, also identified as osteoclastogenesis inhibitory factor, were up-regulated by triclosan treatment (Barros et al., 2010), reinforcing the hypothesis that triclosan may interfere with the levels of specific osteo-inflammatory mediators. It is essential to emphasize that most of the pro- and anti-inflammatory biomarkers and bone-related factors investigated in this study were rarely assessed previously in the peri-implant fluid of smokers, creating a challenge to the comparison of outcomes.

Late implant failure is a result of the inability to maintain osseointegration, the most important cause of which is peri-implantitis (Charalampakis, Leonhardt, Rabe, & Dahlén, 2012). While the management of peri-implant mucositis is required for the prevention of peri-implantitis (Salvi & Zitzmann, 2014), avoidance of the establishment of mucositis needs to be the aim of clinicians, especially if it is considered that peri-implant tissues are most vulnerable to developing inflammatory responses when compared with gingival tissues (Salvi et al., 2012). Taking into account the hopeful effects provided by triclosan in terms of osteo-immunoinflammatory modulation around implants in smoking patients in this study, it would be suggested that triclosan toothpaste could provide benefits in inhibiting the onset of peri-implant mucositis in this patient profile, especially if has been considered that smoking increases the severity and prevalence of peri-implant lesions (Atieh et al., 2013; Heitz-Mayfield, 2008; Mombelli et al., 2012; Saaby et al., 2016). It is important to highlight that this study observed local molecular changes in the short term, so in future studies longer follow-ups would contribute to a better comprehension of the effect of triclosan toothpaste on the modulation of inflammatory and bone-related mediators around implants in smoking patients.

In conclusion, a triclosan-containing dentifrice may offer advantage in the local modulation of osteo-immunoinflammatory response around implants in smokers, reducing the levels of RANKL/OPG, which could represent a method to prevent peri-implant mucositis.

ACKNOWLEDGEMENTS

This study was supported by São Paulo Research Foundation (FAPESP), São Paulo, SP, Brazil—Processes 11/51037-6. The authors report no conflicts of interest related to this study.

REFERENCES

Aboyoussef, H., Carter, C., Jandinski, J. J., & Panagakos, F. S. (1998). Detection of prostaglandin E2 and matrix metalloproteinases in implant crevicular fluid. *The International Journal of Oral & Maxillofacial Implants*, *13*, 689–696.

Ainamo, J., & Bay, I. (1975). Problems and proposals for recording gingivitis and plaque. *International Dental Journal*, *25*, 229–235.

Al Habashneh, R., Farasin, R., & Khader, Y. (2017). The effect of a triclosan/copolymer/fluoride toothpaste on plaque formation, gingivitis, and dentin hypersensitivity: A single-blinded randomized clinical study. *Quintessence International*, *48*, 123–130. https://doi.org/10.3290/j.qi.a37384

American Academy of Periodontology (2013). Peri-implant mucositis and peri-implantitis: A current understanding of their diagnoses and clinical implications. *Journal of Periodontology*, *84*, 436–443. https://doi.org/10.1902/jop.2013.134001

Arora, M., Schwarz, E., Sivaneswaran, S., & Banks, E. (2010). Cigarette smoking and tooth loss in a cohort of older Australians: The 45 and Up Study. *Journal of the American Dental Association*, *141*, 1242–1249. https://doi.org/10.14219/jada.archive.2010.0052

Ata-Ali, J., Flichy-Fernandez, A. J., Ata-Ali, F., Penarrocha-Diago, M., & Penarrocha-Diago, M. (2013). Clinical, microbiologic, and host response characteristics in patients with peri-implant mucositis. *The International Journal of Oral & Maxillofacial Implants*, *28*, 883–890. https://doi.org/10.11607/jomi.2654

Ataoglu, H., Alpektin, N. O., Haliloglu, S., Gursel, M., Ataoglu, T., Serpek, B., & Durmus, E. (2002). Interleukin 1b, tumor necrosis factor a levels and neutrophil elastase activity in peri-implant crevicular fluid. *Clinical Oral Implants Research*, *13*, 470–476.

Atieh, M. A., Alsabeeha, N. H., Faggion, C. M. Jr, & Duncan, W. J. (2013). The frequency of peri-implant diseases: A systematic review and meta-analysis. *Journal of Periodontology*, *84*, 1586–1598. https://doi.org/10.1902/jop.2012.120592

Barros, S. P., Wirojchanasak, S., Barrow, D. A., Panagakos, F., Devizio, W., & Offenbacher, S. (2010). Triclosan inhibition of acute and chronic inflammatory gene pathways. *Journal of Clinical Periodontology*, *37*, 412–418. https://doi.org/10.1111/j.1600-051X.2010.01548.x

Charalampakis, G., Leonhardt, Å., Rabe, P., & Dahlén, G. (2012). Clinical and microbiological characteristics of peri-implantitis cases: A retrospective multicenter study. *Clinical Oral Implants Research*, *23*, 1045–1054. https://doi.org/10.1111/j.1600-0501.2011.02258.x

Costa, F. O., Takenaka-Martinez, S., Cota, L. O., Ferreira, S. D., Silva, G. L., & Costa, J. E. (2012). Peri-implant disease in subjects with and without preventive maintenance: A 5-year follow-up. *Journal of Clinical Periodontology*, *39*, 173–181. https://doi.org/10.1111/j.1600-051X.2011.01819.x

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Duarte, P. M., de Mendonça, A. C., Máximo, M. B., Santos, V. R., Bastos, M. F., & Nociti Júnior, F. H. (2009). Differential cytokine expressions affect the severity of peri-implant disease. *Clinical Oral Implants Research*, *20*, 514–520. https://doi.org/10.1111/j.1600-0501.2008.01680.x

Ebersole, J. L., & Taubman, M. A. (1994). The protective nature of host responses in periodontal disease. *Periodontology*, *2000*(5), 112–141.

Escribano, M., Figuero, E., Martín, C., Tobías, A., Serrano, J., Roldán, S., & Herrera, D. (2016). Efficacy of adjunctive anti-plaque chemical agents: A systematic review and network meta-analyses of the Turesky modification of the Quigley and Hein plaque index. *Journal of Clinical Periodontology*, *43*, 1059–1073. https://doi.org/10.1111/jcpe.12616

Finoti, L. S., Nepomuceno, R., Pigossi, S. C., Corbi, S. C., Secolin, R., & Scarel-Caminaga, R. M. (2017). Association between interleukin-8 levels and chronic periodontal disease: A PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)*, *96*, e6932. https://doi.org/10.1097/MD.0000000000006932

Hallström, H., Lindgren, S., Yucel-Lindberg, T., Dahlén, G., Renvert, S., & Twetman, S. (2013). Effect of probiotic lozenges on inflammatory reactions and oral biofilm during experimental gingivitis. *Acta Odontologica Scandinavica*, *71*, 828–833. https://doi.org/10.3109/00016357.2012.734406

Heitz-Mayfield, L. J. (2008). Peri-implant diseases: Diagnosis and risk indicators. *Journal of Clinical Periodontology*, *35*, 292–304. https://doi.org/10.1111/j.1600-051X.2008.01275.x

Heitz-Mayfield, L. J., & Mombelli, A. (2014). The therapy of peri-implantitis: A systematic review. *The International Journal of Oral & Maxillofacial Implants*, *29*(Suppl), 325–345. https://doi.org/10.11607/jomi.2014suppl.g5.3

Konemann, A., Götz, W., Le, M., Dirk, C., Lossdörfer, S., & Heinemann, F. (2016). Histopathological verification of osteoimmunological mediators in peri-implantitis and correlation to bone loss and implant functional period. *The Journal of Oral Implantology*, *42*, 61–68. https://doi.org/10.1563/aaid-joi-D-13-00355

Kumar, V., & Faizuddin, M. (2011). Effect of smoking on gingival microvasculature: A histological study. *Journal of Indian Society of Periodontology*, *15*, 344–348. https://doi.org/10.4103/0972-124X.92566

Mombelli, A., Müller, N., & Cionca, N. (2012). The epidemiology of peri-implantitis. *Clinical Oral Implants Research*, *23*, 67–76. https://doi.org/10.1111/j.1600-0501.2012.02541.x

Muhlemann, H. R., & Son, S. (1971). Gingival sulcus bleeding – A leading symptom in initial gingivitis. *Helvetica Odontologica Acta*, *15*, 107–113.

Murata, M., Tatsumi, J., Kato, Y., Suda, S., Nunokawa, Y., Kobayashi, Y., … Yoshie, H. (2002). Osteocalcin, deoxypyridinoline and interleukin-1beta in peri-implant crevicular fluid of patients with peri-implantitis. *Clinical Oral Implants Research*, *13*, 637–643. https://doi.org/10.1034/j.1600-0501.2002.130610.x

Mustafa, M., Bakhiet, M., Wondimu, B., & Modeer, T. (2000). Effect of triclosan on interferon-gamma production and major histocompatibility complex class II expression in human gingival fibroblasts. *Journal of Clinical Periodontology*, *27*, 733–737. https://doi.org/10.1034/j.1600-051x.2000.027010733.x

Negri, B. M., Pimentel, S. P., Casati, M. Z., Cirano, F. R., Casarin, R. C., & Ribeiro, F. V. (2016). Impact of a chronic smoking habit on the osteoimmunoinflammatory mediators in the peri-implant fluid of clinically healthy dental implants. *Archives of Oral Biology*, *70*, 55–61. https://doi.org/10.1016/j.archoralbio.2016.05.014

Papathanasiou, E., Finkelman, M., Hanley, J., & Parashis, A. O. (2016). Prevalence, etiology and treatment of peri-implant mucositis and peri-implantitis: A survey of periodontists in the United States. *Journal of Periodontology*, *87*, 493–501. https://doi.org/10.1902/jop.2015.150476

Pera, C., Ueda, P., Casarin, R. C., Ribeiro, F. V., Pimentel, S. P., Casati, M. Z., & Cirano, F. R. (2012). Double-masked randomized clinical trial evaluating the effect of a triclosan/copolymer dentifrice on periodontal healing after one-stage full-mouth debridement. *Journal of Periodontology*, *83*, 909–916. https://doi.org/10.1902/jop.2011.110348

Peruzzo, D. C., Gimenes, J. H., Taiete, T., Casarin, R. C., Feres, M., Sallum, E. A., … Nociti, F. H. Jr (2016). Impact of smoking on experimental gingivitis. A clinical, microbiological and immunological prospective study. *Journal of Periodontal Research*, *51*, 800–811. https://doi.org/10.1111/jre.12363

Petković, A. B., Matić, S. M., Stamatović, N. V., Vojvodić, D. V., Todorović, T. M., Lazić, Z. R., & Kozomara, R. J. (2010). Proinflammatory cytokines (IL-1beta and TNF-alpha) and chemokines (IL-8 and MIP-1alpha) as markers of peri-implant tissue condition. *The International Journal of Oral & Maxillofacial Surgery*, *39*, 478–485. https://doi.org/10.1016/j.ijom.2010.01.014

Pigossi, S. C., Alvim-Pereira, F., Montes, C. C., Finoti, L. S., Secolin, R., Trevilatto, P. C., & Scarel-Caminaga, R. M. (2012). Genetic association study between Interleukin 10 gene and dental implant loss. *Archives of Oral Biology*, *57*, 1256–1263. https://doi.org/10.1016/j.archoralbio.2012.02.020

Pontoriero, R., Tonelli, M. P., Carnevale, G., Mombelli, A., Nyman, S. R., & Lang, N. P. (1994). Experimentally induced peri-implant mucositis. A clinical study in humans. *Clinical Oral Implants Research*, *5*, 254–259. https://doi.org/10.1034/j.1600-0501.1994.050409.x

Prakash, P., Rath, S., Mukherjee, M., Malik, A., Boruah, D., Sahoo, N. K., & Dutta, V. (2014). Comparative evaluation of the marginal gingival epithelium in smokers and nonsmokers: A histomorphometric and immunohistochemical study. *The International Journal of Periodontics & Restorative Dentistry*, *34*, 781–786. https://doi.org/10.11607/prd.1823

Ramberg, P., Lindhe, J., Botticelli, D., & Botticelli, A. (2009). The effect of a triclosan dentifrice on mucositis in subjects with dental implants: A six-month clinical study. *The Journal of Clinical Dentistry*, *20*, 103–107.

Ribeiro, F. V., Casati, M. Z., Casarin, R. C., Corrêa, M. G., Cirano, F. R., Negri, B. M., & Pimentel, S. P. (2018). Impact of a triclosan-containing toothpaste during the progression of experimental peri-implant mucositis: Clinical parameters and local pattern of osteo-immunoinflammatory mediators in peri-implant fluid. *Journal of Periodontology*, *89*, 203–212. https://doi.org/10.1002/JPER.17-0302

Riley, P., & Lamont, T. (2013). Triclosan/copolymer containing toothpastes for oral health. *The Cochrane Database Systematic Reviews*, *5*, CD010514. https://doi.org/10.1002/14651858.CD010514.pub2

Rosling, B., Wannfors, B., Volpe, A. R., Furuichi, Y., Ramberg, P., & Lindhe, J. (1997). The use of a triclosan/copolymer dentifrice may retard the progression of periodontitis. *Journal of Clinical Periodontology*, *24*, 873–880. https://doi.org/10.1111/j.1600-051X.1997.tb01205.x

Ryder, M. I. (2007). The influence of smoking on host responses in periodontal infections. *Periodontology*, *2000*(43), 267–277. https://doi.org/10.1111/j.1600-0757.2006.00163.x

Saaby, M., Karring, E., Schou, S., & Isidor, F. (2016). Factors influencing severity of peri-implantitis. *Clinical Oral Implants Research*, *27*, 7–12. https://doi.org/10.1111/clr.12505

Salvi, G. E., Aglietta, M., Eick, S., Sculean, A., Lang, N. P., & Ramseier, C. A. (2012). Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. *Clinical. Oral Implants Research*, *23*, 182–190. https://doi.org/10.1111/j.1600-0501.2011.02220.x

Salvi, G. E., & Zitzmann, N. U. (2014). The effects of anti-infective preventive measures on the occurrence of biologic implant complications and implant loss: A systematic review. *The International Journal of Oral & Maxillofacial Implants*, *29*, 292–307. https://doi.org/10.11607/jomi.2014suppl.g5.1

Sarmento, H. R., Leite, F. R., Dantas, R. V., Ogliari, F. A., Demarco, F. F., & Faot, F. (2014). A double-blind randomized clinical trial of two techniques for gingival displacement. *Journal of Oral Rehabilitation*, *41*, 306–313. https://doi.org/10.1111/joor.12142

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Scarel-Caminaga, R. M., Trevilatto, P. C., Souza, A. P., Brito, R. B., Camargo, L. E., & Line, S. R. (2004). Interleukin 10 gene promoter polymorphisms are associated with chronic periodontitis. *Journal of Clinical Periodontology*, *31*, 443–448. https://doi.org/10.1111/j.1600-051X.2004.00500.x

Seymour, G. J., Palmer, J. E., Leishman, S. J., Do, H. L., Westerman, B., Carle, A. D., … Cullinan, M. P. (2017). Influence of a triclosan toothpaste on periodontopathic bacteria and periodontitis progression in cardiovascular patients: A randomized controlled trial. *Journal of Periodontal Research*, *52*, 61–73. https://doi.org/10.1111/jre.12369

Sreenivasan, P. K., Vered, Y., Zini, A., Mann, J., Kolog, H., Steinberg, D., … De Vizio, W. (2011). A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. *Journal of Clinical Periodontology*, *38*, 33–42. https://doi.org/10.1111/j.1600-051X.2010.01617.x

Turri, A., Rossetti, P. H., Canullo, L., Grusovin, M. G., & Dahlin, C. (2016). Prevalence of peri-implantitis in medically compromised patients and smokers: A systematic review. *The International Journal of Oral & Maxillofacial Implants*, *31*, 111–118. https://doi.org/10.11607/jomi.4149

Venza, I., Visalli, M., Cucinotta, M., De Grazia, G., Teti, D., & Venza, M. (2010). Proinflammatory gene expression at chronic periodontitis and peri-implantitis sites in patients with or without type 2 diabetes. *Journal of Periodontology*, *81*, 99–108. https://doi.org/10.1902/jop.2009.090358

Zitzmann, N. U., Berglundh, T., Marinello, C. P., & Lindhe, J. (2001). Experimental peri-implant mucositis in man. *Journal of Clinical Periodontology*, *28*, 517–523. https://doi.org/10.1034/j.1600-051x.2001.028006517.x

SUPPORTING INFORMATION

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

How to cite this article: Peres Pimentel S, Vieira Ribeiro F, Correa Casarin R, et al. Triclosan-containing fluoride toothpaste on clinical parameters and osteo-inflammatory mediators when applied in a stent during experimental peri-implant mucositis in smokers. *Clin Oral Impl Res*. 2019;30:187–195. https://doi.org/10.1111/clr.13405

16000501, 2019, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/clr.13405 by UNIP - Universidade Paulista, Wiley Online Library on [13/06/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License