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Antimicrobial photodynamic therapy as an alternative to systemic antibiotics: results from a double-blind, randomized, placebo-controlled, clinical study on type 2 diabetics

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Abstract

Aim: This double-blind, placebo-controlled clinical study compared multiple applications of the antimicrobial photodynamic therapy (aPDT) treatment protocol, to systemic doxycycline as adjuvant to scaling and root planing (SRP) on type 2 diabetic patients on clinical, systemic and immune-inflammatory outcomes.

Materials and Methods: Thirty patients with Hba1c >7% were allocated in two groups, SRP + Doxy (n = 15) using systemic doxycycline 100 mg/day (14 days) and SRP + aPDT (n = 15) with multiple applications (0, 3, 7 and 14 days). Primary outcome was glycated haemoglobin levels (HbA1c). Clinical parameters: plaque score (PS), bleeding on probe, probing depth, suppuration, gingival recession, and clinical attachment level, percentage of pockets with desired clinical endpoint were measured at baseline and 3 months after therapy. Cytokine profile was assessed at 0, 1 and 3 month to measure IL1-β, TNF-α and TGF-β on gingival crevicular fluid.

Results: No significant difference was detected on HbA1c, between treatments. The SRP + aPDT group showed advantage on reducing moderate pockets in single-rooted teeth at 3 months. SRP + aPDT presented better results at 3 months on IL1-β levels. There were no significant differences between TNF-α and TGF-β.

Conclusions: Both treatments improved clinical and systemic outcomes (Hba1c). SRP + aPDT performed better in moderate probing pocket depth on single-rooted teeth, reduced favourably inflammation in short term, and may be an alternative to systemic antibiotics. (Clinicaltrials.org ID NCT01595594).

Key words: antimicrobial photodynamic therapy; doxycycline; glycated haemoglobin A; interleukin-1; type 2 diabetes mellitus

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Conflict of interest and sources of funding statement

The authors declare that there are no conflicts of interest in this study.

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Periodontitis is a polymicrobial inflamatory disease of the gingiva and the adjacent attachment apparatus. It is characterized by loss of clinical attachment due to the destruction of the periodontal ligament and of adjacent supporting bone. Diabetic patients are more susceptible to periodontal disease and have a faster progression, especially, those with poor glycaemic control (HbA1c > 7%) (Bandyopadhyay et al. 2010, Mealey 2006, Mealey & Oates 2006).

Diabetes Mellitus (DM) is characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Based on this, it can be classified in Type I, characterized by the lack of insulin production due to the destruction of β pancreatic cells, or Type II, characterized by insulin resistance due to defect on insulin molecule or on cell receptors.

The hyperglycaemic condition is associated with high plasmatic levels of TNF-α (Engebretson et al. 2007), and has a positive correlation with high levels of IL1-β in gingival crevicular fluid (GCF) of diabetic patients (Correa et al. 2008, Wolff et al. 2009, Engebretson et al. 2002).

Poorly controlled type 2 diabetic patients, shows improvement on glycaemic levels after non-surgical periodontal treatment (Chapple & Genco 2013), especially, when associated with systemic doxycycline (Al-Zahrani et al. 2009, O'Connell et al. 2008). However, the therapy with systemic antimicrobials may present adverse effects such as gastrointestinal disturbance, allergies, headaches, and dizziness. In addition, the recurrent use of antibiotics may lead to bacterial resistance and possible complications in future infections (Levy & Marshall 2004).

Local antibiotics have been proposed as adjunct to scaling and root planing on periodontal treatment of type 2 diabetic patients (Iwamoto et al. 2001). This method can be technically difficult to apply in cases with multiple deep pockets (Greenstein 2006). To overcome those problems, antimicrobial photodynamic therapy (aPDT) has been proposed as adjunctive to mechanical therapy due to its ability to inactivate periodontal pathogens (Packer et al. 2000, Komerik & MacRobert 2006).

Previous studies compared aPDT and scaling and root planing (SRP), finding clinical and immunological similarities between therapies, when treating aggressive periodontitis (de Oliveira et al. 2007, 2009). The use of a single episode of aPDT presented divergent results on treating chronic periodontitis. Some authors achieved better clinical outcomes in favour of aPDT (Braun et al. 2008). Others only presented differences on bleeding on probing (Chondros et al. 2009, Christodoulides et al. 2008). When used in single application of aPDT associated with doxycycline, there were advantages on reducing Hba1c levels (Macedo Gde et al. 2014). More recently, with the use of multiple applications, better results were achieved (Lulic et al. 2009, Moreira et al. 2015).

The aim of this double-blind randomized placebo-controlled clinical trial was to compare, clinically and immunologically, a protocol of multiple aPDT applications and the use of systemic doxycycline as adjuvant to SRP on the treatment of uncontrolled type 2 diabetic patients.

The hypothesis of this study was that antimicrobial photodynamic therapy would improve the glyceamic control and clinical periodontal parameters with the same effectiveness of a systemic antibiotics protocol previously described (O'Connell et al. 2008).

Material and Methods

Experimental population and study design

This study was designed to compare two treatment protocols for treatment of periodontal disease on uncontrolled type 2 diabetic patients. The study protocol was conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subjects, after the approval of the Institution's Human Research Committee (protocol 2010.1.157.58.0).

Two thousand medical records were reviewed between 2010 and 2012 to select 150 patients aged 40 to 76 with HbA1c >7% and, 32 patients followed the inclusion criteria: type 2 DM diagnosed for >5 years and HbA1c >7%, at least one site with probing depth (PD) ≥5 mm on each quadrant and two teeth with attachment loss ≥6 mm. Exclusion criteria were: use of antibiotics or periodontal treatment in previous 6 months, smoking within the past 5 years, pregnancy or lactation, major diabetic complications, and concomitant medical therapy or others systemic complications. The selected patients had a minimum of 15 teeth, after extraction of hopeless teeth (Fig. 1).

Thirty-two patients were eligible to participate and provided informed consent after explanation of all risks and benefits involved in the procedures, two patients did not accepted all terms and received periodontal treatment at the University of São Paulo. A total of 30 patients were enrolled and randomized at the study. The patients were assigned in two groups: SRP + aPDT (applications on 0, 3, 7, and 14 days post-therapy with a placebo capsule) and SRP + Doxy (systemic doxycycline 100 mg/day for 14 days with a first dose of 200 mg and the same protocol used on SRP + aPDT group, without light exposure).

The same operator, UDR, performed the SRP within 24 hours, using hand instruments and an ultrasonic device. The aPDT was applied (Fig. 2) on every tooth with probing pocket depth (PPD) >4 mm, furcation was considered as two single-rooted teeth.

A phenothiazine chloride solution 10 mg/ml (Helbo Blue®, Bredent Medical GmbH & Co, Germany) irrigating the pockets with PPD>3 mm apico-coronally, 5 min. of pre-irradiation time (Qin et al. 2008a,b), followed by irrigation with saline solution (approximately, 1 ml per tooth), and irradiation with a red laser (HELBO® *TheraLite Laser,* Bredent Medical GmbH & Co, Germany) for 10 s at each site (70 mW of power, and a power density of 28mW/cm²), with an optic fibre angulated 60°, 0.06 mm diameter, 8 mm length, delivering a total energy of 2.79J/cm² per site (16.72 J/cm² per tooth). Patients from both groups received dental prophylaxis monthly until the third month.

Sample size estimation

The sample size was estimated based on a previous study that considered HbA1c levels as the primary outcome

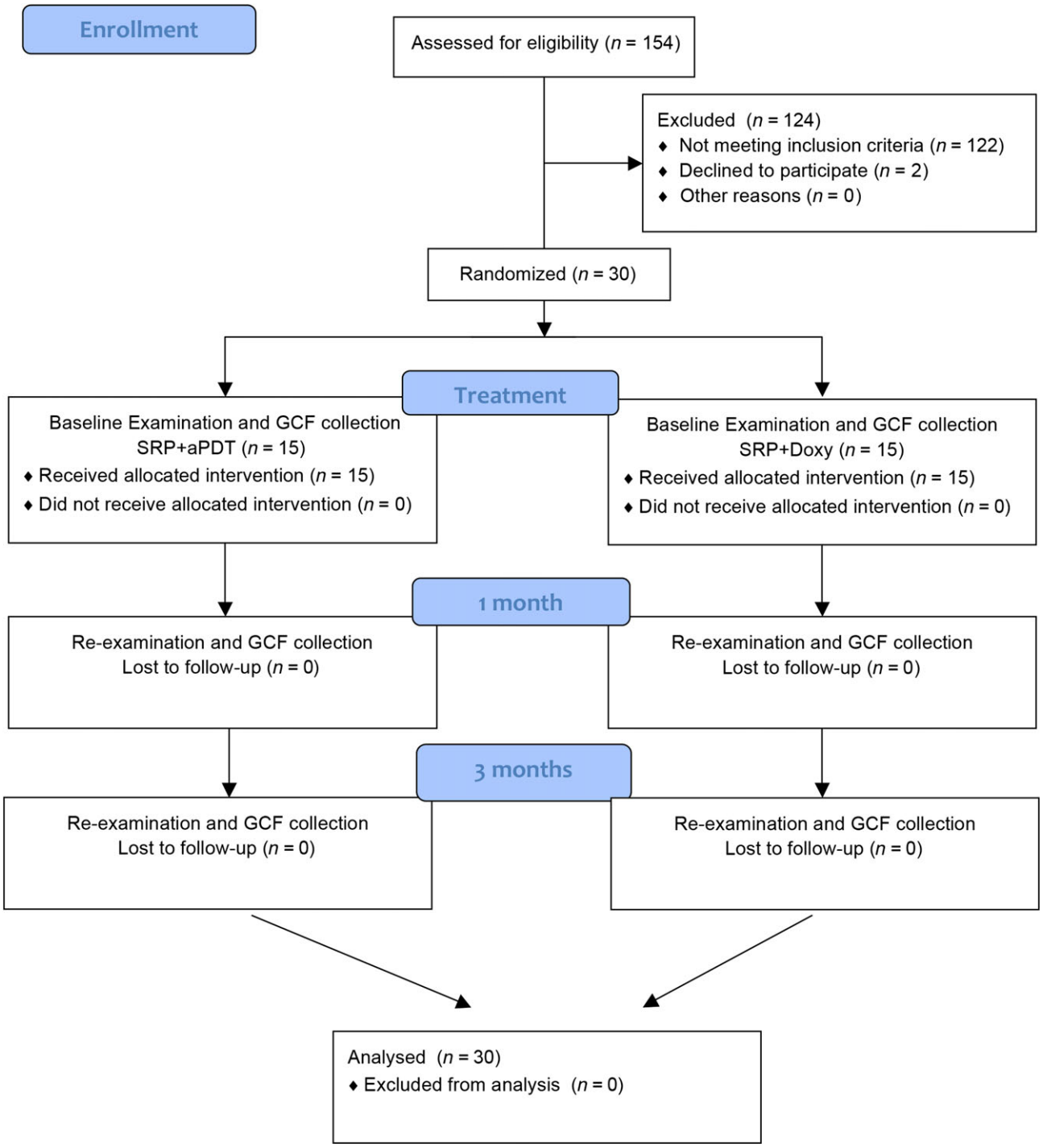

Fig. 1. CONSORT Flow Diagram.

measurement. A sample size of 12 patients/group (26 total), at a power of 80%, to detect differences in 1% at HbA1c $p < 0.05$ in a population with the same characteristics (Al-Zahrani et al. 2009) . A risk of 20% of drop out was estimated, thus, a final sample of 15 patients per group was considered the ideal.

Randomization procedure

Randomization procedure was performed by a single examiner, using a software program (SPSS Inc., Chicago, IL USA) by a computer-generated randomly permuted by (D.M.R). Allocation was performed by A.B.N and was concealed with opaque envelopes. After the SRP was finished, the operator (UDR) was allowed to open the envelopes to perform sham procedure (no light exposure) or aPDT procedure.

The randomization process resulted in comparable mean values of all investigated clinical parameters at baseline in both groups (Table 1).

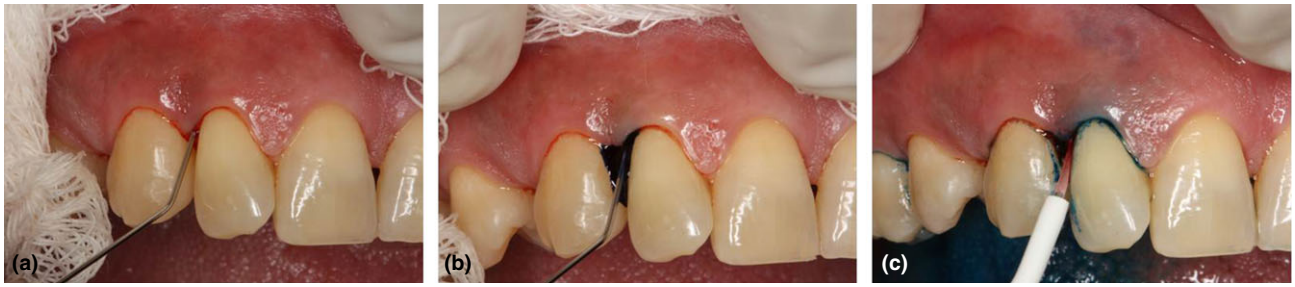

Fig. 2. Application of antimicrobial photodynamic therapy. (a) Aspect after Scaling Root Planing; (b) Application of photosensitizer; (c) Light activation after 5 min. of Pre-irradiation time and saline irrigation.

Table 1. Mean PPD (probing pocket depth), CAL (clinical attachment level), REC (Gingival recession), BoP (bleeding on probing), HbA1 (glycated haemoglobin), and ΔCAL (changes on CAL), ΔPPD (changes on PPD), ΔHbA1c (Changes on HbA1c, in proportion), at different times

	SRP + Doxy			SRP + aPDT		
	Baseline	3 months	*p* value	Baseline	3 months	*p* value
PPD (mm)	4.86 ± 1.39	2.88 ± 0.45	$p < 0.05$	4.89 ± 0.68	3.47 ± 0.58	$p < 0.05$
REC (mm)	1.04 ± 0.72	1.21 ± 0.64	NS	0.72 ± 0.50	1.36 ± 0.82	
CAL (mm)	5.53 ± 0.86	3.87 ± 0.52	$p < 0.05$	5.60 ± 0.68	3.90 ± 0.52	$p < 0.05$
BoP (%)	23.53 ± 9.33	13.47 ± 4.62	NS	28.13 ± 7.79	11.50 ± 5.41	$p < 0.05$
HbA1c (%)	9.69 ± 1.68	8.93 ± 1.37	$p < 0.02$	10.6 ± 1.99	9.61 ± 1.56	$p < 0.02$
ΔHbA1c (%)	–	0.76 ± 0.73		–	0.99 ± 1.00	NS
ΔCAL (mm)		1.66 ± 0.90			1.69 ± 0.94	NS
ΔPPD (mm)		1.98 ± 0.77			1.42 ± 0.88	NS

Clinical parameters and gingival crevicular fluid collection (GCF)

Each patient contributed with four samples from different sites that. GCF was collected from the deepest periodontal pocket from the maxillary anterior area of each quadrant (Bozkurt et al. 2006). Teeth were air-dried and isolated with cotton rolls. Supragingival plaque was gently removed, and GCF was sampled with a pre-cut methylcellulose filter paper strips for 30 s (de Oliveira et al. 2009). The absorbed GCF volume of each strip was determined by an electronic gingival fluid measuring device (Periotron 8000® Oralflow, NY, USA), and converted to an actual volume (microliters) by reference to the standard curve. Samples of each patient were pooled and transferred to Eppendorf tubes isolated with parafilm and stored at −80°C.

The amount of cytokines was measured according to the manufacturer instruction by Multiplex Immunoassay (Luminex Corporation, Austin, TX, USA), using a commercially available kit (Milliplex MAG®, Billerica, MA, USA). Concentration was determined in each GCF pooled sample by dividing the total amount of cytokine by the volume of the sample. The results were expressed as picograms of cytokine per microliter of GCF, from duplicate measurements (de Oliveira et al. 2009).

A computerized periodontal probe (Florida Probe Corporation, Gainsville, FL, USA) was used to perform the periodontal measurements, six sites per tooth, at baseline, at 1 and 3 months post-treatment. The recorded parameters were: PPD, clinical attachment level (CAL), bleeding on probing (BOP), suppuration (SUP), with an acetate guide. Dichotomic plaque index (PI) was measured four sites per tooth. All measure were performed by the same examiner(LGA).

Peripheral blood samples were analysed for HbA1c by the same laboratory (O'Connell et al. 2008). HbA1c was expressed as a percentage, and it was measured by high-pressure liquid chromatography (Labtest Sistemas para Diagnóstico, Lagoa Santa, MG, Brazil.).

Statistical analysis

Data were analysed using statistical software (SPSS Inc.). The primary outcome measures were differences between the groups for changes in HbA1c. Secondary outcome measures included, CAL, PPD, REC, percentage of positive clinical endpoint (pockets with final PPD <4 mm), percentage of pockets with reductions of 2 mm or more on PPD, and GCF levels of IL1-β, TGF-β and TNF-α.

The Lilliefors normality test was applied for all variables studied and the results showed necessity of non-parametric tests. The intergroup analysis for bleeding on probing, plaque index, and desired clinical endpoint (pockets that reached 3 mm PPD, or less, after treatment) was performed with the Friedman test. Mann–Whitney test was used for intergroup analysis of stratified periodontal pockets, reductions above 2 mm, clinical attachment level and gingival recessions. On inter- and intragroup cytokine analysis used Mann–Whitney and Kruskal–Wallis tests were used respectively.

Results

No adverse effects or discomfort were reported by any of the subjects, and both treatments were well tolerated. The final enrolled sample consisted of 30 subjects equally distributed between both groups, with poorly controlled diabetes and a mean HbA1c serum level of 9.69% ± 1.68 (SRP + Doxy) and 10.6% ± 1.99 (SRP + aPDT), respectively, without significant differences between groups (Table 1). Patients presented similar medication prescription towards diabetes treatment, usually presenting glibenclamide or metformin, most of them were using regular insulin at already adjusted dose, and the doses were not changed during experimental period. There was no difference in gender distribution (Table 2). The age ranged between 40 and 70 years old, and did not achieve significant difference between groups (Table 2).

Intragroup comparison showed significant reductions of HbA1c levels between baseline and 3 months in both groups ($p < 0.02$) (Table 1). Mean reductions achieved by treatments were 0.76 ± 0.73 (7.8% in proportion) for SRP + Doxy group, and 0.99 ± 1.00 (9.3% in proportion) for SRP + aPDT. Nevertheless, there was no significant difference between groups regarding the Hb1c reductions (ΔHbA1c).

Both treatments achieved significant reductions on probing pocket depth, clinical attachment level, and gingival recession ($p < 0.05$), with no difference between groups. The percentage of desired clinical endpoints on multirooted teeth did not shown significant differences between groups (Table 3). There were significant differences between groups favouring SRP + aPDT at 3 months post-SRP (SRP + aPDT = 78.38 ± 27.03; SRP + Doxy = 47.53 ± 27.40, $p < 0.01$) on single-rooted teeth (Table 3). Reductions of 2 mm on PPD on multirooted teeth were not significant (Table 4). In moderate pockets, there was significant difference favouring SRP + aPDT at 3 months (SRP + Doxy = 59.00 ± 26.27; SRP + aPDT = 80.25 ± 23.82, $p < 0.01$).

Table 2. Demographic data

Groups	Age	Female	Male
SRP + aPDT	48.9 ± 9.5	8	7
SRP + Doxy	49.3 ± 7.4	8	7

Table 3. Desired clinical endpoint (% of pockets with PPD of 3 mm or less, after treatment). There were only included sites with initial PPD ≤ 3 mm

Initial PPD	SRP + Doxy	SRP + aPDT	*p* value
Single-rooted			
4 mm			
3 months	75.13 ± 25.23	81.20 ± 17.52	NS
5 to 6 mm			
3 months	47.53 ± 27.40	78.38 ± 27.03	$p < 0.01$
≥7 mm			
3 months	35.90 ± 33.16	14.50 ± 17.40	NS
Multirooted			
4 mm			
3 months	72.98 ± 21.61	84.75 ± 25.12	NS
5 to 6 mm			
3 months	59.69 ± 31.20	74.38 ± 28.45	NS
≥7 mm			
3 months	64.29 ± 35.71	49.29 ± 37.01	NS

PPD, probing pocket depth; aPDT, Antimicrobial Photodynamic Therapy; SRP, scaling and root planing.

Table 4. Percentage of pockets with significant reduction (≥2 mm) after treatment.

Initial PPD	SRP + Doxy	SRP + aPDT	*p* value
Single-rooted			
4 mm			
3 months	37.07 ± 28.88	41.29 ± 26.63	NS
5 to 6 mm			
3 months	59.00 ± 26.27	80.25 ± 23.82	$p < 0.01$
≥7 mm			
3 months	54.70 ± 43.76	71.80 ± 43.90	NS
Multirooted			
4 mm			
3 months	24.54 ± 24.27	25.58 ± 27.94	NS
5 to 6 mm			
3 months	60.80 ± 24.69	59.38 ± 35.59	NS
≥7 mm			
3 months	68.75 ± 39.06	74.11 ± 28.77	NS

PPD, probing pocket depth; aPDT, Antimicrobial Photodynamic Therapy; SRP, SRP, scaling and root planing.

The results regarding cytokine profile can be seen on Fig. 3. Baseline levels were not significant between groups (TNF- α: SRP + aPDT = 0.65 ± 0.53 pg/ml; SRP + Doxy = 0.49 ± 0.28 pg/ml; IL-1ß SRP + aPDT = 22.66 ± 11.38 pg/ml SRP + Doxy = 22.72 ± 16.56 pg/ml; TGF-ß: SRP + aPDT = 0.93 ± 0.53 pg/ml SRP + Doxy = 0.87 ± 0.35 pg/ml). Although a tendency for increased levels was detected on SRP + Doxy, while SRP + aPDT showed decreased values at 3 months post-treatment, TNF-α failed to present significant differences between groups (Fig. 3). TGF-ß showed a decreasing tendency in the first month and an increase that reached baseline levels in both groups in the third month post-treatment; there were no intergroup significant differences. Regarding IL1-ß, there were no significant differences at baseline levels. At 1 month post-treatment, the levels were lower in the systemic antibiotic group (SRP + Doxy = 5.40 ± 4.94 pg/ml; SRP + aPDT = 13.4 ± 6.0 pg/ml), but without significant differences. At 3 months, the levels were significant favouring SRP + aPDT (SRP + Doxy = 48.06 ± 20.58 pg/ml; SRP + aPDT = 24.23 ± 13.63 pg/ml).

Discussion

The effect of periodontal treatment on HbA1c reduction has been extensively reported on the literature

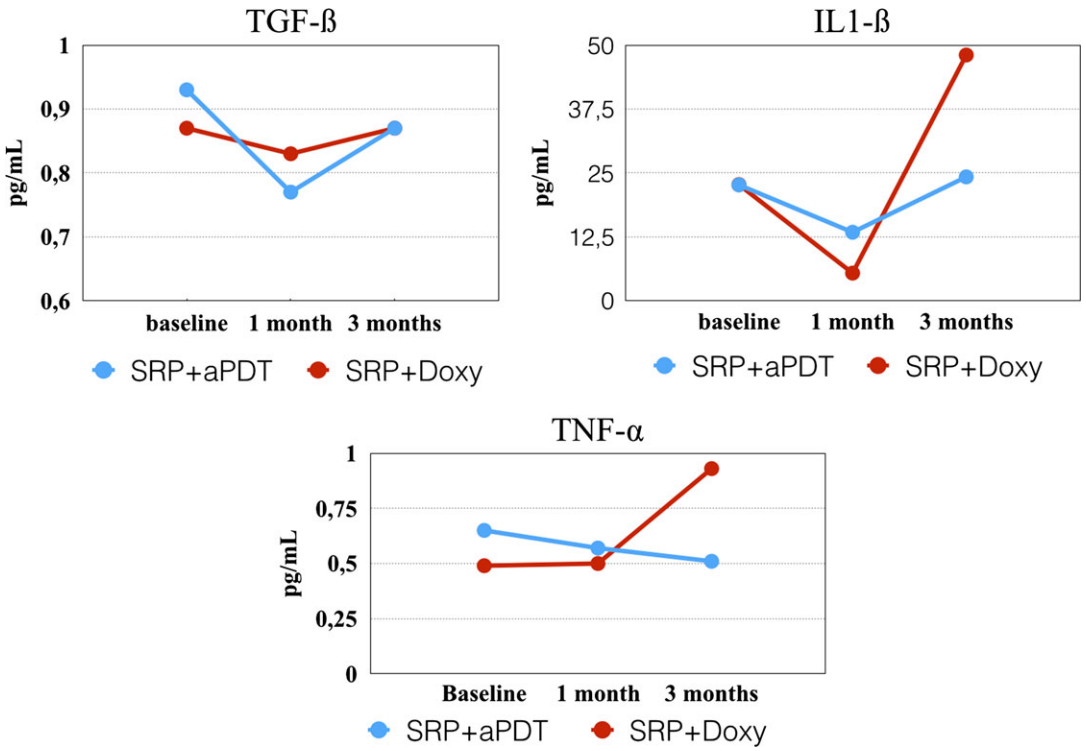

Fig. 3. Cytokine Levels. *$p < 0.005$.

(Chapple & Genco 2013) (Koromantzos et al. 2011, Janket et al. 2005) and has been associated with the reduction in total inflamed areas (Nesse et al. 2009). When the reduction reaches 10% of initial levels, it is considered as clinically relevant (Janket et al. 2005).

Our data presented reductions below the clinically relevant, although SRP + aPDT group reached 9.3% of mean reduction. Both treatments reached higher reduction than is achieved with physical exercises (0.66% of HbA1c reductions) according to ADA (American Diabetes 2009) as can be seen at Table 1.

The use of systemic doxycycline presented different mean reductions compared to previous publications (Al-Zahrani et al. 2009, O'Connell et al. 2008). O'Connell et al. (2008) reached higher reductions, while Al-Zahrani et al. (2009) achieved lower reductions. These differences seem to be related to HbA1c baseline levels: 8.42% (Al-Zahrani et al. 2009), 8% (Macedo Gde et al. 2014), 11.7% (O'Connell et al. 2008), and 9.7% on this study.

Clinical results (PPD, CAL, REC, BoP) demonstrated similarity between the proposed treatment protocols. However, it is important to highlight the increasing worry with systemic antibiotic administration and bacterial resistance and it is referred as a public health issue (Levy & Marshall 2004). This similarity of a local and systemic therapy would be desirable in order to avoid use of common antibiotics. In addition, patients did not report discomfort after treatment with aPDT, and no case of fever or any systemic reaction after treatment was reported.

The achievement of desirable clinical endpoint was significantly better, in single-rooted teeth sites with moderate PPD, on the SRP + aPDT group. Thus, suggesting that in this particular group of teeth, the use of aPDT would avoid additional treatment, such as periodontal surgery (Moreira et al. 2015), especially in areas of aesthetic importance, in patients that have impaired healing capacity. Deep pockets did not presented good results as moderate, despite the tendency to better result favouring SRP + aPDT (Table 3). Previous studies did not analysed desirable clinical endpoint, most of them focused on initial and final number of sites with moderate and deep pockets (Navarro-Sanchez et al. 2007, O'Connell et al. 2008). The overall results from previous studies achieved a reduction on full mouth PPD of 1.1 mm (Correa et al. 2008) and 0.8 mm (O'Connell et al. 2008). Our study showed greater mean PPD reduction of 1.98 mm (SRP + Doxy) and 1.42 mm (SRP + aPDT), but also greater baseline PPD (SRP + Doxy = 4.86 mm; SRP + aPDT = 4.89 mm) then, previous studies 2.9 mm(O'Connell et al. 2008), 3.8 mm (Correa et al. 2008).

Other studies have used aPDT as adjuvant to scaling and root planing to treat chronic periodontitis with conflicting results. Most of them showed BoP differences favouring aPDT (Chondros et al. 2009, Christodoulides et al. 2008). Only one study has shown better results on all parameters (Braun et al. 2008). One study failed to provide differences in all clinical parameters (Polansky et al. 2009). Significant results were found on reduction in HbA1c levels, when associated with systemic doxycycline (Macedo Gde et al. 2014).

The aforementioned studies had used the same photosensitizer of our study (phenothiazine chloride 10

mg/ml). The protocols consisted on irrigation of the pocket and a pre-irradiation time ranging from 1 to 3 min., followed by irrigation with saline solution or hydrogen peroxide, and red laser irradiation of 10 s per site. On our study, a pre-irradiation time of 5 min. was used in accordance to a previous publication that considered it the optimal pre-irradiation time (Qin et al. 2008a).

A previous study compared SRP, aPDT in a single application as adjuvant to SRP and SRP combined with systemic doxycycline to treat periodontal disease on type 2 diabetic patients, with different results. However, a different photosensitizer concentration and light dose was used. (Al-Zahrani et al. 2009). A possible explanation for the difference is the use of multiple applications respecting the same period of systemic antibiotics and a higher concentration of photosensitizer, used on this study (Komerik et al. 2003).

A protocol of multiple aPDT applications adjunctive to SRP showed better results then SRP alone (Lulic et al. 2009) and in aggressive periodontitis treatment (Moreira et al. 2015). This could explain the difference between this study and previous studies (Al-Zahrani et al. 2009, Chondros et al. 2009, Christodoulides et al. 2008, Polansky et al. 2009). It is known that aPDT has a dose-dependent effect, and presence of blood and high protein concentration may jeopardize its action (Meisel & Kocher 2005). There are two hypothesis that may explain those differences and should be tested on future research, one states that the additional effect of multiple applications occurs due to the dose dependency of the therapy, and other states that this effect is due to the applications after the reduction of inflammation and bleeding (post-SRP).

The high levels of IL1-β on baseline were in accordance to previous studies (Engebretson et al. 2002). The capacity to inhibit matrix metalloproteinase, acting like a response modulator (Golub et al. 1995) may have reduced 1 month levels favouring SRP + Doxy group. The time lag between the last systemic doxycycline and the second GCF collection (14 days) may be the explanation for such reduction.

At 3 months, the effects achieved at 1 month were not maintained on the SRP + Doxy group. The GCF levels of IL1-β substantially increased until it reached a twofold increase when compared to the baseline level, probably presenting an inflammatory exacerbation. High levels of IL1-β are associated with disease progression (Yoon et al. 2012), this data can be a sign of periodontal instability, at least on the sites of GCF collection. For further confirmations, a study specifically designed to answer this question would be valuable. On the aPDT group, there was an increase in IL1-β on GCF, but in minor proportions, without significant differences from baseline levels. The increase of IL1-β concentration in GCF is in accordance to previous studies when antibiotics were not used (Correa et al. 2008).

Gingival crevicular fluid levels of TNF-α on SRP + Doxy had an increasing tendency (Fig. 3), while aPDT group presented reduction on TNF-α detections, probably, due to inactivation o TNF-α by aPDT (Braham et al. 2009, de Oliveira et al. 2009). Previous studies with the use of antibiotic and use doxycycline subantimicrobial doses founded reduction on 3 months after treatment (Navarro-Sanchez et al. 2007, Emingil et al. 2011).

TGF-β has been considered an anti-inflammatory cytokine and seems to stimulate IL-11 production by periodontal ligament fibroblasts (Yashiro et al., 2006). TGF-β has its levels increased on inflamed periodontal tissues and contra balances proinflammatory cytokines such as IL1-β (Steinsvoll et al. 1999). Subantimicrobial doxycycline therapy as an adjunct to SRP seems to increase the detection of TGF-β on GCF after 3 months (Gurkan et al. 2005), in accordance with present study. There is no data on literature measuring TGF-β 1 month after non-surgical periodontal treatment. Two weeks after surgical therapy, it seems to increase, remaining high until the seventh week (Kuru et al. 2004).

Study limitations

This study was designed to compare two different treatment protocols in non-surgical periodontal therapy in uncontrolled type 2 diabetic patients. The absence of a negative control group, represented by patients that only received SRP may represent a limitation of the study. There was no established threshold for initial HbA1c levels and it represented a difficulty on homogeneity of treatment response due to a proportionally high standard deviation, and this should be taken in account in future studies with this population. In addition, this study only shows short-term results, and studies with a larger follow-up would be valuable to elucidate how long treatment effect lasts. Although the patient's medication was not changed during the study, dietary control and physical exercises could be affecting patient glycaemic levels, limiting or enhancing HbA1c reductions. Furthermore, the improving of life quality and masticatory function improvement could be aiding patients self-care and diabetes control adherence. The number of patients with deep pockets in this study was low; an inclusion criteria with a minimal number of deep pocket *per* patient could help to elucidate this difference in future studies to confirm treatment effectiveness.

Conclusion

Within the study limitations, both treatments were able to improve the periodontal treatment outcomes in uncontrolled type II diabetic patients. Adjunctive use of aPDT apparently presents advantages towards systemic doxycycline when dealing with moderate PPD in single-rooted teeth, and confirmation should be done with studies with larger follow-up.

The reduction in proinflammatory cytokine levels favouring aPDT may represent better results in longer follow-up periods, but more studies are needed to confirm this hypothesis. The treatment aPDT + SRP can be an alternative to the use of systemic antibiotics.

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Clinical Relevance

Scientific rationale for study: Bacterial resistance is an increasing concern. Alternative therapies such as antimicrobial photodynamic therapy may produce comparable results with reduced risk of resistance. This study compared a protocol of multiple applications of aPDT to a systemic antibiotic protocol on treatment of type 2 uncontrolled diabetic patients.
Principal findings: Antimicrobial photodynamic therapy was more effective on reducing IL1-β levels. Reduction of HbA1c was not significant between therapies. SRP + aPDT performed better in moderate PPD on single-rooted teeth, and reduced favourably inflammation in short term, and may be an alternative to systemic antibiotics.
Practical implications: Reduction of proinflammatory cytokine profiles may represent more stable results, better control of inflammation, and reduced tissue breakdown post-treatment. SRP + aPDT may be an alternative to the use of systemic antibiotics in the periodontal treatment of uncontrolled diabetic patients, and may avoid additional surgical treatment. Although some of the usual clinical parameters such as PPD and CAL did not present statistical differences, the data collected could be pooled in future meta-analyses due to the strict study design.