

Is Photodynamic Therapy with Adjunctive Non-Surgical Periodontal Therapy Effective in the Treatment of Periodontal Disease under Immunocompromised Conditions?

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ABSTRACT

The aim was to assess whether or not photodynamic therapy (PDT) with adjunctive scaling-and-root-planing (SRP) is effective in the treatment of periodontitis under immunocompromised conditions. PubMed/Medline and Google-Scholar databases were searched from 1967 to May 2013 using various key words. Six studies (five experimental and one clinical) were included. In the clinical study, SRP with PDT was reported to be ineffective in treating chronic periodontitis in T2DM patients. All experimental studies reported significantly less bone loss in periodontal defects treated with SRP+PDT than those treated with SRP alone. Efficacy of PDT+SRP in the treatment of periodontal disease under immunocompromised conditions remains unclear.

Key Words: *Immunosuppression. Photodynamic therapy. Scaling and root planning.*

INTRODUCTION

Previous studies recommended local delivery of antimicrobial agents directly into periodontal pockets as an alternative to systemic antibiotics for treating periodontal disease.^{1,2} However, this technique may be technically inapplicable in patients with generalized periodontitis and multiple sites of deep periodontal pockets.³ Photodynamic therapy (PDT) involves dynamic interaction between light, a photosensitizer (PS) and oxygen (present in and around cells) that results in the formation of reactive oxygen species (ROS) that causes oxidative damage to the target cells (such as tumour and bacterial cells).⁴⁻⁷ Several studies have reported that PDT when used as an adjuvant to conventional scaling and root planing (SRP) is more

effective in treating periodontal disease as compared to when SRP is used alone.⁸⁻¹¹ This may possibly be explained by the fact that periodontal microbes are susceptible to photodynamic therapy in planktonic cultures.^{7,12} In addition, photosensitizers when injected in periodontally infected sites flow into deep periodontal pockets that allow subsequent PDT to eliminate periodontopathogenic bacteria such as *Porphyromonas gingivalis*, *Pseudomonas aeruginosa* and *Fusobacterium nucleatum*.¹³⁻¹⁶ Romanos and Brink¹⁶ assessed the antimicrobial effects of PDT during periodontal therapy in 10 patients with chronic periodontitis. The results demonstrated that PDT when used as an adjunct to mechanical debridement resulted in significant reduction in periodontopathogenic bacteria as compared to sites treated with other treatment regimes.¹⁶ Similar results were reported by Chan and Lai.¹⁷

It is well-known that periodontal inflammatory conditions are worse in tobacco-users and immunocompromised patients (such as those with poorly-controlled diabetes and pre-diabetes) as compared to medically-healthy individuals.¹⁸⁻²³ In addition, these factors have also been reported to impair healing following periodontal therapy.²⁴⁻²⁶ The complex interactions between advanced glycation end products and receptors for advanced glycation end products and presence of proinflammatory cytokines in the gingival crevicular fluid of immunocompromised patients seem to play an essential role in impairing periodontal healing in these individuals following treatment.^{27,28} It is, therefore, hypothesized that the outcomes of non-surgical periodontal therapy with adjuvant PDT are compromised in immunosuppressed individuals.

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In the present review, it was aimed to evaluate the pertinent literature and assess whether or not photodynamic therapy (PDT) with adjunctive non-surgical periodontal therapy effective in the treatment of periodontal disease under immunocompromised conditions.

METHODOLOGY

Focused question: The addressed focused question was “Is PDT with adjunctive non-surgical periodontal therapy effective in the treatment of periodontal disease under immunocompromised conditions?”

Eligibility criteria: The following eligibility criteria were imposed: (a) Original studies; (b) Clinical studies; (c) experimental studies; (d) Intervention: outcome of PDT with adjunctive non-surgical periodontal therapy in the treatment of periodontal disease under immunocompromised conditions; (e) use of statistical methods; (f) letters to the editor, short commentaries and review articles were excluded. Studies that fulfilled the eligibility criteria were performed between 2008 and 2013.^{4,29-33}

Search strategy: To address the focused question, PubMed/Medline (National Library of Medicine, Bethesda, Maryland) and Google-Scholar databases were searched from 1967 upto and including May 2013 using the following keywords in different combinations: “diabetes mellitus”; “immunocompromised”, “ovariectomy”; “photodynamic therapy”, “scaling and root planing”, “Periodontal disease”, and “periodontitis”. Furthermore, hand-searching of the reference lists of the potentially relevant original and review articles (that were found to be pertinent in the previous step) were searched and any disagreement between the authors was resolved via discussion.

The initial search yielded 13 studies. Scrutiny of the titles and abstracts of these studies reduced the number of studies to 6.^{4,29-33} The list of excluded studies and main reason for exclusion is shown in Appendix-A.

RESULTS

Characteristics of studies: The 6 studies that were included were performed at universities.^{4,29-33} Five studies²⁹⁻³³ were performed in rats and one study⁴ was performed in humans. The clinical study⁴ was performed on 45 chronic periodontitis (CP) patients with type-2 diabetes mellitus (T2DM). In this study,⁴ the mean age of the participants was 52.2 years (range 35 – 77 years) and CP was defined as clinical attachment loss (CAL) of greater than 3 millimeters at more than 30% of sites (Table I). The mean HbA1c levels among T2DM patients in Groups 1, 2 and 3 were 8.75%, 8.42% and 9.25% respectively.⁴

All experimental studies²⁹⁻³³ were performed in Wistar rats and immunosuppression was induced via ovariec-

tomy,²⁹ tacrolimus (Tac),³⁰ dexamethasone^{31,32} and alloxan-induced diabetes.³³ In one study,²⁹ female Wistar rats were used whereas male Wistar rats were used in 4 studies.³⁰⁻³³ The weight of rats ranged between 120 grams (g) and 300 g. In all experimental studies,²⁹⁻³³ periodontitis was induced using ligatures (Table I). In the study by de Almeida *et al.*³³ animals that had glycemic levels greater than 300 milligrams per deciliter (mg/dl) were considered diabetic. In 4 experimental studies,^{29,30,32,33} histologic and histomorphometric assessments were made.

Clinical parameters of periodontal inflammation and alveolar bone loss: Clinical results by Al-Zahrani *et al.*⁴ reported no significant difference in age, gender, history of tobacco-smoking, education status, glycated haemoglobin A1c (HbA1c) level, proportion of patients on insulin therapy, probing depth (PD), CAL and plaque and gingival bleeding scores among CP patients with T2DM treated with SRP alone, SRP+doxycycline (Doxy) and SRP+PDT.⁴ This study⁴ concluded that SRP with adjunctive PDT is not effective in the treatment of CP among patients with T2DM (Table II).

Results from all experimental studies²⁹⁻³³ showed that alveolar bone loss (BL) was significantly reduced when ligature-induced periodontitis in immunocompromised rats was treated with SRP with adjunct PDT as compared to when these defects were treated with SRP alone.

Histologic and histomorphometric outcomes: In four experimental studies,^{29,30,32,33} (regardless of induced-immunosuppression), most specimens treated with SRP+PDT showed an intact periodontium with abundant collagen fibers, thick bone trabeculae with no signs of inflammation. Garcia *et al.*²⁹ reported significantly low numbers of tartrate-resistant acid-phosphatase (TRAP)-positive cells in induced periodontal defects treated with SRP+PDT as compared to those treated with SRP alone. In this study,²⁹ regardless of induced-estrogen deficiency, proliferation cell nuclear antigen-positive cells were significantly abundant in defects treated with SRP+PDT than those treated with SRP alone. In the study by Bottura *et al.*³⁰ groups that did not receive low level laser therapy (LLLT) or PDT (Groups 1, 2 and 3) showed large numbers of neutrophils, fewer fibroblasts and blood vessels and small amounts of poorly organized bone; whereas periodontal defects treated with SRP+LLLT (Group-4) and SRP+PDT (Group-5) showed moderate numbers of fibroblasts and blood vessels and well-differentiated bone trabeculae across the root length. Despite dexamethasone-induced immunodeficiency and alloxan-induced diabetes in rats in studies by Fernandes *et al.*³² and de Almeida *et al.*³³ respectively histologic results showed that periodontal defects treated with SRP+PDT showed an intact periodontium with organized collagen fibers; whereas

Table I: Characteristics of studies that fulfilled our eligibility criteria.

Authors <i>et al.</i>	Study design	Study subjects / participants	Mean age	Mean weight (range)	Type of periodontal defect	Immunosuppression
Al-Zahrani <i>et al.</i> ⁴	Clinical	45 patients	52.2 years	-	Chronic periodontitis*	Type-2 diabetes mellitus
Garcia <i>et al.</i> ²⁹	Experimental	270 female Wistar rats	3 months	NA (200-300 g)	Ligature-induced periodontitis	Estrogen deficiency via ovariectomy.
Bottura <i>et al.</i> ³⁰	Experimental	30 adult male Wistar rats	NA	NA (250-300 g)	Ligature-induced periodontitis	Tac-induced immunosuppression
Fernandes <i>et al.</i> ³¹	Experimental	120 adult male Wistar rats	NA	NA (120-140 g)	Ligature-induced periodontitis	Dexamethasone-induced immunosuppression
Fernandes <i>et al.</i> ³²	Experimental	120 adult male Wistar rats	NA	NA (120-140 g)	Ligature-induced periodontitis	Dexamethasone-induced immunosuppression
de Almeida <i>et al.</i> ³³	Experimental	240 adult male Wistar rats	NA	NA (120-140 g)	Ligature-induced periodontitis	Alloxan-induced diabetes

*clinical attachment loss ≥ 3 millimeters at $\geq 30\%$ of sites; g: grams; NA: Not available; Tac: Tacrolimus.

Table II: Authors *et al.*, numbers of subjects/participants in each study group, types of treatment, type of statistical test used and main outcomes and conclusion.

Authors <i>et al.</i>	Number of subjects/participants in each study group (n)	Types of treatments	Type of statistical test used	Main outcomes	Conclusion
Al-Zahrani <i>et al.</i> ⁴	Group-1 = 15 Group-2 = 15 Group-3 = 15	(a) Group-1: SRP only (b) Group-2: SRP + Doxy (c) Group-3: SRP + PDT	One way ANOVA and X ² test	No significant differences in periodontal parameters were detected among the three groups.	PDT + SRP does not benefit patients with type-2 diabetes mellitus.
Garcia <i>et al.</i> ²⁹	Normal rats = 90 OVX rats* = 90 Control rats = 90	(a) SRP only (b) SRP + Saline (c) SRP + PDT (d) LLLT (e) SRP + LLLT (f) PDT	One way ANOVA and Shapiro-Wilk test	PDT treatment resulted in reduced BL compared to SRP treatment at all time points.	PDT + SRP was effective in treating periodontitis as compared to when SRP was used alone.
Bottura <i>et al.</i> ³⁰	Group-1 = 6 Group-2 = 6 Group-3 = 6 Group-4 = 6 Group-5 = 6	(a) Group-1=Saline only (b) Group-2= SRP+Saline (c) Group-3=SRP + TAC (d) Group-4= SRP+LLLT. (e) Group-5= SRP+PDT	ANOVA	BL was significantly higher ($p < 0.05$) among animals in Groups 1, 2 and 3 compared to those in Groups 4 and 5.	PDT was an effective adjuncts to SRP in reducing BL. Use of a LLLT (with or without photosensitizer) was a main factor associated with BL.
Fernandes <i>et al.</i> ³¹	Group-1 = 60 (dexamethasone group) Group-2 = 60 (saline group)	(a) Treatment-1/Group=SRP (b) Treatment-2/Group=SRP + PDT	Two way ANOVA and Shapiro-Wilk test	BL was greater among rats in Group-2 as compared to those in Group-1 treated with SRP+ PDT.	PDT+SRP was effective in the treatment of induced periodontitis in rats with dexamethasone-induced immunosuppression.
Fernandes <i>et al.</i> ³²	Group-1 = 90 (dexamethasone group) Group-2 = 90 (saline group)	(a) Treatment-1/Group=SRP (b) Treatment-2/Group=SRP + PDT	Two way ANOVA and Shapiro-Wilk test	BL was significantly less ($p < 0.05$) in rats treated with SRP + PDT as compared to those treated with SRP alone.	PDT + SRP was effective in the treatment of induced periodontitis in rats with dexamethasone-induced immunosuppression.
de Almeida <i>et al.</i> ³³	Group-1 = 120 (Non-diabetic group) Group-2 = 120 (Alloxan -induced diabetes)	(a) Treatment-1/Group=SRP (b) Treatment-2/Group = SRP + TBO (c) Treatment-3/Group=LLLT (d) Treatment-4/Group = SRP + PDT	One way ANOVA and Shapiro-Wilk test	In Groups-1 and 2, rats treated by SRP + PDT showed significantly less ($p < 0.05$) BL compared to those treated by other regimes.	PDT + SRP was effective in the treatment of induced periodontitis in rats with alloxan-induced diabetes.

ANOVA: Analysis of variance; BL: Bone loss; Doxy: Doxycycline; NA: Not available; SRP: Scaling and root planing LLLT: Low level laser therapy; OVX: ovariectomized; PDT: Photodynamic therapy; TAC: Tacrolimus; TBO: Toluidine blue-O; X² test: Chi-square test.

* Without estrogen replacement therapy.

In all studies,^{4,29-33} level of significance was set at $p < 0.05$.

defects treated with SRP alone (in rats with and without alloxan-induced diabetes) displayed fewer fibroblasts, areas of cementum resorption and disorganized connective tissues.

DISCUSSION

The literature search revealed six studies^{4,29-33} where the outcome of SRP with adjunct PDT on the treatment of periodontal defects was investigated under immunocompromised conditions. Since a limited number of studies addressed the focused question, the pattern of

the present review was customized to primarily summarize the pertinent data.

Several studies^{18,19,24,34,35} have reported that chronic hyperglycemia (such as that in patients with poorly-controlled diabetes) is associated with a worse periodontal status and impaired healing following periodontal therapy. A possible explanation in this regard may be derived from the fact that interactions between advanced glycation end products (AGEs) (created as a result of chronic hyperglycemia) and their receptors (RAGE) in the periodontal tissues impairs the chemo-

tactic and phagocytic function of polymorphonuclear leukocytes and produce proinflammatory cytokines that may aggravate periodontitis and retard healing.^{24,36-38} Short-term clinical results by Al-Zahrani *et al.*⁴ demonstrated no beneficial effects of PDT when used as an adjunct to SRP for treating CP in patients with T2DM. It is, however, noteworthy in the Al-Zahrani study⁴ that all patients with T2DM undergoing periodontal therapy (either with or without adjuvant PDT) had hyperglycemia (HbA1c ~ 8%).^{39,40} This suggests that persistent hyperglycemia in these individuals may have hampered periodontal healing following PDT due to the intense AGE-RAGE interactions and increased the production of destructive inflammatory cytokines in periodontal tissues. Studies^{18,34} have reported that patients with well-controlled T2DM have a periodontal status similar to that of medically-healthy individuals and these patients also respond well to non-surgical periodontal therapy. We hypothesize that patients with well-controlled diabetes (HbA1c 4-5.4%)³⁹ respond well to PDT for the treatment of periodontitis as compared to that in patients with poorly-controlled T2DM; however, further clinical studies are warranted in this regard. Interestingly, experimental histologic results by de Almeida *et al.*³³ showed that despite being hyperglycemic, rats with alloxan-induced diabetes displayed significantly less BL following SRP+PDT as compared to those treated with SRP alone for the treatment of induced periodontitis. It is pertinent to mention that in this study,³³ rats in each experimental group and treatment subgroup were euthanized at 7, 15, and 30 days (long-term data are not available. These experimental results³³ are contradictory to the clinical results reported by Al-Zahrani *et al.*⁴ This variation may possibly be attributed to short-term hyperglycemia that was induced in rats in the study by de Almeida *et al.*³³ It is postulated that the short-term induction of diabetes in these rats may have been insufficient to upsurge AGE-RAGE interactions and augment the local and systemic production of proinflammatory cytokines that could have otherwise hampered the outcome of PDT. Further studies with long-term induction of diabetes (to represent a clinical scenario of chronic hyperglycemia) are warranted.

Immunosuppressants including corticosteroids (such as dexamethasone) and Tac (a systemic corticosteroid-free immunosuppressant) are used to reduce the incidence and severity of allograft rejection after organ transplantation;⁴¹ however, these immunosuppressants have been reported to induce BL by triggering the activity of osteoclasts and decreasing osteoclastic activity.^{42,43} The literature search revealed three experimental studies³⁰⁻³² where immunosuppression was induced via systemic administration of the afore-mentioned drugs. The results demonstrated alveolar BL was significantly less when

SRP was performed with adjunct PDT as compared to when SRP was performed alone. The beneficial effects of PDT adjunct to conventional treatment of periodontal disease was most likely due to the photodestructive effect (ROS production) on the different bacterial species present in the areas of induced periodontal disease mediated by type-I (initiated by superoxide, hydroxyl radicals or anionic) or type-II reactions (initiated by singlet oxygen). The ROS destroy the bacterial cytoplasmic membrane and permanently damage the microbial proteins and nucleic acids.⁴⁴

In summary, the efficacy of PDT in treating periodontal disease under immunocompromised conditions remains unclear. This is possibly due to the fact that only a limited number of studies have addressed our focused question. A limitation of these studies is that most of the studies²⁹⁻³³ were experimental. It is, therefore, tempting to speculate that in clinical scenarios, other risk-factors (such as tobacco habits,^{18,20} advancing age¹⁸ and poor oral hygiene maintenance)⁴⁵ may also influence the outcomes of PDT in individuals with and without immunosuppression. Further long-term clinical trials are warranted to determine the efficacy of PDT as an adjunct to SRP in the treatment of periodontal disease in immunocompromised patients.

CONCLUSION

The efficacy of PDT as an adjunct to SRP for the treatment of periodontal disease under immunosuppressed conditions remains unclear.

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Appendix I: List of excluded studies (Reason for exclusion is shown in parenthesis).

- a. Garcia VG, Fernandes LA, Macarini VC, et al. Treatment of experimental periodontal disease with antimicrobial photodynamic therapy in nicotine-modified rats. *J Clin Periodontol* 2011; 38:1106-14. (Focused question not answered)
- b. Prates RA, Yamada AM, Suzuki LC, et al. Histomorphometric and microbiological assessment of photodynamic therapy as an adjuvant treatment for periodontitis: a short-term evaluation of inflammatory periodontal conditions and bacterial reduction in a rat model. *Photomed Laser Surg* 2011; 29: 835-44. (Focused question not answered)
- c. Carvalho AS, Napimoga MH, Coelho-Campos J, Silva-Filho VJ, Thedei G. Photodynamic therapy reduces bone resorption and decreases inflammatory response in an experimental rat periodontal disease model. *Photomed Laser Surg* 2011; 29:735-40. (Focused question not answered)
- d. Lin J, Bi LJ, Zhang ZG, Fu YM, Dong TT. Toluidine blue-mediated photodynamic therapy of oral wound infections in rats. *Lasers Med Sci* 2010; 25:233-8. (Focused question not answered)
- e. de Almeida JM, Theodoro LH, Bosco AF, Nagata MJ, Oshiiwa M, Garcia VG. In vivo effect of photodynamic therapy on periodontal bone loss in dental furcations. *J Periodontol* 2008; 79:1081-8. (Focused question not answered)
- f. Qin YL, Luan XL, Bi LJ, Sheng YQ, Zhou CN, Zhang ZG. Comparison of toluidine blue-mediated photodynamic therapy and conventional scaling treatment for periodontitis in rats. *J Periodontal Res* 2008; 43:162-7. (Focused question not answered)
- g. de Almeida JM, Theodoro LH, Bosco AF, Nagata MJ, Oshiiwa M, Garcia VG. Influence of photodynamic therapy on the development of ligature-induced periodontitis in rats. *J Periodontol* 2007; 78:566-75. (Focused question not answered).

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