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Review

Efficacy of scaling and root planing with and without adjunct antimicrobial photodynamic therapy on the expression of cytokines in the gingival crevicular fluid of patients with periodontitis: A systematic review

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ABSTRACT

Background: The aim of the present review was to study the efficacy of scaling and root planing (SRP) with and without adjunct antibacterial photodynamic therapy (aPDT) on the expression of cytokines in the gingival crevicular fluid (GCF) of patients with periodontitis.
Methods: In order to address the focused question: "What is the efficacy of SRP with and without aPDT on the expression of cytokines in the GCF of patients with periodontitis" an electronic search without time or language restrictions was conducted up to and including July 2016 in indexed databases using various key words. The exclusion criteria included reviews, laboratory and experimental studies, case reports, commentaries, letters to the editor, interviews, updates, studies where intervention group received aPDT without previous SRP, and studies where local delivery of antibiotics was used as adjunctive therapy to aPDT.
Results: Six randomized control trials were included in the present systematic review. All studies included a control group which received only SRP. Results from 34% of studies reported lower cytokine levels among individuals receiving adjunct aPDT to SPT compared to patients receiving SRP alone. Selective cytokines reduction in the GCF following SRP with adjunct aPDT compared with SRP alone was reported in 50% of the studies. In one study SRP with adjunct aPDT failed to reduce GCF cytokine concentration.
Conclusion: From the literature reviewed the efficacy aPDT as adjunct to SRP in downregulating GCF cytokines remains debatable. Further well-designed studies are needed in this regard.

Contents

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1. Introduction

Periodontitis is an inflammatory disease that compromises the supporting and protective connective tissues of teeth such as gingiva, periodontal ligament, cementum and alveolar bone [1,2]. The most common microbes associated with the etiology of periodontitis include *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum* and *Porphyromona gingivalis* [3]. Besides its classical clinical features (such as bleeding on probing [BOP], clinical attachment loss [CAL] and probing depth [PD] $\geq$4 mm) periodontitis also triggers a cascade of inflammatory events from an immunological aspect. This includes the increased formation and expression of destructive inflammatory cytokines (such as interleukin [IL]-1, tumor necrosis factor [TNF]-α, macrophage activator factor) in oral fluids (such as gingival crevicular fluid [GCF]) that enhance osteoclastic activity and impair bone formative capacity of osteoblasts. [4–6]. In an experimental study on Rhesus monkeys, Ebersole et al. [7] investigated the expression of cytokines associated with ligature-induced periodontitis (LiP). The results showed that the initiation and progression of LiP is characterized by up-regulation of T-helper (Th)17/T-regulatory cytokine genes (such as IL-1β, IL-6 and transforming growth factor [TGF]-β) and down-regulation of Th1/Th2 cytokine genes (IL-18 and IL-25) in the gingival tissue [7]. Likewise, Toyman et al. [8] reported higher gingival crevicular fluid (GCF) IL-1β, matrix metalloproteinase (MMP)-3 and tissue type plasminogen activator concentrations in patients with periodontal disease as compared to individuals with healthy periodontum. Furthermore, Ongoz Dede et al. [9] reported higher GCF IL-32 and TNF-α, and lower IL-10 levels among patients with periodontitis.

Traditionally, mechanical debridement (synonym scaling and root planing [SRP]) of teeth and root surfaces is performed for the treatment of periodontitis [10,11]. However, antimicrobial photodynamic therapy [aPDT] when performed as an adjunct to SRP has been reported to significantly improve the clinical periodontal status (by reducing BOP and PD) compared with SRP alone [12–14]. Moreover, following SRP with adjunct aPDT, a significant reduction in the expression of pro-inflammatory cytokines (such as IL-1β, and MMP-8) in the GCF has also been reported among patients with periodontitis compared with SRP alone [15,16]. Luchesi et al. [17] reported a significant reduction in the expression of interferon [IFN]-γ, IL-6, IL-8 levels, and IL- 1β in the GCF of patients that received SRP with adjunct aPDT compared with those that received SRP alone. Similar results were reported by Souza et al. [18] and Queiroz et al. [16]. However, conflicting results have been also reported. Lui et al. [19] reported comparable GCF IL-1 β concentration among patients treated with adjunct aPDT and low level laser therapy to SRP and those patients treated with SRP alone. Likewise, Pourabbas et al. [20] reported similar levels of IL-1β, MMP-8 and MMP- 9 in GCF of patients treated with SRP with and without adjunct aPDT. In this regard, there is a controversy in indexed literature regarding the efficacy of SRP with adjunct aPDT in reducing the expression of pro-inflammatory cytokines in the GCF of patients with periodontitis.

With this background, the aim of the present review was to study the efficacy of SRP with and without adjunct aPDT on the expression of cytokines in the GCF of patients with periodontitis.

2. Material and methods

2.1. Focused question

This systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. A specific question was developed according to the Participants, Interventions, Control, and Outcomes (PICO) format. The focused question was "What is the efficacy of SRP with and without aPDT on the expression of cytokines in the GCF of patients with periodontitis?"

2.2. Eligibility criteria

A study was considered eligible for inclusion if it met the following criteria: (a) randomized controlled clinical trials; (b) conducted in adult patients (> 18 years) diagnosed with chronic and/or aggressive periodontitis; (c) presence of control group (patients receiving SRP without adjunctive aPDT); (d) interventions evaluating efficacy of aPDT as adjunctive therapy to SRP; and (e) studies reporting one or more cytokine levels as outcome. The exclusion criteria included qualitative and/or quantitative reviews, laboratory (*in vitro)* and experimental (animal models) studies, case reports, commentaries, letters to the editor, interviews, updates, studies where intervention group received aPDT without previous SRP, and studies where local delivery of antibiotics was used as adjunctive therapy to aPDT.

2.3. Literature search protocol

The international database of Prospectively Registered Systematic Reviews in Health and Social Care (PROSPERO) and the Cochrane Register of Systematic Reviews were searched in July 2016, and presented no existing or current review protocols assessing the GCF cytokine profile among individuals with periodontitis treated with SRP compared to those individuals treated with adjunct aPDT to SRP. In order to identify studies relevant to the focused question, two authors (SVK and FJ) conducted a structured and logical electronic search without time or language restrictions up to and including July 2016 in PubMed (National Library of Medicine), Google-Scholar, Scopus, EMBASE, MEDLINE (OVID) and Web of Knowledge databases. The following Medical Subject Headings (MeSH) were used: (1) periodontal debridement, (2) periodontal diseases, (3) periodontitis, (4) photochemotherapy, and (5) cytokines. Other related non-MeSH terms were used in the search strategy to detect articles discussing periodontal parameters and periodontal treatment. These included: (6) non surgical periodontal therapy, (7) mechanical curettage, (8) photodynamic

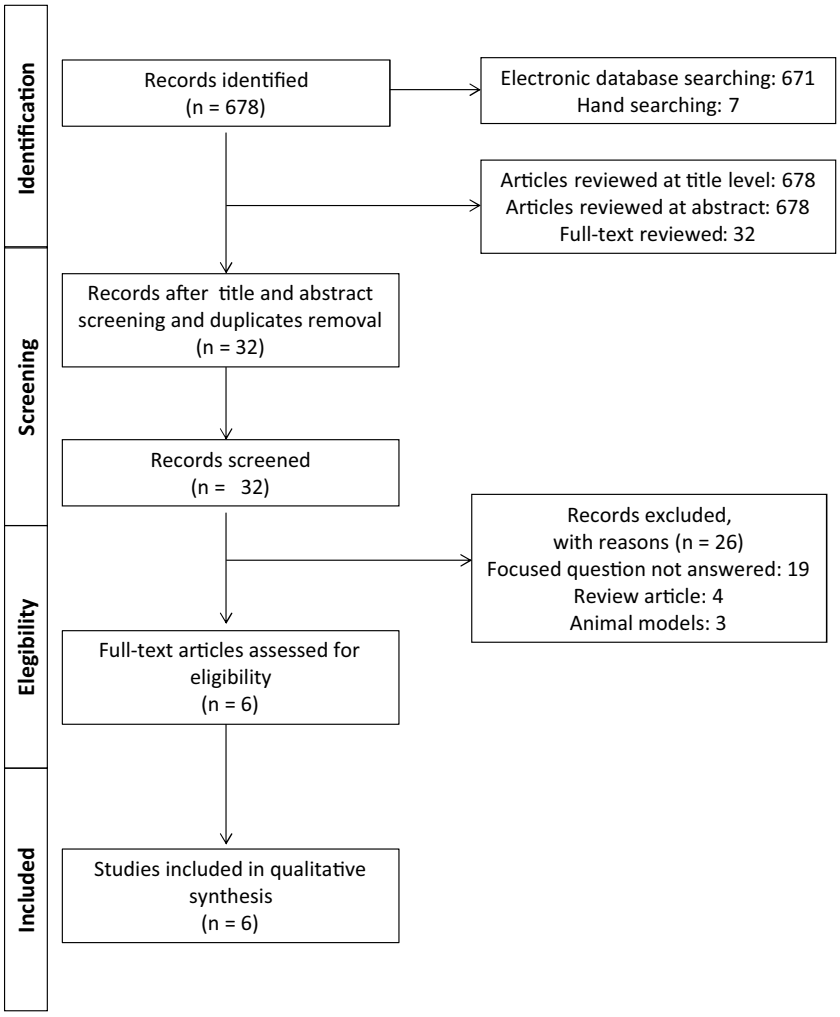

Fig. 1. Article selection flow chart for the systematic review according to PRISMA guidelines.

therapy, (9) bleeding on probing, (10) clinical attachment loss, (11) marginal bone loss and (12) probing depth. These keywords were used in the following combinations: (a) 1 or 6 or 7; and 2 or 3; and 4 or 8; (b) 1 or 6 or 7; and 2 or 3; and 4 or 8; and 5; (c) 1 or 6 or 7; and 4; and 5; (d) 1 or 6 or 7; and 4 or 8; (e) 1 or 6 or 7; and 4 or 8; and 9 or 10 or 11 or 12.

To minimize the potential for reviewer bias, titles and abstracts of studies identified using the above-described protocol were independently screened by 2 reviewers (SVK and FJ) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of original studies were hand searched to identify any articles that could have been missed during the initial search. Hand searching of the following journals was performed: Clinical Oral Investigation, Journal of Clinical Periodontology, Journal of Periodontology, Lasers in Medical Science, Journal of Photochemistry and Photobiology, and Photodiagnosis and Photodynamic Therapy. Any disagreements in the study selection were resolved via discussion and consensus. A third reviewer (VRM) was consulted if no consensus could be reached. Cohen's kappa value [22] was used to determine the inter-reviewer reliability between the 3 reviewers. The kappa coefficient for inter-reviewer agreement was 0.87.

2.4. Quality assessment

In an attempt to increase the strength of the present systematic review the studies that were included underwent a quality assessment following the recommendations of the CONsolidated Standards of Reporting Trials (CONSORT) statement [23]. The CONSORT tool uses a systematic approach based on 7 specific criteria which are: (A) sample size calculation (minimum number of participants required to detect a significant difference among compared groups); (B) randomization and allocation concealment methods; (C) clear definition of inclusion and/or exclusion criteria; (D) complete follow-up; (E) experimental and control groups comparable at study baseline; (F) presence of masking; and (G) appropriate statistical analysis. After determining the scores, an overall estimation of risk of bias (low, moderate or high) was estimated for each selected study. When all the criteria were met, a low risk of bias was estimated; those studies which partly met one or more criteria were estimated as moderate risk of bias; and the risk of bias was estimated as high when one or more criteria were not met [24].

3. Results

3.1. Study selection

Six hundred seventy-eight potential articles were initially identified, out of which 671 were identified thru electronic database searching and seven with hand searching. After title and abstract screening 647 publications, which did not fulfill the eligibility criteria were excluded. In the second step, 26 more articles were excluded because did not answer the focused question, were

Table 1
General characteristics of included studies.

Investigators (Region of study and year)	Study design	Number of patients	Mean age (age range in years)	Gender (F/M) (N = number)	Criteria for diagnosis of periodontitis	Confounding variables assessed
Ge et al. [25] (China, 2008)	RCT (Parallel)	58 Control: 20 Test 1: 18 Test 2: 20	43 (25–66) Control: 42 Test 1: 42 Test 2: 42	28/30	CP; ≥4 sites in 2 quadrants with PD ≥ 5 mm	Antibiotic; systemic diseases; methylene blue allergy; phosphate dehydrogenase deficiency
Lui et al. [19] (Hong Kong, 2011)	RCT (Split mouth-design)	24	50	14/10	CP; ≥2 bilateral sites with PD ≥5 mm, CAL of ≥3 mm, and radiographic signs of bone loss	Pregnancy; antibiotics, anti-inflammatory and immunosuppressive medications; systemic conditions; periodontal treatment
Moreira et al. [15] (Brazil, 2015)	RCT (Split mouth-design)	20	30.6 ± 4.25 (18–35)	18/2	AP; ≥3 teeth other than first molars and incisors with generalized interproximal CAL	Pregnancy; smoking; antibiotics and anti-inflammatory medications; systemic diseases; periodontal treatment
Pourabbas et al. [20] (Iran, 2014)	RCT (Split mouth-design)	22	46 ± 8	12/10	CP; ≥30% of sites with attachment loss ≥3 mm, and ≥1 site per quadrant with BOP and PD ≥ 4 mm	Pregnancy; smoking; antibiotics, anti-inflammatory and hormone medications; systemic conditions; allergy to toluidine blue; periodontal treatment
Queiroz et al. [16] (Brazil, 2015)	RCT (Split-mouth design)	20	46.05 ± 6.38 (35–55)	11/9	CP; ≥2 bilateral sites with PD ≥5 mm	AP; pregnancy and lactation; anti-inflammatory medications; systemic conditions; periodontal treatment
Souza et al. [18] (Brazil, 2013)	RCT (Split-mouth design)	15	NA (36–65)	9/6	CP; bilateral lower molars with class III furcation	Pregnancy and lactation; antibiotics, anti-inflammatory and hormone medications; systemic conditions; periodontal treatment

RCT: Randomized control trial CP: Chronic periodontitis AP: Aggressive periodontitis F: Female M: Male N: Number. PD: Probing depth NA: Not available BOP: Bleeding on probing CAL: Clinical attachment loss.

Table 2
Periodontal parameters and cytokine profile among study groups.

Investigators	Study groups	Follow-up (weeks)	Periodontal parameters	Measurement of cytokines level	Cytokines studied	Periodontal outcomes	Cytokines outcomes
Ge et al. [25]	Control: SRP Test 1: SRP + aPDT Test 2: SRP + aPDT baseline + aPDT 6 after weeks	Up to 12	CAL, PD, BOP	GCF: ELISA	IL-1β MMP-8	Improvements for both groups at follow up were comparable	IL-1 β concentration was significantly lower in both test groups compared to control at follow up. MMP-8 level was significantly lower in test 2 group compared to control at follow up.
Lui et al. [19]	Control: SRP Test: SRP + LLLT + aPDT + LLLT	Up to 4	BOP, PD, GR, PI	GCF: ELISA	IL-1β	BOP and PD were significantly lower for the test group compared to control at follow up	IL-1 β concentration for both groups at follow up were comparable
Moreira et al. [15]	Control: SRP Test: SRP + aPDT	Up to 12	PI, BOP, PD, GR, CAL	GCF: ELISA	IL-1β IL-10 TNF-α	PD reduction and CAL gain were significantly higher for the test group compared to control at follow up. Frequency of residual pockets was significantly lower in the test group	IL-1β expression was significantly lower for the test group as compared to control at follow up in deep periodontal pockets. IL-10 and TNF-α levels were comparable in both groups at follow up.
Pourabbas et al. [20]	Control: SRP Test: SRP + aPDT	Up to 12	BOP, CAL, GR, PD	GCF: ELISA	IL-1β MMP-8 MMP-9 TNF-α	Improvements in PD, BOP, GR and CAL for both groups at follow up were comparable	TNF-α level was significantly lower for the test group as compared to control at follow up. IL-1β, MMP-8 and MMP-9 concentrations were comparable in both groups at follow up.
Queiroz et al. [16]	Control: Smokers + SRP Test: Smokers + SRP + aPDT	Up to 12	PI, BOP, GR, PD,CAL	GCF: ELISA	IL-1β MMP-8	Improvements in PD and CAL for both groups at follow up were comparable	IL-1β level and MMP-8 concentration were significantly lower for the test group as compared to control at 1 week and 12 weeks follow up, respectively.
Souza et al. [18]	Control: SRP Test: SRP + aPDT	Up to 6	PD, PI, BOP	GCF: ELISA	TGF-β1	Improvements in PD for both groups at follow up were comparable	TGF-β1 expression was significantly lower for the test group as compared to control at follow up

SRP: Scaling and root planing aPDT: Antimicrobial photodynamic therapy GCF: Gingival crevicular fluid IL: Interleukin. MMP: Matrix metalloproteinase ELISA: Enzyme-linked immunosorbent assay kits TGF: Transforming growth factor. TNF: Tumor necrosis factor LLLT: Low level laser therapy RT-qPCR: Real time quantitative polymerase chain reaction.

experimental studies (animal models), or reviews (Appendix A). A total of 6 studies [15,16,18–20,25] were included in the present systematic review and processed for data extraction (Fig. 1). Five studies [15,16,18–20] were published in English and one study [25] in Chinese.

3.2. General characteristics

All studies [15,16,18–20,25] were conducted under healthcare or university settings between 2008 and 2015, in the following countries: Brazil, China, Hong Kong, and Iran. All studies [15,16,18–20,25] were randomized control trials, out of which 5 studies [15,16,18–20] used a split-mouth design and 1 study [25] used a parallel design. One hundred fifty-nine patients were included, 92 female and 67 male. The number of study participants ranged between 15 and 58 individuals, with age ranging between 18 years and 66 years, and a mean age ranging between 30.6 ± 4.25 years to 50 years. In all studies [15,16,18–20,25] systemically healthy individuals were included and confounding variables including pregnancy and lactation, antibiotics or anti-inflammatory medication, and/or recent periodontal treatment were assessed. In the study by Queiroz et al. [16] only smokers with aggressive periodontitis were included; whereas, in 2 studies [15,20] smokers were excluded (Table 1).

Five studies [15,18–20,25] assessed clinical parameters and inflammatory biomarkers in patients diagnosed with chronic periodontitis (CP). Queiroz et al. [16] studied patients with aggressive periodontitis (3 or more teeth other than first molars and incisors with generalized interproximal CAL). All studies [15,16,18–20,25] included a control group which received only SRP. In 5 studies [15,16,18,20,25], test group received aPDT as adjunctive treatment to SRP. Lui et al. [19] treated patients with combined low level laser therapy and aPDT after SRP. In all studies [15,16,18–20,25] the follow-up ranged between 4 weeks and 12 weeks after aPDT. All studies [15,16,18–20,25] assessed cytokine levels in GCF using enzyme-linked immunosorbent assay (Table 2).

3.3. Laser and photosensitizer parameters

Three studies [15,16,18] used 10 mg/ml phenotiazine chloride. Two studies [19,25] applied methylene blue with concentrations ranging between 0.1 mg/ml and 10 mg/ml. Pourabbas et al. [20] filled periodontal pockets with toluidine blue photosensitizer. The photosensitization period prior laser application ranged between 10 s and 180 s [15,16,18–20,25].

In all studies [15,16,18–20,25] diode lasers with wavelengths ranging between 638 nm and 940 nm were used. Five studies [15,16,18,19,25] reported the optic fiber diameter which ranged between 0.3 and 0.6 mm. One study [20] did not report the laser optic fiber diameter. In all studies [15,16,18–20,25] duration of laser application per tooth ranged between 30 s and 120 s. Four studies [15,16,18,20] applied adjunct aPDT to SRP at baseline (only one application). Ge et al. [25] used 2 aPDT sessions, baseline and 42 days after initial therapy. Whereas, Moreira et al. [15] applied diode laser at baseline, 2 days, 7 days and 14 days (Table 3).

3.4. Biomarkers main outcomes

The concentration of IL-1β was assessed in 5 studies [15,16,19,20,25]. Three studies [15,16,25] reported lower IL-1β levels in the GCF of patients treated with adjunct aPDT to SRP compared to controls after follow-up. In 2 studies [19,20], there was no significant difference in the IL-1β concentrations among patients with and without adjunctive aPDT to SRP at follow-up. Levels of TNF- α were explored in 2 studies [15,20], out of which, 1 study [20] reported lower levels of TNF- α in the GCF of patients treated

Table 3
Laser and photosensitizer parameters of included studies.

Investigators	Types of PS (concentration)	Duration of PS application (seconds)	Type of laser	Optic fiber diameter (mm)	Wavelength (nm)	Power (mW)	Power density (mW/cm^2)	Energy fluence (J/cm^2)	Duration of laser application (seconds per tooth)	Number of applications (Time interval)
Ge et al. [25]	MB (0.1 mg/ml)	10	Diode	0.6	675	100–140	NA	6	60	2 (42 days)
Lui et al. [19]	MB (10 mg/ml)	180	Diode	0.3	940	5000	NA	NA	< 30	1
Moreira et al. [15]	PTC (10 mg/ml)	60	Diode	0.6	670	75	250	14.94	60	4 (2, 7 and 14 days)
Pourabbas et al. [20]	TB (NA)	60	Diode	NA	638	NA	NA	8 – 10	120	1
Queiroz et al. [16]	PTC (10 mg/ml)	60	Diode	0.6	660	60	28	16.72	60	1
Souza et al. [18]	PTC (10 mg/ml)	60	Diode	0.6	660	NA	60	NA	60	1

PS: Photosensitizer MB: Methylene blue PTC: Phenotiazine chloride TB: Toluidine blue NA: Not available.

Table 4
Quality assessment of included studies following CONSORT statement.

Investigators	A(0–2)	B(0–2)	C(0–1)	D(0–1)	E(0–2)	F(0–2)	G(0–2)	Total score	Estimated risk of bias
Ge et al. [25]	0	2	1	1	2	2	2	10	High
Lui et al. [19]	0	1	1	1	2	1	2	8	High
Moreira et al. [15]	2	2	1	1	2	2	2	12	Low
Pourabbas et al. [20]	2	1	1	1	2	1	2	10	High
Queiroz et al. [16]	2	2	1	1	2	1	2	11	Moderate
Souza et al. [18]	2	2	1	1	2	1	2	11	Moderate

(A) sample size calculation (minimum number of participants required to detect a significant difference among compared groups); (B) randomization and allocation concealment methods; (C) clear definition of inclusion and/or exclusion criteria; (D) complete follow up; (E) experimental and control groups comparable at study baseline; (F) presence of masking; and (G) appropriate statistical analysis.

with aPDT compared to control; and one study [15], reported no significant difference in TNF- α levels between test and control group up to 12 months follow-up. The expression of MMP-8 in GCF among patients treated with and without adjunctive aPDT was reported in 3 studies [16,20,25], out of which 2 studies [16,25] reported significantly lower MMP-8 levels in test group compared to control. Pourabbas et al. [20] identified comparable MMP-8 and MMP-9 concentration in GCF of patients treated with SRP versus SRP and aPDT. Souza et al. [18] reported lower transforming growth factor (TGF)-β1 levels after aPDT adjunct to SRP compared to SRP alone. One study [15] identified similar IL-10 concentration in GCF and gingival tissue among patients receiving SRP or SRP with adjunctive aPDT up to 12 weeks follow-up (Table 2).

3.5. Periodontal main outcomes

All studies [15,16,18–20,25] reported improvement in periodontal parameters in both groups (SRP alone versus SRP and aPDT) at follow-up compared to baseline. Four studies [16,18,20,25] reported comparable results in terms of periodontal parameters (PD, CAL, BOP) among individuals in control and test groups at follow-up. In the study by Lui et al. [19] sites receiving SRP and aPDT presented lower BOP and PD after 4 weeks follow-up compared to sites receiving SRP alone. One study [15] reported significantly PD reduction and CAL gain for the test group compared to control. Likewise, the frequency of residual pockets was significantly lower in the test group [15].

3.6. Quality assessment

All the included studies [15,16,18–20,25] in this systematic review were randomized controlled trials. Quality score of the studies according to CONSORT guidelines ranged from 8 to 12. Quality assessment identified that in general, recruitment of the patients, comparability of control and test group at baseline for periodontal parameter and appropriate statistical analysis were adequately performed in these studies.

In 4 studies randomization was performed by the use of computer-generated random number tables [15,16,18] or coin toss [20]. Two studies [19,25] did not report the method used for randomization. Four studies [15,16,18,20] described the power and sample size calculation. Low risk of bias was regarded as low in one study [15] since this study received a CONSORT score of 12. Studies by Queiroz et al. [16] and Souza et al. [18] were graded as moderate risk of bias because partly met one criteria (presence of masking); whereas the remaining 3 studies [19,20,25] were catalogued as high risk of bias because one or more criteria were not met. Quality assessment of the manuscripts included in the systematic review is summarized in Table 4.

4. Discussion

To our knowledge from indexed literature, this is the first study that systematically reviewed the efficacy of SRP with and without adjunct aPDT on the expression of cytokines in the GCF of patients with periodontitis. It is pertinent to mention that the significant heterogeneity among all the studies [15,16,18–20,25] did not allow pooling of the results and statistical analysis. Results from approximately 34% of studies [16,18] reported lower pro-inflammatory (IL-1β, TGF-β1 and MMP-8) cytokines among individuals that underwent SRP with adjunct aPDT compared with patients that received SRP alone. One explanation for these findings is the production of reactive oxygen species, which occurs as a result of the interaction between the photosensitizer and light. These singlet oxygen molecules are toxic to pathogenic microbes and their products [26–28]. Moreover, aPDT reduces the biological activities of toxic lippolysaccharides produced by these microbes [29]. PDT has been also linked to the activation of other immune processes, including acute phase response, complement cascade and production of chemokines [30]. This suggests that aPDT as adjunct therapy to SRP offers additional improvements in biomarkers expression compared with SRP alone. Interestingly, 50% of the studies [15,20,25] included in the present systematic review reported reduction in selective cytokines in the GCF following SRP with adjunct aPDT compared with SRP alone. Several factors may have influenced these results. First, the diode laser wavelength and frequency of application varied significantly among the included studies [15,20,25]. For example, in the studies by Ge et al. [25] and Moreira et al. [15] there was a significant reduction in GCF IL-1β levels following SRP with adjunct aPDT; however, levels of MMP-8 and TNF- remained unchanged following SRP + aPDT in the studies by Ge et al. [25] and Moreira et al. [15], respectively. In these primary studies [15,25] the photosensitizer and its concentration varied dramatically. Moreira et al. [15] used phenothiazine chloride (10 mg/ml). Whereas, Ge et al. [25] administerd methylene blue (0.1 mg/ml). In addition the power density of the laser was not reported in the studies by Ge et al. [25] and Pourabbas et al. [20] In the study by Lui et al. [19] SRP with adjunct aPDT failed to reduce GCF IL-1β at follow-up. This could be possible associated with the duration of aPDT, its frequency and case selection criteria. It is hypothesized that increased number of aPDT applications with a longer follow-up duration would have significantly reduced the expression of IL-1β in the GCF of patients included in the study by Lui et al. [19] Furthermore, the number of application of aPDT and the frequency also varies among these studies [15,19,20,25]. These factors may have influenced the results reported. To our knowledge there is not agreement among researchers and clinicians regarding the choice of photosensitizer that would yield optimal outcomes. Mahdi et al. [31] reported that erythrosine, curcumin and hydrogen peroxide as photosensitizers in aPDT are effective reducing gram-negative periodontal pathogens (such as *P. gingivalis*); whereas, in the study by Monzavi et al. [32] aPDT using indocyanine green as a photosensitizer was reported to yield optimal results. Therefore, it

is hypothesized that the choice of photosensitizer plays a role in the efficacy of aPDT in reducing GCF pro-inflammatory cytokine levels. Further studies are warranted to test this hypothesis.

It is worth mentioning that strict eligibility criteria were imposed for the studies included in the present systematic review. Due to this reason only 6 studies [15,16,18–20,25] were included and processed for data extraction. Although the study by Luchesi et al. [17] assessed the effect of SRP with adjunct aPDT on the expression of several cytokines including IL-6, IL-1β and TNF-α, it was excluded. This was done primarily because individuals in the control group in the study by Luchesi et al. [17] did not receive SRP alone (photosensitizer was used). From the literature reviewed it is apparent the need for further well-designed studies that could clarify the influence of aPDT when used as an adjunct to SRP in terms of reducing pro-inflammatory cytokines in the GCF of patients with periodontitis. These clinical studies should include a split-mouth design with standardized light sources parameters (such as wavelength and optic fiber diameter), with different photosensitizes (to assess the more effective in reduction of inflammatory cytokines) and assessing expression of the main pro-inflammatory cytokines associated to periodontal disease.

5. Conclusion

From the literature reviewed the efficacy of aPDT as adjunct to SRp in downregulating GCF cytokines remains debatable. Further well-designed studies are needed in this regard.

Conflict of interest

None declared.

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Appendix A. : List of excluded studies. Reason for exclusion is shown in parenthesis

A. Akram Z, Al-Shareef SA, Daood U, Asiri FY, Shah AH, AlQahtani MA, et al. Bactericidal Efficacy of Photodynamic Therapy Against Periodontal Pathogens in Periodontal Disease: A Systematic Review. Photomed Laser Surg. 2016;34:137-49. [Review]

B. Al-Zahrani MS, Austah ON. Photodynamic therapy as an adjunctive to scaling and root planing in treatment of chronic periodontitis in smokers. Saudi medical journal. 2011;32:1183-8.[Focus question not answered]

C. Andersen R, Loebel N, Hammond D, Wilson M. Treatment of periodontal disease by photodisinfection compared to scaling and root planing. The Journal of clinical dentistry. 2007;18:34-8. [Focus question not answered]

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