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Adjunctive laser or antimicrobial photodynamic therapy to non-surgical mechanical instrumentation in patients with untreated periodontitis. A systematic review and meta-analysis.

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Abstract

Aim: To compare the adjunctive effects of lasers or antimicrobial photodynamic therapy (aPDT) to non-surgical mechanical instrumentation alone in untreated periodontitis patients.

Materials and Methods: Two focused questions were addressed using the Population, Intervention, Comparison and Outcome criteria as follows: in patients with untreated periodontitis, i) does laser application provide adjunctive effects on probing pocket depth (PPD) changes compared with non-surgical instrumentation alone? and ii) does application of aPDT provide adjunctive effects on PPD changes compared with non-surgical instrumentation alone? Both randomized controlled clinical trials (RCTs) and controlled clinical trials (CCTs) were included. Results of the meta-analysis are expressed as weighted mean differences (WMD) and reported according to the PRISMA guidelines.

Results: Out of 1'202 records, 10 articles for adjunctive laser and 8 for adjunctive aPDT were included. With respect to PPD changes, 1 meta-analysis including 2 articles (total n=42; split-mouth design) failed to identify a statistically significant difference (WMD=0.35 mm; 95%CI:-0.04/0.73; p=0.08) in favour of adjunctive aPDT (wavelength range 650-700 nm). In terms of adjunctive laser application a high variability of clinical outcomes at 6 months was noted. Two articles included patient-reported outcomes and 10 reported on the presence/absence of harms/adverse effects.

Conclusions: Available evidence on adjunctive therapy with lasers and aPDT is limited by (i) the low number of controlled studies and (ii) the heterogeneity of study designs. Patient-reported benefits remain to be demonstrated.

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1. Introduction

Non-surgical subgingival mechanical instrumentation aims at eliminating the etiologic factors on the root surface and is considered the standard of care of cause-related therapy in patients with untreated periodontitis (Badersten, Nilveus, & Egelberg, 1984a,b). Subgingival mechanical instrumentation may be performed by either hand and/or power-driven instruments and results in improved clinical outcomes such as reduced bleeding on probing (BoP) and decreased probing pocket depth (PPD) (Badersten et al.,1984a, b). However, in sites with impaired access such as deep periodontal pockets and furcation areas, residual subgingival calculus and bacterial deposits may remain on the root surface (Caffesse, Sweeney, & Smith, 1986; Oda & Ishikawa, 1989). Therefore, the adjunctive use of lasers and antimicrobial photodynamic therapy (aPDT) has been increasingly investigated as adjunctive approaches to non-surgical mechanical instrumentation alone (Schwarz, Aoki, Becker, & Sculean, 2008; Sgolastra, Severino, Gatto, & Monaco, 2013; Sgolastra, Severino, Petrucci, Gatto, & Monaco, 2014; Mizutani et al., 2016).

The most common laser applications for periodontal therapy include diode, carbon dioxide (CO_2), neodymium-doped: yttrium aluminium garnet (Nd:YAG), erbium-doped: yttrium aluminium garnet (Er:YAG) and erbium, chromium-doped: yttrium, scandium, gallium, garnet (Er,Cr:YSGG) lasers with wavelengths ranging from 635 to 10'600 nm. All of these wavelengths can be used adjunctively to mechanical non-surgical instrumentation to debride connective tissue and epithelium within periodontal pockets, inactivate bacteria and ablate subgingival calculus (Eberhard, Ehlers, Falk, Acil, Albers & Jepsen, 2003; Jepsen, Deschner, Braun, Schwarz & Eberhard, 2011). In fact, the Er:YAG laser with a wavelength of 2940 nm displays high absorption in water and hydroxide ions thereby providing the possibility to remove subgingival calculus without causing thermal side effects to adjacent tissue (Aoki, Ando, Watanabe, & Ishikawa, 1994; Eberhard et al., 2003; Schwarz et al., 2008). However, to be recommended for clinical applications, adjunctive use of any type of lasers to non-surgical mechanical instrumentation must yield predictable and safe outcomes superior to those obtained with mechanical instrumentation alone (Cobb, 2017).

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An additional application of laser photons known as aPDT aims at destroying bacterial cells in periodontal pockets by means of highly reactive oxygen radicals produced by a combination of a low-level laser light in conjunction with a photosensitizer (Dobson & Wilson, 1992). Several oral bacteria are susceptible to low-level laser light in the presence of photosensitizers such as toluidine blue O, methylene blue and malachite green. This procedure is expected not only to reduce both the bacterial burden and inflammation in periodontal tissues but also to provide biostimulatory effects with photonic energy. Conflicting and short-term outcomes of clinical studies, however, were reported when comparing the adjunctive effects of aPDT to non-surgical mechanical instrumentation alone (Sgolastra et al., 2013; Pourabbas, Kashefimehr, Rahmanpour, Babaloo, Kishen, Tenenbaum & Azarpazhooh, 2014).

Despite reports of positive outcomes on the use of adjunctive lasers in the management of untreated periodontitis (Qadri, Javed, Johannsen & Gustafsson, 2015) and aPDT (Meimandi, Talebi Ardakani, Esmaeil Nejad, Yousefnejad, Saebi & Tayeed, 2017) in the management of untreated periodontitis, clinically relevant benefits for the patient need to be systematically appraised.

Hence, the aim of the present systematic review was to investigate the adjunctive effects of laser or aPDT to non-surgical periodontal therapy in patients with untreated periodontitis after a follow-up of 6 months.

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2. Material and methods

2.1. Study registration

The review protocol was registered and allocated the identification number CRD42019128262 in the PROSPERO international prospective register of systematic reviews hosted by the National Institute for Health Research (NIHR), University of York, UK, Center for Reviews and Dissemination.

2.2. Reporting format

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were adopted throughout the process of the present systematic review (Moher et al., 2009; Moher et al., 2015).

2.3. Population (P), Intervention (I), Comparison (C) and Outcomes (O) (PICO)

Population**:** Patients with untreated periodontitis

Intervention**:** Adjunctive use of laser or aPDT to non-surgical mechanical instrumentation by means of hand and/or power-driven instrumentation

Comparison**:** Non-surgical mechanical instrumentation by means of hand and/or power-driven instrumentation alone

Outcome measures

Primary outcome

Change in PPD

Secondary outcomes

Change in clinical attachment level (CAL)

Residual PPD

Change in BoP

Change in plaque level

Change in subgingival biofilm composition

Change in gingival crevicular fluid (GCF) biomarker levels

Patient-reported outcome measures (PROMs)

Harms and adverse effects

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2.4. Focused questions

The following focused questions were adapted using the PICO criteria (Stone, 2002):

- In patients with untreated periodontitis, does laser application provide adjunctive effects on PPD change compared with non-surgical mechanical instrumentation alone?
- In patients with untreated periodontitis, does application of aPDT provide adjunctive effects on PPD change compared with non-surgical mechanical instrumentation alone?

2.5. Search strategy

2.5.1. Electronic search

A comprehensive and systematic electronic search of MEDLINE via PubMed, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) databases was conducted for studies in humans published in English up to April 9th, 2019. Language was limited to English due to time constraints.

The following search terms were used:

PubMed search terms

For the search in the PubMed library, combinations of controlled terms (MeSH) and keywords were used whenever possible:

("periodontal diseases" [MeSH Terms] OR "periodontitis" [MeSH Terms]) AND ("laser" [All Fields] OR "photodynamic" [All Fields]) AND ("non-surgical" [All Fields] OR "non surgical" [All Fields] OR "scaling" [All Fields] OR "root planing"[All Fields] OR "debridement"[All Fields] OR “conventional periodontal therapy”[All Fields])

Scopus search terms

(KEY ("periodontal diseases" OR "periodontitis")) AND (TITLE-ABS-KEY ("laser" OR "photodynamic")) AND (TITLE-ABS-KEY ("non-surgical" OR "non-surgical" OR "scaling" OR root planing" OR "root planning" OR "debridement" OR “conventional periodontal therapy”))

Cochrane database for randomized controlled trials search terms

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(MeSH descriptor: [Periodontitis] explode all trees OR MeSH descriptor: [Periodontal Diseases] explode all trees) AND (All text ("laser" OR "photodynamic")) AND (All text ("non-surgical" OR "non-surgical" OR "scaling" OR root planing" OR "debridement" OR “conventional periodontal therapy”))

2.5.2. Manual search

A manual search of the reference lists of relevant reviews and systematic reviews on the topics as well as of the reference lists of the included full-text articles was performed.

2.5.3. Unpublished literature search

In order to further identify potential articles for inclusion, grey literature was searched in the register of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov) and in the multidisciplinary European database (www.opengrey.eu).

2.6. Study design

The following study designs were considered:

- Randomized controlled clinical trials (RCTs)
- Prospective controlled clinical trials (CCTs)
- Studies with split-mouth and parallel arms designs

2.7. Inclusion criteria

The following inclusion criteria were applied:

- Follow-up of 6 months
- ≥ 20 patients per treatment arm at 6-month follow-up
- ≥ 20 patients at 6-month follow-up for studies with split-mouth design
- Clinical examination at 6-month follow-up
- Non-surgical instrumentation by means of hand and/or power-driven instruments
- Studies including subgingival adjunctive laser application
- For meta-analysis

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- Studies including only 1x non-surgical mechanical instrumentation combined with only 1x adjunctive application of lasers or aPDT
- Studies reporting PPD changes between baseline and 6-month follow-up

2.8. Exclusion criteria

The following exclusion criteria were applied:

- Studies including patients with treated periodontitis
- Referred patients with pre-treated periodontitis
- Studies including patients treated in the course of supportive periodontal therapy (SPT)
- Studies including the use of ≥ 2 laser types
- Studies including a combination of laser and aPDT application
- Abstracts
- Letters to editors
- Narrative reviews
- Case reports
- Case series
- Insufficient/unclear informations not allowing data extraction
- No author response to inquiry e-mail for data clarification

2.9. Screening

Screening was performed independently by 4 reviewers (A. S., G. E. S., C. W. and J. C. S.). A Cohen's kappa score was calculated to assess inter-examiner agreement (Landis & Koch 1977) Eligibility assessment was performed firstly through title and abstract analysis and secondly through full-text analysis. In order to avoid exclusion of potentially relevant articles, abstracts providing unclear results were included in the full-text analysis. If necessary, authors were contacted for clarifications. From all studies of potential relevance, full-text was obtained for independent assessment by 2 reviewers against the stated inclusion criteria. Any disagreement was resolved by discussion among the reviewers. In the event of multiple publications on the same patient sample, relevant data

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on the primary and secondary outcome measures were extracted from the publication with the 6-month follow-up.

2.10. Data extraction

From the selected articles fulfilling the inclusion criteria, data addressing the primary and secondary outcome measures were extracted in duplicate by two independent reviewers for qualitative and quantitative analysis.

2.11. Quality Assessment

The criteria used to evaluate the quality of the selected controlled trials were adopted from the checklist of the Cochrane Center and the CONSORT (Consolidated Standards of Reporting Trials) statement, providing guidelines for the following parameters: a) sequence generation; b) allocation concealment method; c) masking of the examiner; d) address of incomplete outcome data and e) free of selective outcome reporting. The degree of bias was categorized as low risk if all the criteria were met and high risk if two or more criteria were missing (Moher et al., 2010; Schulz, Altman, Moher, & Fergusson, 2010; Higgins, Altman, & Sterne, 2011). Potential impact of risk of bias for sample size calculation, patient selection, and reporting were considered for each selected study.

2.12. Data analysis

To assess changes in PPD (i.e. primary outcome) at the 6-month follow-up, mean values and standard deviations were used and analyzed with weighted mean differences (WMD) and 95% confidence intervals (CIs).

Results documenting PPD change were extracted from RCTs and used to evaluate the potential benefits of adjunctive laser or aPDT therapy. Meta-analyses were performed using random effect methods by grouping laser types according to their wavelength. For these meta-analyses, only studies using a single adjunctive application of laser or aPDT (test) and a single episode of non-surgical mechanical instrumentation (control) were included. Forest plots were used to illustrate the outcomes of the meta-analyses. Mean prediction intervals and their 95% lower and upper limits were only calculated and reported for meta-analyses including at least 3 studies.

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The statistical heterogeneity among studies was explored by the I^2 index (Higgins et al., 2003).

Statistical significance was set to $p<0.05$. All analyses were performed with Review Manager (RevMan Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

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3. Results

3.1. Search

A total of 1'202 records were identified through the electronic search. After removal of duplicates, 659 records remained for abstract screening. No citations from the manual search and the grey literature search were identified (Figure 1).

Upon exclusion of 604 articles based on their abstracts, 55 articles remained for full-text evaluation. Following exclusion of 38 articles based on full-text analysis (Table 1), 17 articles remained for qualitative and quantitative analysis.

An inter-examiner Cohen's kappa score of 0.749 was calculated according to the results from title and abstract screening.

3.2. Adjunctive laser therapy

Description of included studies

The characteristics of the 10 articles evaluating the adjunctive use of laser are summarized in Table 2 (Üstün, Hatipoglu, Daltaban, Felek, & Firat, 2018; Matarese, Ramaglia, Cicciu, Cordasco, & Isola, 2017; Hatipoglu, 2017; Dereci, Hatipoglu, Sindel, Tozoglu, & Üstän, 2016; Dilsiz, Canakci, & Aydin, 2013; Euzebio Alves et al., 2013; Eltas & Orbak, 2012a; Kelbauskiene, Baseviciene, Goharkhay, Moritz, & Machiulskiene, 2011; Rotundo et al., 2010; Kamma, Vasdekis, & Romanos, 2009).

Study design

One article included two experimental and two control groups, respectively (Eltas & Orbak, 2012a). Two studies (Kamma et al., 2009; Rotundo et al., 2010) included 3 experimental and 1 control groups, respectively. One study included two experimental groups and one control group (Dilsiz et al., 2013) while the remaining 6 articles included one experimental group and one control group.

Three articles (Dereci et al., 2016; Hatipoglu et al., 2017; Üstün et al., 2018) reported on a parallel arm design while 7 articles reported on a split-mouth design (Dilsiz et al., 2013; Eltas & Orbak, 2012a; Euzebio Alves et al., 2013; Kamma et al., 2009; Kelbauskiene et al., 2011; Matarese et al., 2017; Rotundo et al., 2010).

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The total number of patients treated was 370 of whom 230 were included in studies with a split-mouth and 140 in studies with a parallel arm design, respectively.

Study samples

Sample sizes varied from 24 to 60 patients and a power calculation was described in 5 of the 10 included articles (Euzebio Alves et al., 2013; Eltas & Orbak, 2012a; Kelbauskiene et al., 2011; Rotundo et al., 2010; Kamma et al., 2009).

The mean age of the included patients ranged from 34.9 to 50.5 years. The percentage of females ranged from 33 to 67% and of males from 33 to 66%, respectively. Smokers were reported in 3 articles (Kamma et al., 2009; Rotundo et al., 2010; Eltas & Orbak, 2012a) smokers were excluded in 6 articles (Kelbauskiene et al., 2011; Euzebio Alves et al., 2013; Dilsiz et al., 2013; Hatipoglu, 2017; Matarese et al., 2017; Üstün et al., 2018). Two articles reported on patients diagnosed with aggressive periodontitis (Kamma et al., 2009; Matarese et al., 2017), 7 articles on patients diagnosed with chronic periodontitis (Rotundo et al., 2010; Eltas & Orbak, 2012a; Dilsiz et al., 2013; Euzebio Alves et al., 2013; Hatipoglu et al., 2017; Dereci et al., 2016; Üstün et al., 2018) and periodontal diagnosis was not reported in 1 article (Kelbauskiene et al., 2011).

All studies were conducted in one center. One study (Kamma et al., 2009) was conducted in a private dental clinic limited to periodontics while the remaining 9 studies were conducted in a university setting.

Intervention/comparison

Five different types of laser were used in the 10 included articles. The use of a diode laser was reported in 4 articles (Kamma et al., 2009; Euzebio Alves et al., 2013; Matarese et al., 2017; Hatipoglu et al., 2017), Er:YAG laser in 1 article (Rotundo et al., 2010), Er,Cr:YSGG laser in 3 articles (Kelbauskiene et al., 2011; Dereci et al., 2016; Üstün et al., 2018), Nd:YAG laser in 1 article (Eltas & Orbak, 2012a) and potassium titanyl phosphate (KTP) laser in the remaining 1 article (Dilsiz et al., 2013).

In a total of 6 articles, non-surgical mechanical instrumentation and laser application was reported to be performed in one session (Üstün et al., 2018; Matarese et al., 2017; Hatipoglu et al., 2017; Eltas & Orbak, 2012a; Rotundo et al., 2010; Kamma et al., 2009) while in the remaining 4 articles (Euzebio Alves et al., 2013; Dilsiz et al., 2013;

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Kelbauskiene et al., 2011, Dereci et al., 2016) non-surgical mechanical instrumentation and/or laser application was delivered in multiple sessions.

With respect to non-surgical mechanical instrumentation, 2 articles reported the use of hand instruments only (Kamma et al., 2009; Euzebio Alves et al., 2013) and the remaining 8 articles reported a combination of hand and power-driven instruments.

In 7 articles the use of local anesthesia in conjunction with periodontal treatment was reported (Üstün et al., 2018; Matarese et al., 2017; Hatipoglu et al., 2017; Dereci et al., 2016; Euzebio Alves et al., 2013; Eltas & Orbak, 2012a; Kamma et al., 2009), in 1 article local anesthesia was reported to be delivered if needed (Rotundo et al., 2010) whereas lack of information with respect to the use of local anesthesia was observed in 2 articles (Dilsiz et al., 2013; Kelbauskiene et al., 2011).

Outcomes

The outcomes of the 10 articles evaluating adjunctive laser therapy are summarized in Table 3. The data of the included RCTs provide an inconclusive picture regarding benefits of adjunctive laser application. Meta-analyses on the primary outcome measure could not be performed for lasers grouped with a wavelength range of 810-980 nm and a wavelength range of 2780-2940 nm due to (i) the low number of comparable studies, (ii) the heterogeneity of study designs and/or (iii) the lack of reporting of mean PPD changes between baseline and the 6-month follow-up in the original articles.

Table 6a summarizes the percentages of studies reporting on secondary outcomes. CAL change (i.e. 100%), Plaque Index change (i.e. 90%) and change in BoP (i.e. 90%) were reported with the highest frequency. Harms or adverse effects and change in subgingival biofilm composition were reported in 4 articles (i.e. 40%) while change in GCF biomarkers levels/volumes were reported in 3 articles (i.e. 30%). Residual PPD and PROMs were reported in 1 article (i.e. 10%).

3.3. Adjunctive aPDT

Description of included studies

The characteristics of the 8 included articles (Theodoro et al., 2012; Berakdar, Callaway, Eddin, Ross, & Willershausen, 2012; Dilsiz et al., 2013, Betsy, Prasanth, Baiju, Prasanthila, & Subhash, 2014; Malgikar et al., 2016; Al-Askar et al., 2017; Bundidpun,

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Srisuwantha, & Laosrisin, 2018; Raut, Sethi, Kohale, Mamajiwala, & Warang, 2018) are summarized in Table 4.

Study design

All studies were designed as RCTs. Five out of 8 studies applied a split-mouth design, i.e. test and control interventions were compared within a patient (Theodoro et al., 2012; Berakdar et al., 2012; Dilsiz et al., 2013; Malgikar et al., 2016; Bundidpun et al., 2018). Three studies used 2 separate patient groups, i.e. non-surgical mechanical debridement without (control group) and with adjunctive aPDT treatment (test group) (Betsy et al., 2014; Al-Askar et al., 2017; Raut et al., 2018).

None of the included studies was funded by an industrial partner. Examiner calibration was reported in 6 articles (Theodoro et al. 2012; Dilsiz et al. 2013; Betsy et al. 2014; Al-Askar et al. 2017; Raut et al. 2018) (Malgikar et al. 2016). A formal power calculation was described in 5 (Theodoro et al., 2012; Betsy et al., 2014; Al-Askar et al., 2017; Raut et al., 2018) (Bundidpun et al. 2018) of the 8 included articles.

All studies were conducted in a single university or specialist center.

Study samples

Samples sizes varied from 20 to 88 patients. The total number of patients observed was 331, i.e. 123 patients received test and control interventions in a split-mouth design, and 208 patients received either mechanical debridement without (104 patients as controls) or with adjunctive aPDT treatment (104 patients as test group). Mean age of included patients ranged from 41 to 59 years, and the proportion of females varied from 0 to 65%.

In all studies, patients with systemic conditions, pregnant or lactating women and patients who had taken antibiotics in the past 3 to 12 months were excluded. One study included exclusively patients with medically diagnosed prediabetes (Al-Askar et al., 2017). Smoking was an exclusion criterion in all studies.

Dental and periodontal characteristics of the patients included varied considerably between studies. While case definitions and requirements in terms of PPD differed among studies, in all studies but 1 (Al-Askar et al. 2017) patients were diagnosed with

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chronic periodontitis according to the 1999 classification (Armitage, 1999). Nine articles specified a minimum of PPD ≥ 4 to 7mm in at least 3 to 6 teeth or sites. One article defined the presence of PPD > 5mm and CAL > 4mm without definition of a minimum number of teeth (Raut et al. 2018). Three articles (Theodoro et al., 2012; Dilsiz et al., 2013; Berakdar et al. 2012) called for the presence of BoP. Five articles defined the presence of at least 20 teeth (Theodoro et al., 2012; Dilsiz et al., 2013; Betsy et al., 2014; Malgikar et al., 2016; Bundidpun et al., 2018)

The number of tooth sites treated with adjunctive aPDT (test procedure) ranged from 33 to 839 sites. Four articles did not specify the exact number of teeth or sites treated per patient and/or treatment arm (Dilsiz et al., 2013; Malgikar et al., 2016; Al-Askar et al., 2017; Raut et al., 2018). In 4 articles, treated sites were specified in terms of PPD and the presence of BoP (Theodoro et al., 2012; Berakdar et al., 2012; Betsy et al., 2014; Al-Askar et al., 2017). One article reported exclusively single-rooted teeth in the analysis (Betsy et al., 2014).

Intervention/comparison

A diode laser was used in the 8 articles included. All articles but 1 (Raut et al., 2018) stated the laser manufacturer which differed among studies. The most commonly used laser tips were fiber optic tips (Theodoro et al., 2012; Dilsiz et al., 2013; Betsy et al., 2014; Malgikar et al., 2016; Bundidpun et al., 2018). In the remaining three articles, the material of the laser tip was not reported. If reported, diameter of the laser tip ranged from 200 to 400μm. The output power of the lasers ranged from 30 to 1000mW with an irradiation time of 10 to 150s per site. Wavelengths of lasers ranged from 655 to 980nm. In 3 articles, laser densities were reported, and ranged from 5.4 to 60J/cm^2 (Theodoro et al., 2012; Betsy et al., 2014; Raut et al., 2018).

Five articles reported the application of methylene blue in different concentrations as photosensitizer, while three articles (Theodoro et al., 2012; Bundidpun et al., 2018; Raut et al., 2018) reported the use of toluidine blue O, phenothiazine chloride or indocyanine green for laser activation. Application time of the photosensitizer per site amounted to 1 minute (Bundidpun et al., 2018; Raut et al., 2018) or 3 minutes (Dilsiz et al., 2013; Betsy et al., 2014; Malgikar et al., 2016), if reported.

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All studies included test and control groups. In both groups, non-surgical mechanical instrumentation was performed by hand instruments, i.e. curettes (Berakdar et al., 2012; Theodoro et al., 2012), or power-driven instruments, i.e. ultrasonic devices (Al-Askar et al., 2017; Bundidpun et al., 2018), or a combination of both (Dilsiz et al., 2013; Betsy et al., 2014; Malgikar et al., 2016; Raut et al., 2018). In all studies but 1 (Dilsiz et al., 2013), non-surgical mechanical instrumentation was performed in one single session. Five articles reported full-mouth instrumentation (Dilsiz et al., 2013; Betsy et al., 2014; Malgikar et al., 2016; Al-Askar et al., 2017; Bundidpun et al., 2018). Treatment in controls consisted of non-surgical mechanical instrumentation without adjunctive measures. In 2 studies, a placebo laser was additionally used in the control group (Dilsiz et al. 2013; Raut et al., 2018). Treatment in the test groups consisted of non-surgical mechanical instrumentation with adjunctive aPDT, which was applied immediately after mechanical instrumentation in 5 studies (Berakdar et al., 2012; Theodoro et al., 2012; Betsy et al., 2014; Al-Askar et al., 2017; Raut et al., 2018). In 3 studies, aPDT was applied with a time lag after mechanical instrumentation, i.e. after 24 h (Malgikar et al., 2016) or 1 week (Dilsiz et al., 2013; Bundidpun et al., 2018). In all studies, aPDT was applied once.

In all studies, maximum follow-up time amounted to 6 months. None of the included articles reported on PPD measurements and/or subgingival mechanical debridement within 6 months after initial treatment. Oral hygiene instructions and/or professional prophylaxis were performed after 1, 3 and 6 months in 3 studies (Dilsiz et al., 2013; Malgikar et al., 2016; Bundidpun et al., 2018) and in weekly to monthly intervals in 1 study (Theodoro et al., 2012).

Outcomes

The outcomes of the 8 studies evaluating the adjunctive use of aPDT are summarized in Table 5. In order to conduct meta-analyses on reported mean PPD changes between baseline and the 6-month follow-up, studies were grouped according to wavelength, frequency of mechanical instrumentation (i.e. only 1x) and frequency of aPDT application (i.e. only 1x). Based on the small number of studies in the meta-analysis (i.e. <10), funnel plots were not included to display publication bias.

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Primary outcome: Change in PPD

Five studies were excluded from meta-analysis based on the fact that treatment was repeated after one week (Dilsiz et al., 2013), mean PPD changes were not reported (Raut et al., 2018; Theodoro et al., 2012), mean PPD values were not reported (Betsy et al., 2014) and only treated sites with PPD ≥ 4 mm were reported (Al Askar et al., 2017).
Figure 2 illustrates the results of the meta-analysis for changes in PPD based on 2 studies with split-mouth design including a total of 42 patients (Bundidpun et al., 2018; Berakdar et al., 2012). No statistically significant difference (WMD=0.35 mm; 95%CI:-0.04/0.73; p=0.08) was observed comparing adjunctive use of aPDT (wavelength range: 650-700 nm) to non-surgical periodontal therapy alone.

Secondary outcomes

Table 6b summarizes the percentages of studies reporting on secondary outcomes. Changes in Plaque Index were reported in all studies. CAL changes and the report of harms or adverse effects represented the second most cited outcomes (i.e. 88%) followed by BoP changes (i.e. 75%). Changes in subgingival biofilm composition were reported in 25% of articles. Patient-reported outcome measures and residual PPD were reported in 1 article each (i.e. 13%) and no article reported on changes in GCF biomarker levels/volumes.

3.4. Quality assessment

The assessment of risk of bias of the included studies is illustrated in Table 7a+b and was based on the Cochrane Center and CONSORT guidelines (Consolidated Standards of Reporting Trials) to evaluate the quality of RCTs (Moher et al., 2010; Schulz et al., 2010). No single study demonstrated high risk of bias and the majority of studies displayed a low or unclear risk of bias.

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4. Discussion

The aim of the present systematic review was to investigate the adjunctive effects of laser application or aPDT to non-surgical periodontal therapy of at least 20 patients with untreated periodontitis after a follow-up of 6 months. It should be noted that studies reporting on laser application or aPDT as a monotherapy as well as studies conducted in treated periodontitis patients and in patients enrolled in supportive periodontal therapy were not considered for the present systematic review. Moreover, studies reporting on the use of airpolishing devices were not considered as it is not regarded the standard of care for untreated periodontitis patients.

The adjunctive use of lasers with 8 different wavelengths was identified. The potential benefits compared to control procedures were evaluated in 10 studies with a total of 370 patients for adjunctive laser therapy and in 8 studies with a total of 331 patients for adjunctive aPDT. The results of one meta-analysis including 2 studies with split-mouth design indicated that adjunctive aPDT application to non-surgical periodontal therapy failed to yield statistically significant improvements with respect to mean PPD changes between baseline and the 6-month follow-up.

The term “untreated periodontitis” was selected in order to differentiate adjunctive application of lasers or aPDT between patients with untreated periodontitis and those enrolled in supportive periodontal therapy. Moreover, a potential wash-over effect could not be completely ruled out when applying aPDT in studies with a split-mouth design and may bias the outcomes.

In addition, keeping in mind the observed great heterogeneity among the studies identified by the systematic search, in particular in terms of laser type, tip diameter, wavelength, photosensitizer, mode of periodontal treatment, number of treated sites, population and several possible combinations of these parameters, a careful attempt was developed to conduct meta-analyses only when PPD changes between baseline and the 6-month follow-up were reported in the original articles. Within the highly heterogeneous set of confounding variables, a selection of parameters including wavelength, type of laser, single episode of non-surgical periodontal therapy and single application of laser/aPDT for grouping the studies was considered and applied for further analysis in case studies were suitable.

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Two articles included PROMs and 10 articles reported the presence/absence of harms or adverse effects. Nine studies did not observe any adverse or side effects (Kelbauskiene et al., 2011; Bundidpun et al., 2018; Dilsiz et al., 2013; Berakdar et al., 2012; Malgikar et al., 2016; Betsy et al., 2014; Raut et al., 2018; Theodoro et al., 2012; Dereci et al., 2016). In one study, two periodontal abscesses occurred in the test group (Rotundo et al., 2010).

All but 1 study (Kamma et al., 2009) were performed in a university setting. Interestingly, no study reported on cost/benefit ratio related to adjunctive laser/aPDT application.

The results of the present systematic review are in accordance with those presented in recent narrative reviews on the topic (Mizutani et al., 2016; Cobb, 2017). Collectively, available evidence is limited and highly heterogeneous.

If both statistical and clinical significance are considered to be equally important when comparing adjunctive laser therapy or aPDT to non-surgical mechanical instrumentation alone, future RCTs should define which criteria determine clinical significance. Defining PPD changes as the primary outcome has some limitations. The reporting of the percentage of PPDs ≤ 5 mm or the percentage of PPDs > 5 mm would be meaningful from a clinical perspective. Unfortunately, only one study on adjunctive lasers and one study on adjunctive aPDT reported on residual PPDs. This is of critical importance when planning dissemination of evidence-based guidelines for periodontal therapy. In this context, guidelines for periodontal therapy should include a list of criteria for the assessment of (i) thresholds of reduction in PPD, BoP and gain in CAL, (ii) percentage of residual PPD > 5 mm requiring additional periodontal therapy, (iii) frequency distribution of sites exhibiting a substantial improvement from baseline with respect to PPD, BoP and CAL, (iv) harms and adverse events, (v) PROMs and (vi) costs of treatment. Ideally, future studies should adopt the CONSORT guidelines, apply sufficient statistical power, use appropriate randomization and avoid split-mouth designs.

It is well known that smoking adversely affects periodontal treatment outcomes. Therefore the results of studies with adjunctive laser application including smokers (Kamma et al., 2009; Rotundo et al., 2010) need to be interpreted accordingly. Furthermore, clinicians should be aware that the evidence on the effects of adjunctive therapy with different types of lasers or aPDT is affected by a number of factors such as: (i) the variation in diagnosis and risk profiles of patients with untreated periodontitis, (ii)

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the variation in protocols and frequency of non-surgical mechanical instrumentation, (iii) the variation in laser types/wavelengths, (iv) the variation in aPDT protocols, and (v) the variation in frequency of application of adjunctive laser or aPDT. Hence, in patients with untreated periodontitis, current evidence on the adjunctive use of lasers or aPDT to non-surgical periodontal therapy is limited and heterogeneous.

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Clinical relevance

Scientific rationale for review: Periodontitis is a biofilm-initiated disease and its treatment is accomplished by means of non-surgical mechanical instrumentation. The aim of the present systematic review was to investigate whether or not adjunctive application of laser or antimicrobial photodynamic therapy (aPDT) provides benefits to non-surgical periodontal therapy alone after a follow-up of 6 months.

Principal findings: Evidence on adjunctive therapy with laser or aPDT is limited and heterogeneous. One meta-analysis based on 2 articles (total n=42; split-mouth design) failed to identify a statistically significant difference (WMD=0.35 mm; 95%CI:-0.04/0.73; p=0.08) in mean PPD changes in favour of adjunctive aPDT with a wavelength range of 650-700 nm.

Out of 17 articles, 2 reported on patient-reported outcome measures and 10 reported on presence/absence of harms or adverse effects.

Practical implications: Available evidence on adjunctive therapy with lasers and aPDT is limited by (i) the low number of controlled studies and (ii) the heterogeneity of study designs. A high variability of clinical outcomes at 6 months was noted. Patient-reported benefits remain to be demonstrated.

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Conflict of interest

The authors do not report any conflicts of interest.

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References

Abduljabbar, T., Vohra, F., Kellesarian, S. V., & Javed, F. (2017) Efficacy of scaling and root planing with and without adjunct Nd:YAG laser therapy on clinical periodontal parameters and gingival crevicular fluid interleukin 1-beta and tumor necrosis factor-alpha levels among patients with periodontal disease: A prospective randomized split-mouth clinical study. *Journal of Photochemistry and Photobiology, 169*, 70-74. doi:10.1016/j.jphotobiol.2017.03.001.

Al-Askar, M., Al-Kheraif, A. A., Ahmed, H. B., Kellesarian, S. V., Malmstrom, H., & Javed, F. (2017). Effectiveness of mechanical debridement with and without adjunct antimicrobial photodynamic therapy in the treatment of periodontal inflammation among patients with prediabetes. *Photodiagnosis and Photodynamic Therapy, 20*, 91-94. doi:10.1016/j.pdpdt.2017.09.005

Al-Falaki, R., Cronshaw, M., & Parker, S. (2016). The adjunctive use of the Erbium, Chromium:Yttrium Scandium Gallium Garnet Laser in closed flap periodontal therapy. A retrospective cohort study. *Open Dentistry Journal, 13*(10) ,298-307. doi: 10.2174/1874210601610010298.

Angelov, N., Pesevska, S., Nakova, M., Gjorgoski, I., Ivanovski, K., Angelova, D., Hoffmann, O., & Andreana, S. (2009). Periodontal treatment with a low-level diode laser: clinical findings. *General Dentistry, 57*(5), 510-513.

Aoki, A., Ando, Y., Watanabe, H., & Ishikawa, I. (1994). In vitro studies on laser scaling of subgingival calculus with an erbium:YAG laser. *Journal of Periodontology, 65*(12), 1097-1106. doi:10.1902/jop.1994.65.12.1097

Armitage, G. C. (1999). Development of a classification system for periodontal diseases and conditions. *Annals of Periodontology, 4*(1), 1-6. doi:10.1902/annals.1999.4.1.1

Badersten, A., Nilveus, R., & Egelberg, J. (1984a). Effect of nonsurgical periodontal therapy. II. Severely advanced periodontitis. *Journal of Clinical Periodontology, 11*(1), 63-76.

Badersten, A., Nilveus, R., & Egelberg, J. (1984b). Effect of nonsurgical periodontal therapy. III. Single versus repeated instrumentation. *Journal of Clinical Periodontology, 11*(2), 114-124.

Balata, M. L., Andrade, L. P., Santos, D. B., Cavalcanti, A. N., Tunes Uda, R., Ribeiro Édel, P., & Bittencourt, S. (2013). Photodynamic therapy associated with full-

This article is protected by copyright. All rights reserved

mouth ultrasonic debridement in the treatment of severe chronic periodontitis: a randomized-controlled clinical trial. *Journal of Applied Oral Sciences, 21*(2), 208-14. doi: 10.1590/1678-7757201302366.

Berakdar, M., Callaway, A., Eddin, M. F., Ross, A., & Willershausen, B. (2012). Comparison between scaling-root-planing (SRP) and SRP/photodynamic therapy: six-month study. *Head & Face Medicine, 8*, 12. doi:10.1186/1746-160X-8-12

Betsy, J., Prasanth, C. S., Baiju, K. V., Prasanthila, J., & Subhash, N. (2014). Efficacy of antimicrobial photodynamic therapy in the management of chronic periodontitis: a randomized controlled clinical trial. *Journal of Clinical Periodontology, 41*(6), 573-581. doi:10.1111/jcpe.12249

Bundidpun, P., Srisuwantha, R., & Laosrisin, N. (2018). Clinical effects of photodynamic therapy as an adjunct to full-mouth ultrasonic scaling and root planing in treatment of chronic periodontitis. *Laser Therapy, 27*(1), 33-39. doi:10.5978/islsm.18-OR-03

Caffesse, R. G., Sweeney, P. L., & Smith, B. A. (1986). Scaling and root planing with and without periodontal flap surgery. *Journal of Clinical Periodontology, 13*(3), 205-210.

Castro Dos Santos, N. C., Andere N. M., Araujo C. F., de Marco A. C., Dos Santos L. M., Jardini M. A., & Santamaria M. P. (2016). Local adjunct effect of antimicrobial photodynamic therapy for the treatment of chronic periodontitis in type 2 diabetics: split-mouth double-blind randomized controlled clinical trial. *Lasers in Medical Science, 31*(8):1633-1640.

Ciurescu, C., Teslaru, S., Zetu, L., & Ciurescu D. (2016). Laser-assisted periodontal treatment: from bactericidal effect to local modificatiion of the host response. *Proceedings of SPIE* Vol. 9670 96700P-9.

Cobb, C. M. (2002). Discussion on laser curettage continues. *Journal of the California Dental Association, 30*(10), 718.

Cobb, C. M. (2017). Lasers and the treatment of periodontitis: the essence and the noise. *Periodontology 2000, 75*(1), 205-295. doi:10.1111/prd.12137

Crespi, R., Capparè, P., Toscanelli, I., Gherlone, E., & Romanos, G. E. (2007). Effects of Er:YAG laser compared to ultrasonic scaler in periodontal treatment: a 2-year follow-up split-mouth clinical study. *Journal of Periodontology, 78*(7), 1195-200.

This article is protected by copyright. All rights reserved

Accepted Article

Derdilopoulou, F. V., Nonhoff, J., Neumann K., & Kielbassa, A. M. (2007). Microbiological findings after periodontal therapy using curettes, Er:YAG laser, sonic, and ultrasonic scalers. *Journal of Clinical Periodontology, 34*(7), 588-598.

Dereci, O., Hatipoglu, M., Sindel, A., Tozoglu, S., & Üstün, K. (2016). The efficacy of Er,Cr:YSGG laser supported periodontal therapy on the reduction of peridodontal disease related oral malodor: a randomized clinical study. *Head & Face Medicine, 12*(1), 20. doi:10.1186/s13005-016-0116-y

Dilsiz, A., Canakci, V., & Aydin, T. (2013). Clinical effects of potassium-titanyl-phosphate laser and photodynamic therapy on outcomes of treatment of chronic periodontitis: a randomized controlled clinical trial. *Journal of Periodontology, 84*(3), 278-286. doi:10.1902/jop.2012.120096

Dilsiz, A., & Sevinc, S. (2014). KTP laser therapy as an adjunctive to scaling and root planing in treatment of chronic periodontitis. *Acta Odontologica Scandinavica, 72*(8), 681-686. doi:10.3109/00016357.2014.898088

Dobson, J., & Wilson, M. (1992). Sensitization of oral bacteria in biofilms to killing by light from a low-power laser. *Archives of Oral Biology, 37*(11), 883-887.

Eberhard, J., Ehlers, H., Falk, W., Acil, Y., Albers, H. K., & Jepsen, S. (2003). Efficacy of subgingival calculus removal with Er:YAG laser compared to mechanical debridement: an in situ study. *Journal of Clinical Periodontology, 30*(6), 511-518.

Eltas, A., & Orbak, R. (2012a). Clinical effects of Nd:YAG laser applications during nonsurgical periodontal treatment in smoking and nonsmoking patients with chronic periodontitis. *Photomedicine and Laser Surgery, 30*(7), 360-366. doi:10.1089/pho.2011.3184

Eltas, A., & Orbak, R. (2012b). Effect of 1,064-nm Nd:YAG laser therapy on GCF IL-1beta and MMP-8 levels in patients with chronic periodontitis. *Lasers in Medical Science, 27*(3), 543-550. doi:10.1007/s10103-011-0939-5

Euzebio Alves, V. T., de Andrade, A. K., Toaliar, J. M., Conde, M. C., Zezell, D. M., Cai, S., & De Micheli, G. (2013). Clinical and microbiological evaluation of high intensity diode laser adjutant to non-surgical periodontal treatment: a 6-month clinical trial. *Clinical Oral Investigations, 17*(1), 87-95. doi:10.1007/s00784-012-0703-7

Franco, E. J., Pogue, R. E., Sakamoto, L. H., Cavalcante, L. L., Carvalho, D. R., & de Andrade R. V. (2014). Increased expression of genes after periodontal treatment

This article is protected by copyright. All rights reserved

with photodynamic therapy. *Photodiagnosis and Photodynamic Therapy,* 11(1), 41-7. doi: 10.1016/j.pdpdt.2013.10.002.

Giannelli, M., Formigli, L., Lorenzini, L., & Bani, D. (2012). Combined photoablative and photodynamic diode laser therapy as an adjunct to non-surgical periodontal treatment: a randomized split-mouth clinical trial. *Journal of Clinical Periodontology*, *39*(10), 962-970. doi: 10.1111/j.1600-051X.2012.01925.x.

Giannelli, M., Formigli, L., Lorenzini, L., & Bani, D. (2015). Efficacy of combined photoablative-photodynamic diode laser therapy adjunctive to scaling and root planing in periodontitis: randomized split-mouth trial with 4-year follow-up. *Photomedicine and Laser Surgery*, *33*(9), 473-480. doi: 10.1089/pho.2015.3955.

Giannelli, M., Materassi, F., Fossi, T., Lorenzini, L., & Bani, D. (2018). Treatment of severe periodontitis with a laser and light-emitting diode (LED) procedure adjunctive to scaling and root planing: a double-blind, randomized, single-center, split-mouth clinical trial investigating its efficacy and patient-reported outcomes at 1 year. *Lasers in Medical Science*, *33*(5), 991-1002. doi: 10.1007/s10103-018-2441-9.

Grzech-Leśniak, K., Matys, J., & Dominiak, M. (2018). Comparison of the clinical and microbiological effects of antibiotic therapy in periodontal pockets following laser treatment: An in vivo study. *Advances in Clinical Experimental Medicine*, *27*(9), 1263-1270. doi: 10.17219/acem/70413.

Grzech-Leśniak, K., Sculean, A., & Gašpirc, B. (2018). Laser reduction of specific microorganisms in the periodontal pocket using Er:YAG and Nd:YAG lasers: a randomized controlled clinical study. *Lasers in Medical Science*, *33*(7), 1461-1470. doi: 10.1007/s10103-018-2491-z.

Gündogar, H., Senyurt, S. Z., Erciyas, K., Yalim, M., & Üstün, K. (2016). The effect of low-level laser therapy on non-surgical periodontal treatment: a randomized controlled, single-blind, split-mouth clinical trial. *Lasers in Medical Science, 31*(9), 1767-1773. doi:10.1007/s10103-016-2047-z

Hatipoglu, M., Aytekin, Z., Daltaban, Ö., Felek, R., Firat, M.Z., & Üstün, K. (2017). The effect of diode laser as an adjunct to periodontal treatment on clinical periodontal parameters and halitosis: a randomized controlled clinical trial. *Cumhuriyet Dental Journal, 20*(3), 152-160. doi:10.7126/cumudj.369035

This article is protected by copyright. All rights reserved

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Mdecial Journal, 327*(7414), 557-560. doi:10.1136/bmj.327.7414.557

Higgins, J. P., Altman, D. G., & Sterne, J. A. C. (2011). Assessing risk of bias in included studies (Chapter 8). In J. P. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*. Retrieved from www.handbook.cochrane.org.

Hill, G., Dehn, C., Hinze, A. V., Frentzen, M., & Meister, J. (2019). Indocyanine green-based adjunctive antimicrobial photodynamic therapy for treating chronic periodontitis: A randomized clinical trial. *Photodiagnosis and Photodynamic Therapy*, *26*, 29-35. doi:10.1016/j.pdpdt.2019.02.019.

Jepsen, S., Deschner, J., Braun, A., Schwarz, F., & Eberhard, J. (2011). Calculus removal and the prevention of its formation. *Periodontology 2000 55*, 167-188. doi:10.1111/j.1600-0757.2010.00382.x.

Kamma, J. J., Vasdekis, V. G., & Romanos, G. E. (2009). The effect of diode laser (980 nm) treatment on aggressive periodontitis: evaluation of microbial and clinical parameters. *Photomedicine and Laser Surgery, 27*(1), 11-19. doi:10.1089/pho.2007.2233

Kelbauskiene, S., Baseviciene, N., Goharkhay, K., Moritz, A., & Machiulskiene, V. (2011). One-year clinical results of Er,Cr:YSGG laser application in addition to scaling and root planing in patients with early to moderate periodontitis. *Lasers in Medical Science, 26*(4), 445-452. doi:10.1007/s10103-010-0799-4

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, 33(1), 159 - 174.

Malgikar, S., Reddy, S. H., Sagar, S. V., Satyanarayana, D., Reddy, G. V., & Josephin, J. J. (2016). Clinical effects of photodynamic and low-level laser therapies as an adjunct to scaling and root planing of chronic periodontitis: A split-mouth randomized controlled clinical trial. *Indian Journal of Dental Research, 27*(2), 121-126. doi:10.4103/0970-9290.183130

Matarese, G., Ramaglia, L., Cicciu, M., Cordasco, G., & Isola, G. (2017). The Effects of Diode Laser Therapy as an Adjunct to Scaling and Root Planing in the Treatment

Accepted Article

This article is protected by copyright. All rights reserved

of Aggressive Periodontitis: A 1-Year Randomized Controlled Clinical Trial. *Photomedicine and Laser Surgery,* 35(12), 702-709. doi:10.1089/pho.2017.4288

Meimandi, M., Talebi Ardakani, M. R., Esmaeil Nejad, A., Yousefnejad, P., Saebi, K., & Tayeed, M. H. (2017). The effect of photodynamic therapy in the treatment of chronic periodontitis: A review of literature. *Journal of Lasers in Medical Science*, *8* (Suppl 1), S7-S11. doi:10.15171/jlms.2017.s2.

Mizutani, K., Aoki, A., Coluzzi, D., Yukna, R., Wang, C. Y., Pavlic, V., & Izumi, Y. (2016). Lasers in minimally invasive periodontal and peri-implant therapy. *Periodontol 2000, 71*(1), 185-212. doi:10.1111/prd.12123

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., & Devereaux, P. J. Consolidated Standards of Reporting Trials, G. (2010). CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology, 63*(8), e1-37. doi:10.1016/j.jclinepi.2010.03.004

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*, 21, 6, e1000097. doi: 10.1371/journal.pmed.1000097

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., & Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews, 4*, 1. doi:10.1186/2046-4053-4-1

Moritz, A., Schoop, U., Goharkhay, K., Schauer, P., Doertbudak, O., Wernisch, J., & Sperr W. (1998). Treatment of periodontal pockets with a diode laser. *Lasers in Surgical Medicine*, 22(5), 302-311.

Obradović, R., Kesić, L., Mihailović, D., Jovanović, G., Antić, S., & Brkić, Z. (2012). Low-level lasers as an adjunct in periodontal therapy in patients with diabetes mellitus. *Diabetes and Technology Therapy*, *14*(9), 799-803. doi: 10.1089/dia.2012.0027.

Oda, S., & Ishikawa, I. (1989). In vitro effectiveness of a newly-designed ultrasonic scaler tip for furcation areas. *Journal of Periodontology*, *60*(11), 634-639. doi:10.1902/jop.1989.60.11.634

Pesevska, S., Gjorgoski, I., Ivanovski, K., Soldatos, N. K., & Angelov, N. (2017). The effect of low-level diode laser on COX-2 gene expression in chronic periodontitis

This article is protected by copyright. All rights reserved

patients. *Lasers in Medical Science*,s*32*(7),1463-1468. doi: 10.1007/s10103-017-2231-9.

Petrović, M. S., Kannosh, I. Y., Milašin, J. M., Mihailović, D. S., Obradović, R. R., Bubanj, S.R., & Kesić, L. G. (2018). Clinical, microbiological and cytomorphometric evaluation of low-level laser therapy as an adjunct to periodontal therapy in patients with chronic periodontitis. *International Journal of Dental Hygiene*, *16*(2), e120-e127. doi: 10.1111/idh.12328.

Pinheiro, S. L., Donegá, J. M.S., Seabra, L. M., Adabo, M. D., Lopes, T., do Carmo, T. H., Ribeiro, M. C., & Bertolini, P. F. (2010). Capacity of photodynamic therapy for microbial reduction in periodontal pockets. *Lasers in Medical Science*, *25*(1), 87-91. doi: 10.1007/s10103-009-0671-6

Pourabbas, R., Kashefimehr, A., Rahmanpour, N., Babaloo, Z., Kishen, A., Tenenbaum, H. C., & Azarpazhooh, A. (2014). Effects of photodynamic therapy on clinical and gingival crevicular fluid inflammatory biomarkers in chronic periodontitis: a split-mouth randomized clinical trial. *Journal of Periodontology, 85*(9), 1222-1229. doi:10.1902/jop.2014.130464

Qadri, T., Javed, F., Johannsen, G., & Gustafsson, A. (2015). Role of diode lasers (800-980 nm) as adjuncts to scaling and root planing in the treatment of chronic periodontitis: a systematic review. *Photomedicine and Laser Surgery*, *33*(11): 568-575. doi:10.1089/pho.2015.3914.

Qadri, T., Javed, F., Poddani, P., Tuner, J., & Gustafsson, A. (2011). Long-term effects of a single application of a water-cooled pulsed Nd:YAG laser in supplement to scaling and root planing in patients with periodontal inflammation. *Lasers in Medical Science, 26*(6), 763-766. doi:10.1007/s10103-010-0807-8

Quigley, G. A., & Hein, J. W. (1962). Comparative cleansing efficiency of manual and power brushing. *Journal of the American Dental Association*, *65*, 26-29.

Raut, C. P., Sethi, K. S., Kohale, B. R., Mamajiwala, A., & Warang, A. (2018). Indocyanine green-mediated photothermal therapy in treatment of chronic periodontitis: A clinico-microbiological study. *Journal of the Indian Society of Periodontology, 22*(3), 221-227. doi:10.4103/jisp.jisp_128_18

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Romero, S. S., Pinto, E. H., Longo, P. L., Dal Corso, S., Lanza, F. C., Stelmach, R., & Horliana, A. C. (2017). Effects of periodontal treatment on exacerbation frequency and lung function in patients with chronic periodontitis: study protocol of a 1-year randomized controlled trial. *BMC Pulmonary Medicine, 17*(1), 23. doi:10.1186/s12890-016-0340-z

Roncati, M., Gariffo, A., Barbieri, C., & Vescovi, P. (2017). Ten-Year Nonsurgical Periodontal Treatment Protocol with Adjunctive Use of Diode Laser Monitoring Clinical Outcomes in >/= 6 mm Pockets: A Retrospective Controlled Case Series. *The International Journal of Periodontics & Restorative Dentistry, 37*(5), 647-654. doi:10.11607/prd.2934

Rotundo, R., Nieri, M., Cairo, F., Franceschi, D., Mervelt, J., Bonaccini, D., & Pini-Prato, G. (2010). Lack of adjunctive benefit of Er:YAG laser in non-surgical periodontal treatment: a randomized split-mouth clinical trial. *Journal of Clinical Periodontology, 37*(6), 526-533. doi:10.1111/j.1600-051X.2010.01560.x

Ruiz Magaz, V., Santos Alemany, A., Hernández Alfaro, F., & Nart Molina, J. (2016). Efficacy of adjunctive Er, Cr:YSGG laser application following scaling and root planing in periodontally diseased patients. *International Journal of Periodontics and Restorative Dentistry*, *36*, 715–721. doi: 10.11607/prd.2660

Saglam, M., Kantarci, A., Dundar, N., & Hakki, S. S. (2014). Clinical and biochemical effects of diode laser as an adjunct to nonsurgical treatment of chronic periodontitis: a randomized, controlled clinical trial. *Lasers in Medical Science, 29*(1), 37-46. doi:10.1007/s10103-012-1230-0

Salgado, D., Noro-Filho, G. A., Cortes, A. R. G., Arita, E. S., Casarin, R. C. V., Costa, C., & Giovani, E. M. (2017). Effect of photodynamic therapy with malachite green on non-surgical periodontal treatment in HIV patients: a pilot split-mouth study. *Lasers in Medical Science, 32*(5), 1213-1217. doi:10.1007/s10103-016-2083-8

Sanz-Sanchez, I., Ortiz-Vigon, A., Matos, R., Herrera, D., & Sanz, M. (2015). Clinical efficacy of subgingival debridement with adjunctive erbium:yttrium-aluminum-garnet laser treatment in patients with chronic periodontitis: a randomized clinical trial. *Journal of Periodontology, 86*(4), 527-535. doi:10.1902/jop.2014.140258

This article is protected by copyright. All rights reserved

Schulz, K. F., Altman, D. G., Moher, D., & Fergusson, D. (2010). CONSORT 2010 changes and testing blindness in RCTs. *Lancet, 375*(9721), 1144-1146. doi:10.1016/S0140-6736(10)60413-8

Schwarz, F., Sculean, A., Georg, T., & Reich, E. (2001). Periodontal treatment with an Er: YAG laser compared to scaling and root planing. A controlled clinical study. *Journal of Periodontology, 72*(3), 361-367. doi:10.1902/jop.2001.72.3.361

Schwarz, F., Sculean, A., Berakdar, M., Georg, T., Reich, E., & Becker, J. (2003). Periodontal treatment with an Er:YAG laser or scaling and root planing. A 2-year follow-up split-mouth study. *Journal of Periodontology, 74*(5), 590-596. doi:10.1902/jop.2003.74.5.590

Schwarz, F., Sculean, A., Georg, T., & Becker, J. (2003). Clinical evaluation of the Er:YAG laser in combination with an enamel matrix protein derivative for the treatment of intrabony periodontal defects: a pilot study. *Journal of Clinical Periodontology, 30*(11), 975-981. doi:10.1034/j.1600-051x.2003.00412.x

Schwarz, F., Aoki, A., Becker, J., & Sculean, A. (2008). Laser application in non-surgical periodontal therapy: a systematic review. *Journal of Clinical Periodontology, 35*(8 Suppl), 29-44. doi:10.1111/j.1600-051X.2008.01259.x

Sculean, A., Schwarz, F., Berakdar, M., Romanos, G. E., Arweiler, N. B., & Becker, J. (2004). Periodontal treatment with an Er:YAG laser compared to ultrasonic instrumentation: a pilot study. *Journal of Periodontology, 75*(7), 966-973. doi:10.1902/jop.2004.75.7.966

Segarra-Vidal, M., Guerra-Ojeda, S., Valles, L. S., Lopez-Roldan, A., Mauricio, M. D., Aldasoro, M., & Vila, J. M. (2017). Effects of photodynamic therapy in periodontal treatment: A randomized, controlled clinical trial. *Journal of Clinical Periodontology, 44*(9), 915-925. doi:10.1111/jcpe.12768

Sgolastra, F., Severino, M., Gatto, R., & Monaco, A. (2013). Effectiveness of diode laser as adjunctive therapy to scaling root planning in the treatment of chronic periodontitis: a meta-analysis. *Lasers in Medical Science, 28*(5), 1393-1402. doi:10.1007/s10103-012-1181-5

Sgolastra, F., Severino, M., Petrucci, A., Gatto, R., & Monaco, A. (2014). Nd:YAG laser as an adjunctive treatment to nonsurgical periodontal therapy: a meta-analysis. *Lasers in Medical Science, 29*(3), 887-895. doi:10.1007/s10103-013-1293-6

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Silness, J., & Löe, H. (1964). Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontologica Scandinavica*, *22*, 121-135.

Sjöström, L., & Friskopp, J. (2002). Laser treatment as an adjunct to debridement of periodontal pockets. *Swedish Dental Journal, 26*(2), 51-57.

Stone, P. W. (2002). Popping the (PICO) question in research and evidence-based practice. *Applied Nurse Research, 15*(3), 197-198.

Theodoro, L. H., Silva, S. P., Pires, J. R., Soares, G. H., Pontes, A. E., Zuza, E. P., & Garcia, V. G. (2012). Clinical and microbiological effects of photodynamic therapy associated with nonsurgical periodontal treatment. A 6-month follow-up. *Lasers in Medical Science, 27*(4), 687-693. doi:10.1007/s10103-011-0942-x

Üstün, K., Erciyas, K., Sezer, U., Senyurt, S. Z., Gundogar, H., Ustun, O., & Oztuzcu, S. (2014). Clinical and biochemical effects of 810 nm diode laser as an adjunct to periodontal therapy: a randomized split-mouth clinical trial. *Photomedicine and Laser Surgery, 32*(2), 61-66. doi:10.1089/pho.2013.3506

Üstün, K., Hatipoglu, M., Daltaban, O., Felek, R., & Firat, M. Z. (2018). Clinical and biochemical effects of erbium, chromium: yttrium, scandium, gallium, garnet laser treatment as a complement to periodontal treatment. *Nigerian Journal of Clinical Practice, 21*(9), 1150-1157. doi:10.4103/njcp.njcp_51_18

Yadwad, K. J., Veena, H. R., Patil, S. R., & Shivaprasad, B. M. (2017). Diode laser therapy in the management of chronic periodontitis - A clinico-microbiological study. *Interventional Medicine & Applied Science, 9*(4), 191-198. doi:10.1556/1646.9.2017.38

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Tables

Table 1. Studies excluded based on full-text analysis and reasons for exclusion.

First author (year of publication)	Reason for exclusion
Abduljabbar et al. 2017	4*
Al-Falaki et al. 2016	3
Angelov et al. 2009	6*
Balata et al. 2013	4*
Castro Dos Santos et al. 2016	3
Ciurescu et al. 2016	3
Crespi et al. 2007	3
Derdilopoulou et al. 2007	4
Dilsiz & Sevinc 2014	5
Eltas & Orbak 2012b	5
Franco et al. 2014	1
Giannelli et al. 2012	3
Giannelli et al. 2015	3
Giannelli et al. 2018	3
Grzech et al. 2018a	3
Grzech et al. 2018b	3
Gündogar et al. 2016	3
Hill et al. 2019	4*
Moritz et al. 1998	1
Obradodovic et al. 2012	4
Pesevska et al. 2017	4
Petrovic et al. 2018	2
Pinheiro et al. 2010	1
Qadri et al. 2011	5
Romero et al. 2017	3
Roncati et al. 2017	1
Ruiz Magaz et al. 2016	4*
Saglam et al. 2014	1

Salgado et al. 2017	1
Sanz-Sanchez et al. 2015	1
Schwarz et al. 2001	3
Schwarz et al. 2003a	3
Schwarz et al. 2003b	3
Sculean et al. 2004	3
Segarra-Vidal et al. 2017	1
Sjöström & Friskopp 2002	2
Üstün et al. 2014	1
Yadwad et al. 2017	3
1, number of subjects < 20; 2, follow-up time < 6 months; 3, study protocol does not match with stated focused question; 4, endpoints do not match with stated inclusion criteria; 5, no data at 6-month follow-up; 6, other reasons (e.g. follow-up time unknown); * no author response to inquiry e-mail for data clarification	

Table 2. Characteristics of studies on adjunctive laser therapy to non-surgical mechanical instrumentation.

First author (year)	Study	Patient characteristics	Laser	Physical data	Treatment	Follow-up
	type design n center industrial funding calibration	n patients (n female) mean age ± SD (range) periodontal diagnosis smoking status n treated teeth/sites per treatment arm type of probe sites of probing per tooth	laser type (product name) material of tip (diameter)	laser power laser energy irradiation time wavelength laser intensity laser density		time points (mo) treatment adverse effects
Kamma et al. (2009)	RCT split-mouth single-center none examiner calibrated	30 patients (16 female) 41.8 ± 6.2 AgP 18 smokers, 12 non-smokers one quadrant per patient (1 site per treatment group per patient analyzed) Goldman/Fox-Williams 6	diode laser (SmilePro980™, Biolitec, Jena, Germany) flexible glass fiber optic guide (300 µm)	2 W n.r. 30 s/site 980 nm 2830 W/cm² 94.3 J/cm²	test group: SRP (hand) + laser control group: SRP (hand)	2 weeks – 3 – 6 n.r. n.r.
Rotundo et al. (2010)	RCT split-mouth single-center none examiner calibrated	27 patients* (18 female) 50.5 ± 11.7 ChP 12 smokers (<10 cigarettes/day), 15 non-smokers 419 sites for test and 422 sites for control group; one quadrant per patient§ n.r. 6	Er:YAG laser (Smart 2940 Plus, DEKA M.E.L.A. srl, Calenzano, Firenze, Italy) conic fiber tip (0.5 mm)	n.r. n.r. n.r. 2940 nm n.r. 150 mJ/pulse at 10 Hz	test group: laser + SRP (hand + ultrasonic) control group: SRP (hand + ultrasonic)	3 – 6 SPT after 1 week, 1, 3 and 6 mo 2 periodontal abscesses in the test group, 1 patient with fever, 1 patient lost 1 day of work, 1 patient with 1 day of daily-life interference
Kelbauskiene et al. (2011)	RCT split-mouth single-center n.r. examiner calibrated	30 patients (14 female) n.r. (26-58) early or moderate periodontitis non-smokers 143 teeth for control and 135 teeth for test group mean 8.4 (1.3) teeth per patient for control and mean 9.5 (2.2) teeth for test group (single-rooted teeth)§§ PCP 12 (Hu-Friedy, USA) 6	Er,Cr:YSGG laser (Waterlase, Biolase, Culver City, USA) fiber optic tip (600 µm)	1 W n.r. n.r. 2780 nm n.r. n.r.	test group: SRP (hand + ultrasonic) + laser** control group: SRP (hand + ultrasonic)	2 – 3 – 6 – 12 OHI, supragingival scaling and polishing none
Eltas and Orbak (2012a)	RCT split-mouth single-center none examiner calibrated	52 patients (26 female) 43.5 (32-52) ChP 26 smokers, 26 non-smokers 104, i.e. 2 teeth per patient n.r. 6	Nd:YAG laser (n.r.) fiber optic tip (n.r.)	1 W, 10 Hz 100 mJ 30 s/site 1064 nm n.r. n.r.	test group: SRP (hand + ultrasonic) + laser control group: SRP (hand + ultrasonic) + placebo laser	1 – 6 n.r. n.r.
Dilsiz et al. (2013)c	RCT split-mouth single-center none examiner calibrated	24 patients (14 female) 40.7 ± 7.3 (30-58) ChP non-smokers 144 teeth distributed over three treatment groups Florida Probe (Gainesville, USA) with an occlusal stent n.r.	KTP laser (SmartLite, DEKA, Florence, Italy) fiber optic tip (200 µm)	0.8 W n.r. n.r. 532 nm n.r. 11.7 J/cm²	test group: SRP in two sessions within 7 days (ultrasonic and hand) + laser control group: SRP in two sessions within 7 days (ultrasonic and hand) + placebo laser	6 prophylaxis after 1 and 3 mo none
Euzebio Alves et al. (2013)	RCT split-mouth single-center none examiner calibrated	36 patients (23 female) 46.8 ± 8.11 (37-64) ChP non-smokers 36 (single-rooted tooth) PCPUNC 15 (Hu-Friedy) 6	diode laser (ZAP Softlase, Pleasant Hill, USA) fiber optic tip (400 µm)	1.5 W n.r. 20 s/site 808 ± 5 nm 1193.7 W/cm² n.r.	test group: SRP (hand) + laser (2 applications: 1 day and 1 week after SRP) control group: SRP (hand) + placebo laser	1.5 – 6 SPT at 3 mo n.r.
Dereci et al. (2016)	RCT parallel arms single-center none	60 patients (29 female) 43.7 ± 3.1 ChP n.r. n.r.	Er,Cr:YSGG laser (Biolase, Irvine, California, USA fiber optic tip RFPT 5-14 (n.r.)	1.5 W, 30 Hz n.r. n.r. n.r. n.r. n.r.	test group: SRP (hand + ultrasonic) 1 time + laser, 3 times within 7 days control group:	1 – 3 – 6 n.r. none

	n.r.	Williams 6			SRP (hand + ultrasonic) 3 times within 7 days + placebo laser	
Hatipoglu et al. (2017)	RCT parallel arms single-center n.r. n.r.	40, (20^a/20^b) (20 female) n.r. ChP non-smokers n.r. n.r. 6	indium-gallium-aluminium-phosphate diode laser (Epic, Biolase, Irvine, CA, USA) fiber optic tip (300 µm)	1.5 W n.r. 20 s/tooth 940 nm n.r. 15 J/cm^2	test group: SRP (hand + ultrasonic) + laser control group: SRP (hand + ultrasonic)	1 – 3 – 6 n.r. n.r.
Matarese et al. (2017)	RCT split-mouth single-center none examiner calibrated	31 patients (17 female) 34.9 ± 1.2 AgP non-smokers n.r. (one maxillary quadrant with at least 6 teeth per patient) UNC-15 (Hu-Friedy, USA) 6	diode laser (Wiser Laser, Doctor smile, Lambda, Vicenza, Italy) fiber optic tip (300 µm)	1 W, 50 Hz n.r. 20 s/tooth 810 nm n.r. 24.84 J/cm^2	test group: SRP (ultrasonic) + laser control group: SRP (ultrasonic) + placebo gel solution	0.5 – 1 – 2 – 6 – 12 n.r. n.r.
Üstün et al. (2018)	RCT parallel arms single-center none n.r.	40, (20^a/20^b) (19 female) 45.8 ± 6.53 (36-59)[a], 44.05 ± 6.16 (35-58)[b] ChP non-smokers n.r. PWD (Hu-Friedy, USA) 6	Er,Cr:YSGG laser (Waterlase iplus, Biolase, Irvine, CA, USA) fiber optic tip RFPT 5-14 (n.r.)	1.5 W, 30 Hz n.r. n.r. n.r. n.r.	test group: SRP (hand + ultrasonic) + laser control group: SRP (hand + ultrasonic)	1 – 3 – 6 supragingival cleaning after 1, 3 and 6 mo n.r.

AgP, aggressive periodontitis; ChP, chronic periodontitis; Er:YAG, erbium-doped: yttrium aluminium garnet; Er,Cr:YSGG, erbium, chromium-doped: yttrium, scandium, gallium and garnet; GaAlAs, aluminium-gallium-arsenide; KTP, potassium-titanyl-phosphate; n, number; n.r., not reported; Nd:YAG, neodymium-doped: yttrium aluminium garnet; mo, months; OHI, oral hygiene instructions; SRP, scaling and root planning; SPT, supportive periodontal therapy; [a], test group; [b], control group; [c] study has 2 test groups see table 4; *, 1 patient lost to follow-up (26 patients were included in the analyses); **, laser application once a week for each millimeter of pocket reduction (on average 3 appointments); [§] finally analyzed: 405 sites for test and 399 for control group; [§§] finally analyzed: 509 for test and 579 for control group.

Table 3. Clinical outcome parameters of studies on adjunctive laser therapy to non-surgical mechanical instrumentation. If not otherwise indicated, parameters are presented as means ± standard deviation.

First author (year)	Group	Time point	PPD (mm)	PPD change (mm)	CAL (mm)	CAL change (mm)	BOP (%)	BOP change (%)	PI (%)
Kamma et al. (2009)	test	baseline	6.67 ± 1.29	-	7.07 ± 1.71	-	82.4	-	52.7
		6 mo	3.87 ± 0.92*	-	4.93 ± 1.62*	-	24.3	-	29.2
	control	baseline	6.47 ± 1.36	-	7.07 ± 1.58	-	81.6	-	54.1
		6 mo	4.13 ± 1.06*	-	5.20 ± 1.66*	-	25.8	-	32.6
Rotundo et al. (2010)	test	baseline	5.1 ± 1.1	-	5.7 ± 1.5	-	71	-	63
		6 mo	3.9 ± 1.5	1.2 ± 1.6	5.2 ± 1.8	0.5 ± 1.7	53	-	47
	control	baseline	5.2 ± 1.2	-	6.1 ± 1.6	-	73	-	68
		6 mo	4.3 ± 1.7	1.0 ± 1.5	5.6 ± 2.0	0.5 ± 1.8	57	-	48
Kelbauskiene et al. (2011)	test	baseline	4.33 ± 1.08**	-	4.47 ± 1.2**	-	79.0	-	3.5[a]
		6 mo	-	2.13 ± 1.24**	-	2.1 ± 1.26**	10.5	-	9.1[a]
	control	baseline	4.07 ± 0.79**	-	4.23 ± 0.92**	-	74.1	-	3.7[a]
		6 mo	-	1.64 ± 1.06**	-	1.57 ± 1.11**	17.0	-	14.1[a]
Eltas and Orbak (2012a)	test[b]	baseline	5.4 ± 0.8	-	6.7 ± 1.1	-	-	-	1.9 ± 0.6[d]
		6 mo	3.8 ± 0.6	-	6.4 ± 1.1	-	-	-	0.8 ± 0.5[d]
	control[b]	baseline	5.4 ± 0.7	-	6.6 ± 1.2	-	-	-	1.7 ± 0.6[d]
		6 mo	4.2 ± 0.5	-	6.5 ± 1.1	-	-	-	0.7 ± 0.5[d]
	test[c]	baseline	5.3 ± 0.7	-	6.1 ± 1.1	-	-	-	1.7 ± 0.8[d]
		6 mo	3.1 ± 0.5*	-	5.6 ± 1.0	-	-	-	0.6 ± 0.4[d]
	control[c]	baseline	5.3 ± 0.8	-	6.1 ± 0.9	-	-	-	1.8 ± 0.5[d]
		6 mo	3.6 ± 0.5*	-	5.8 ± 1.0	-	-	-	0.6 ± 0.5[d]
Dilsiz et al. (2013)	test	baseline	5.96 ± 0.91	-	7.75 ± 0.61	-	96 ± 0.20	-	1.42 ± 0.58[e]
		6 mo	3.92 ± 0.41*	2.08 ± 1.02	5.33 ± 1.05*	2.42 ± 1.14	42 ± 0.50*	-	0.75 ± 0.44[e]
	control	baseline	5.83 ± 0.76	-	7.50 ± 0.72	-	92 ± 0.28	-	1.46 ± 0.51[e]
		6 mo	4.42 ± 0.88*	1.42 ± 0.88	6.04 ± 1.00*	1.50 ± 0.88	46 ± 0.51	-	0.71 ± 0.46[e]
Euzebio Alves et al. (2013)	test	baseline	6.13 ± 1.35	-	6.91 ± 1.94	-	97.2 ± 16.6	-	1.25 ± 0.99[d]
		6 mo	3.63 ± 1.49	2.56 ±1.79	5.33 ± 2.13	1.70 ± 1.72	40.1 ± 49.3	57.1	0.66 ± 0.88[d]
	control	baseline	5.69 ± 0.95	-	6.50 ± 1.74	-	94.4 ± 23.2	-	1.47 ± 0.90[d]
		6 mo	2.93 ± 1.33	2.76 ±1.13	4.30 ± 2.08	2.10 ± 1.64	33.6 ± 47.2	60.8	0.60 ± 0.77[d]
Dereci et al. (2016)	test	baseline	5.3 ± 1.8	-	2.9 ± 0.6	-	75.1 ± 7.2	-	2.4 ± 0.5[e]
		6 mo	1.9 ± 0.7	-	1.8 ± 0.5	-	37.8 ± 7.7*	-	1.5 ± 0.5[e]
	control	baseline	5.3 ± 1.8	-	2.9 ± 0.4	-	77.7 ± 7.4	-	2.5 ± 0.5[e]
		6 mo	2.1 ± 0.6	-	1.9 ± 0.4	-	41.6 ± 8.6*	-	1.5 ± 0.5[e]
Hatipoglu et al. (2017)	test	baseline	4.05 ± 0.64	-	3.03 ± 0.65	-	75.9 ± 6.79	-	1.88 ± 0.27
		6 mo	1.88 ± 0.55	-	1.75 ± 0.58	-	21.7± 8.16*	-	1.25 ± 0.15*
	control	baseline	4.00 ± 0.53	-	2.74 ± 0.59	-	74.8 ± 7.59	-	1.86 ± 0.28
		6 mo	1.95 ± 0.81	-	1.81 ± 0.60	-	31.5 ± 7.23*	-	1.41 ± 0.16
Matarese et al. (2017)	test	baseline	5.25 ± 0.66	-	5.36 ± 0.39	-	75.26 ± 3.6	-	28.21 ± 5.12
		6 mo	2.24 ± 0.35		3.19 ± 0.22	-	22.79 ± 4.2	-	24.55 ± 3.36
	control	baseline	5.18 ± 0.57	-	4.88 ± 0.55	-	78.12 ± 2.2	-	28.54 ± 5.23
		6 mo	2.68 ± 0.29	-	3.11 ± 0.25	-	24.67 ± 3.2	-	25.04 ± 3.69
Üstün et al. (2018)	test	baseline	3.88 ± 0.50	-	2.69 ± 0.47	-	74.75 ± 7.59	-	1.72 ± 0.32
		6 mo	1.83 ± 0.80	-	1.76 ± 0.56	-	26.85 ± 7.39	-	1.32 ± 0.16
	control	baseline	3.97 ± 0.72	-	2.88 ± 0.58	-	77.30 ± 7.64	-	1.78 ± 0.35
		6 mo	2.03 ± 0.73	-	1.76 ± 0.57	-	32.70 ± 7.55	-	1.21 ± 0.15

BOP, bleeding on probing; CAL, clinical attachment loss; PI, plaque index; PPD, probing pocket depth; *, $p<0.05$; **, $p<0.001$; [a], percentage of teeth presenting visible plaque; [b], smokers; [c], non-smokers; [d], according to Silness & Löe (1964); [e], according to Löe (1967).

Table 4. Characteristics of studies on adjunctive aPDT to non-surgical mechanical instrumentation.

First author (year)	Study	Patient characteristics	Laser	Physical data	Treatment	Follow-up
	type design n center industrial funding calibration	n patients (n female) mean age ± SD (range) periodontal diagnosis smoking status n treated teeth/sites per treatment arm sites of probing per tooth	laser type (product name) material of tip (diameter) photosensitizer application time/site	laser power laser energy irradiation time wavelength laser intensity laser density		time points (mo) supportive therapy adverse effects
Berakdar et al. (2012)	RCT split-mouth single-center none n.r.	22 patients (10 female) 59.3 ± 11.7 (38-74) ChP non-smokers 44 teeth (with ≥ 1 site with BoP and PPD ≥ 5 mm) PCP 12 (Hu-Friedy, USA) 6	diode laser (Periowave, Ondine Biopharma, Vancouver, Canada) n.r. (600 µm) methylene blue 0.005 % n.r.	150 mW n.r. 60 s 670 nm n.r. n.r.	test group: SRP (hand) + aPDT control group: SRP (hand)	1 – 3 – 6 n.r. none
Theodoro et al. (2012)	RCT split-mouth single-center none examiner calibrated	33 patients (21 female) 43.12 ± 8.2 (n.r.) ChP non-smokers 33 sites (BoP, PPD 5-9 mm, approximal) PCP-UNC 15 (Hu-Friedy), occlusal stent n.r.	diode laser/GaAlAs laser (BioWave, Kondortech Equipment, São Carlos, Brazil) fiber optic tip (n.r.) toluidine blue O 100 µg/ml n.r.	30 mW 4.5 J 150 s/site 660 nm 0.4 W/cm^2 64.28 J/cm^2	test group: SRP (hand) + aPDT control group: SRP (hand)	2 – 3 – 6 OHI and professional prophylaxis (weekly in month 1, bimonthly in month 2-3, monthly in month 4-6) none
Dilsiz et al. (2013)[e]	RCT split-mouth single-center none examiner calibrated	24 patients (14 female) 40.7 ± 7.3 (30-58) ChP non-smokers 144 teeth distributed over three treatment groups Florida Probe (Gainesville, USA) with an occlusal stent n.r.	diode laser/AlGaAs laser (Doctor Smile diode, LAMBDA Scientifica, Vicenza, Italy) fiber optic tip (300 µm) methylene blue 1 % 3 min	100 mW 6 J 60 s 808 nm n.r. n.r.	test group: FM-SRP (ultrasonic) without time restriction + 1 week later SRP (hand) + aPDT control group: FM-SRP (ultrasonic) without time restriction + 1 week later SRP (hand) + placebo laser	6 professional prophylaxis after 1 and 3 mo none
Betsy et al. (2014)	RCT parallel arms single-center none examiner calibrated	88[#] patients (44[a], 44[b]) 51 female (22 [a], 29[b]) 40.8 ± 8.3[a], 38.4 ± 9.6[b] ChP non-smokers 109[a], 120[b] teeth (PPD 4-6 mm, single-rooted) Williams 4	diode laser (CNI Opto-electronics Tech. Co. Ltd, Changchun, China) fiber optic tip (200 µm) methylene blue 10 mg/ml 3 min	1000 mW n.r. 60 s/site 655 nm n.r. 60 mW/cm^2	test group: FM-SRP (hand + ultrasonic) without time restriction + aPDT control group: FM-SRP (hand + ultrasonic) without time restriction	0.5 – 1 – 3 – 6 n.r. none
Malgikar et al. (2016)	RCT split-mouth single-center none	24 patients (9 female) 36.73 ± 8.46[c], 34.33 ± 6.80[d] (24-55) ChP non-smokers	diode laser (DenLase; China Daheng Group, Inc., Beijing China) fiber optic tip (400 µm)	1000 mW (5.0 W peak power, with 200 µs pulse length + 200 µs pulse interval) n.r.	test group: FM-SRP (hand + ultrasonic) + aPDT (24 h later) control group	1 – 3 – 6 OHI after 1, 3 and 6 mo none

	examiner calibrated	n.r. UNC-15, occlusal stent n.r.	methylene blue 1 % 3 min	30-45 s/site 980 nm n.r. n.r.	FM-SRP (hand + ultrasonic)	
Al-Askar et al. (2017)	RCT parallel arms single-center none examiner calibrated	70 patients (35[a], 35[b]) 0 female 45.7 ± 0.8[a], 42.5 ± 2.6[b] n.r. non-smokers n.r. (≥ 6 sites with PPD ≥ 4 mm per patient) graded probe (Hu-Friedy,USA) 6	diode laser (Periowave, Ondine Biopharma, Vancouver, Canada) flexible tip methylene blue 0.005 % n.r.	150 mW n.r. 60 s/site 670 nm n.r. n.r.	test group: FM-SRP (ultrasonic) + aPDT control group: FM-SRP (ultrasonic)	3 – 6 n.r. n.r.
Bundipun et al. (2018)	RCT split-mouth single-center none n.r.	20 patients (13 female) 47.25 ± 8.91 (35-70) ChP non-smokers 839[a], 789[b] sites UNC-15 (Hu-Friedy, USA) 6	diode laser (HELBO Photodynamic Systems, Senden, Germany) fiber optic tip (n.r.) phenothiazine chloride 1 min	100 mW n.r. 10 s/site (6 sites per tooth) 660 nm n.r. n.r.	test group: FM-SRP (ultrasonic) + aPDT (1 week later) control group: FM-SRP (ultrasonic)	1 – 3 – 6 OHI and supragingival cleaning after 1, 3 and 6 mo none
Raut et al. (2018)	RCT parallel arms single-center none examiner calibrated	50 patients* (25[a], 25[b]) 22 female (9[a], 13[b]) 51 ± 2.83[a], 46.90 ± 4.32[b] ChP non-smokers n.r. University of North Carolina no15 (Hu-Friedy, USA) 6	diode laser/GaAlAs laser (n.r.) n.r. indocyanine green 5 mg/ml 1 min	800 mW n.r. 60 s/tooth 810 nm n.r. 5.4 J/cm^2	test group: SRP (hand + ultrasonic) + aPDT control group: SRP (hand + ultrasonic) + placebo laser	6 n.r. none

AlGaAs, aluminium-gallium-arsenide laser; BoP, bleeding on probing; ChP, chronic periodontitis; FM, full mouth; hand, hand instruments; GaAlAs, aluminium-gallium-arsenide laser; n, number; n.r., not reported; mo, months; OHI, oral hygiene instruction; aPDT, antimicrobial photodynamic therapy; PPD, probing pocket depth; RCT; randomized controlled clinical trial; SRP, scaling and root planing; [a], test; [b], control; [c], males; [d], females; [e], study has 2 test groups see table 2; *, 5 patients lost to follow-up; [#], 3 patients lost to follow-up and 2 patients discontinued intervention.

Table 5. Clinical outcome parameters of studies on adjunctive aPDT to non-surgical mechanical instrumentation. If not otherwise indicated, parameters are presented as means ± standard deviation.

First author (year)	Group	Time point	PPD (mm)	PPD change (mm)	CAL (mm)	CAL change (mm)	BOP (%)	BOP change (%)	PI (%)
Berakdar et	test	baseline	6.4 ± 0.8	-	8.1 ± 1.3	-	100[c]	-	-

		6 mo	-	2.9 ± 0.8*	-	-	13.6[c]	-	-
	control	baseline	5.9 ± 0.8	-	7.2 ± 1.2	-	100[c]	-	-
		6 mo	-	2.4 ± 0.6	-	-	22.7[c]	-	-
Theodoro et al. (2012)	test	baseline	5.75 ± 1.44	-	6.52 ± 2.11	-	93.9	-	90.9
		6 mo	3.42 ± 1.15	-	4.96 ± 2.07	-	45.5	-	27.3
	control	baseline	5.81 ± 1.0	-	6.23 ± 1.25	-	97.0	-	93.9
		6 mo	3.1 ± 0.83	-	4.25 ± 1.73	-	27.3	-	15.2
Dilsiz et al. (2013)	test	baseline	5.88 ± 0.74	-	7.67 ± 0.56	-	88 ± 0.34	-	1.50 ± 0.51[d]
		6 mo	4.33 ± 0.48	1.54 ± 0.59	6.13 ± 0.99	1.54 ± 1.10	38 ± 0.49	-	0.79 ± 0.41[d]
	control	baseline	5.83 ± 0.76	-	7.50 ± 0.72	-	92 ± 0.28	-	1.46 ± 0.51[d]
		6 mo	4.42 ± 0.88	1.42 ± 0.88	6.04 ± 1.00	1.50 ± 0.88	46 ± 0.51	-	0.71 ± 0.46[d]
Betsy et al. (2014)	test	baseline	5.7 (5.0-6.0;1.0)[a]	-	6.5 (5.0-8.0;1.4)[a]	-	-	-	2.0 (0.5-3.0;0.8)[a,e]*
		6 mo	3.0 (2.0-6.0;1.0)[a]*	-	4.0 (2.6-7.0;2.0)[a]*	-	-	-	1.0 (0.0-2.5;1.0)[a,e]
	control	baseline	5.5 (4.2-6.0;1.0)[a]	-	6.0 (4.2-8.0;1.7)[a]	-	-	-	1.2 (0.5-3.0;1.0)[a,e]*
		6 mo	4.0 (2.0-6.0;1.0)[a]*	-	4.5 (2.0-7.0;2.0)[a]*	-	-	-	0.5 (0.0-2.0;0.5)[a,e]
Malgikar et al. (2016)	test	baseline	6.13 ± 0.38	-	6.59 ± 0.50	-	-	-	2.54 ± 1.70[e]
		6 mo	3.57 ± 0.41*	2.57 ± 0.53	4.04 ± 0.37	2.55 ± 0.44	-	-	1.73 ± 0.49[e]
	control	baseline	6.16 ± 0.40	-	6.63 ± 0.53	-	-	-	2.49 ± 1.73[e]
		6 mo	3.65 ± 0.49*	2.50 ± 0.54	4.00 ± 0.39	2.63 ± 0.47	-	-	1.60 ± 0.52[e]
Al-Askar et al. (2017)	test	baseline	15.8 ± 3.4[b]	-	-	-	51.6 ± 7.9	-	54.4 ± 8.4
		6 mo	10.4 ± 2.5[b]	-	-	-	40.3 ± 5.6	-	42.5 ± 6.7
	control	baseline	17.2 ± 3.4[b]	-	-	-	56.4 ± 9.3	-	51.6 ± 7.5
		6 mo	13.6 ± 2.8[b]	-	-	-	44.5 ± 8.2	-	47.2 ± 7.4
Bundidpun et al. (2018)	test	baseline	4.96 ± 1.11	-	5.15 ± 1.56	-	85.50	-	3.01 ± 1.07[f]
		6 mo	2.97 ± 0.74	1.99 ± 0.89	3.99 ± 1.23	1.16 ± 1.16	33.30*	52.20	2.06 ± 1.09[f]
	control	baseline	4.91 ± 1.02	-	5.01 ± 1.57	-	83.60	-	3.02 ± 1.08[f]
		6 mo	3.02 ± 0.81	1.89 ± 0.92	3.89 ± 1.33	1.12 ± 1.16	40.50*	43.10	2.15 ± 1.06[f]
Raut et al. (2018)	test	baseline	6.04 ± 0.82	-	5.80 ± 0.70	-	100	-	1.52 ± 0.46[e]
		6 mo	3.53 ± 0.58**	-	4.12 ± 0.78**	-	10*	-	0.60 ± 0.47[e]
	control	baseline	6.08 ± 0.73	-	5.68 ± 0.69	-	100	-	1.48 ± 0.44[e]
		6 mo	5.08 ± 0.66**	-	4.96 ± 0.73**	-	40*	-	0.68 ± 0.45[e]

BOP, bleeding on probing; CAL, clinical attachment loss; PI, plaque index; PPD, probing pocket depth; *, p<0.05; **, p< 0.001; [a], median (range;inter-quartile range); [b], number of sites with PPD ≥ 4 mm; [c], % cases with ≥ 1 tooth with BOP; [d], according to Löe (1967); [e], according to Silness & Löe (1964); [f], Turesky modification of Quigley & Hein (1962).

Table 6a. Frequency of reported secondary outcomes of included articles on adjunctive laser therapy.

First author (year)	CAL change	BoP change	Plaque Index change	Residual PPD	Change in subgingival biofilm composition	Changes in GCF biomarker levels/volumes	PROMS	Harms or adverse effects

Üstün et al. (2018)	+	+	+	NR	NR	+	NR	NR
Matarese et al. (2017)	+	+	+	NR	+	+	NR	NR
Hatipoglu et al. (2017)	+	+	+	NR	NR	NR	NR	NR
Dereci et al. (2016)	+	+	+	NR	+	NR	NR	+
Euzebio Alves et al. (2013)	+	+	+	+	+	NR	NR	NR
Dilsiz et al. (2013)	+	+	+	NR	NR	NR	NR	+
Eltas & Orbak (2012a)	+	NR	+	NR	NR	+	NR	NR
Kelbauskiene et al. (2011)	+	+	NR	NR	NR	NR	NR	+
Rotundo et al. (2010)	+	+	+	NR	NR	NR	+	+
Kamma et al. (2009)	+	+	+	NR	+	NR	NR	NR
Total	**10 (100%)**	**9 (90%)**	**9 (90%)**	**1 (10%)**	**4 (40%)**	**3 (30%)**	**1 (10%)**	**4 (40%)**

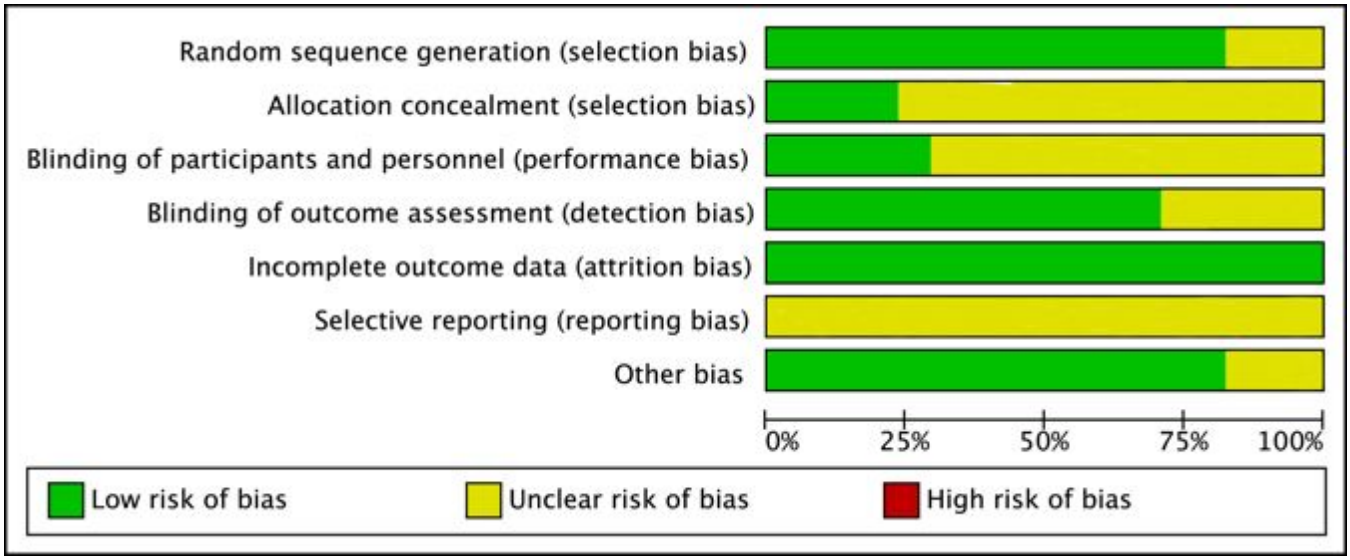
PPD	Probing Pocket Depth
CAL	Clinical Attachment Level
BoP	Bleeding on Probing
GCF	Gingival Crevicular Fluid
PROMs	Patient-Reported Outcome Measures
NR	Outcome not reported
+	Outcome reported

Table 6b. Frequency of reported secondary outcomes of included articles on adjunctive antimicrobial photodynamic therapy (aPDT).

First author (year)	CAL change	BoP change	Plaque Index change	Residual PPD	Changes in subgingival biofilm composition	Changes in GCF biomarker levels/volumes	PROMs	Harms or adverse effects
Raut et al. (2018)	+	+	+	NR	+	NR	NR	+
Bundipun et al. (2018)	+	+	+	+	NR	NR	NR	+
Al-Askar et al. (2017)	NR	+	+	NR	NR	NR	NR	NR
Malgikar et al. (2016)	+	NR	+	NR	NR	NR	NR	+
Betsy et al. (2014)	+	NR	+	NR	NR	NR	+	+
Dilsiz et al. (2013)	+	+	+	NR	NR	NR	NR	+
Berakdar et al. (2012)	+	+	+	NR	NR	NR	NR	+
Theodoro et al. (2012)	+	+	+	NR	+	NR	NR	+
Total	**7 (88%)**	**6 (75%)**	**8 (100%)**	**1 (13%)**	**2 (25%)**	**0 (0%)**	**1 (13%)**	**7 (88%)**

PPD	Probing Pocket Depth
CAL	Clinical Attachment Level
BoP	Bleeding on Probing
GCF	Gingival Crevicular Fluid
PROMs	Patient-Reported Outcome Measures
NR	Outcome not reported
+	Outcome reported

Table 7a+b. Parameters provided in the Cochrane Center and CONSORT guidelines (Consolidated Standards of Reporting Trials) to evaluate the quality of randomized controlled trials (RCTs).



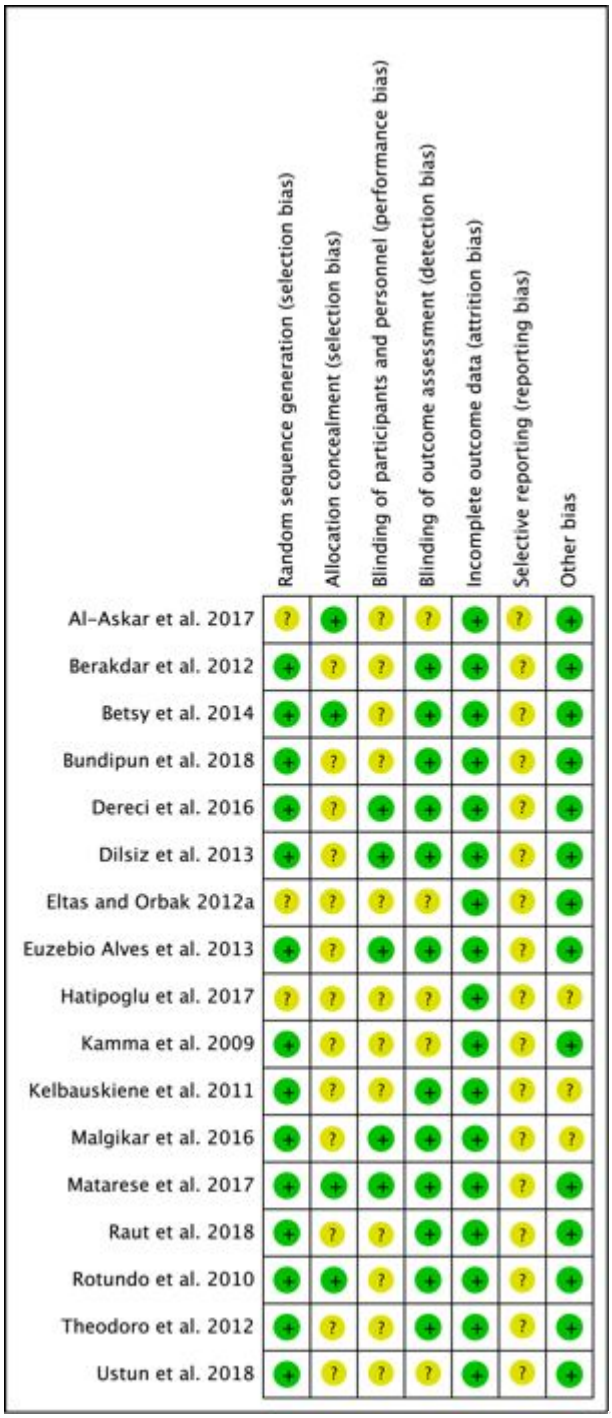

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Al-Askar et al. 2017
Berakdar et al. 2012
Betsy et al. 2014
Bundipun et al. 2018
Dereci et al. 2016
Dilsiz et al. 2013
Eltas and Orbak 2012a
Euzebio Alves et al. 2013
Hatipoglu et al. 2017
Kamma et al. 2009
Kelbauskiene et al. 2011
Malgikar et al. 2016
Matarese et al. 2017
Raut et al. 2018
Rotundo et al. 2010
Theodoro et al. 2012
Ustun et al. 2018

Figure 1. PRISMA flow chart depicting the selection process.

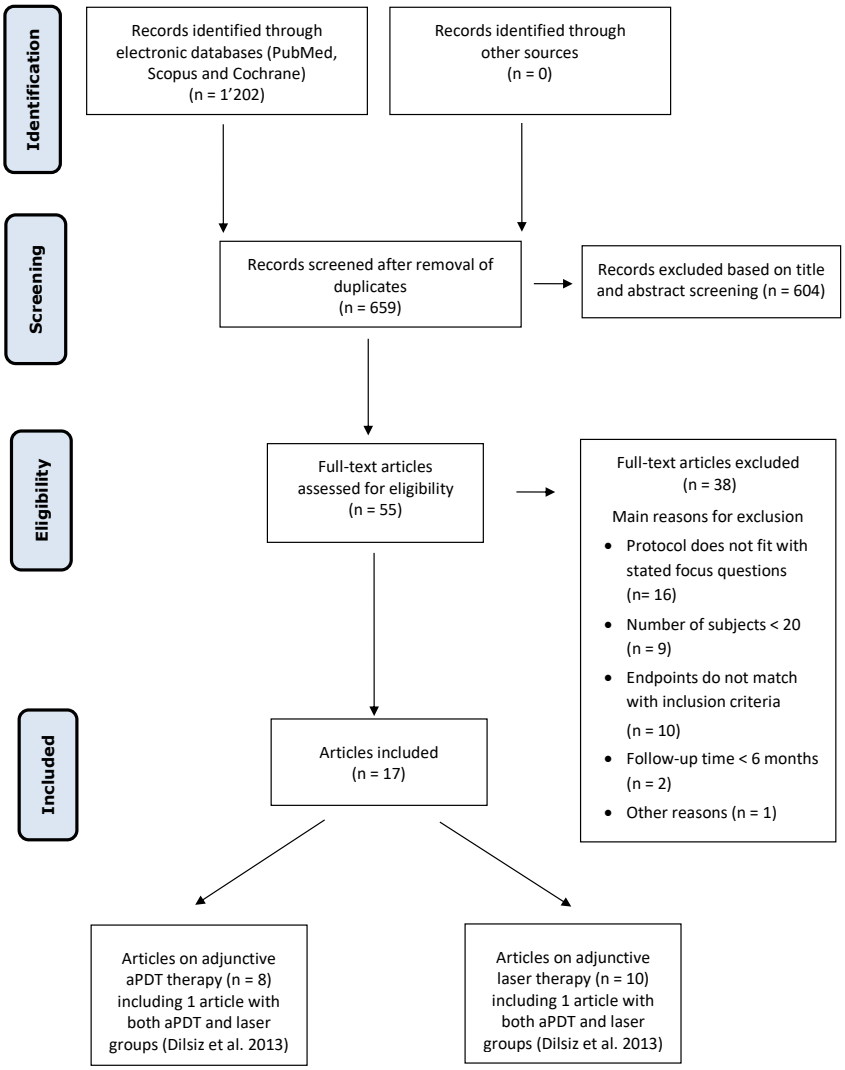


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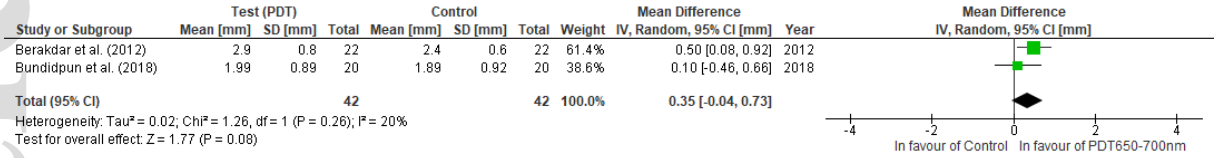
Figure 2. Forest plot of the weighted mean change in PPD at 6 months with adjunctive aPDT with diode lasers (wavelength range 650-700 nm; test) compared with non-surgical mechanical instrumentation alone (control).



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