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Comparison of Photothermal and Photodynamic Diode Laser Therapy in Patients with Peri-implant Mucositis: A Systematic Review

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LIST OF SYMBOLS AND ACRONYMS

- AlGaAs: Aluminum Gallium Arsenide
- aPDT: antimicrobial photodynamic therapy
- GaAs: Gallium Arsenide
- He: Helium
- HILT: High-Intensity Laser Therapy
- LLLT: Low-Level Laser therapy
- LED: Light-Emitting Diode
- MeSH: Medical Subject Heading
- Ne: Neon
- PICO: Population/ Patient, Intervention, Comparison, Outcome
- PRISMA: Preferred Reporting Items for Systematic Review and Meta- Analysis
- PT: Photothermal therapy
- RCT: Randomized Controlled Trial

ABSTRACT

Title: Comparison of Photothermal and Photodynamic Diode Laser Therapy in Patients with Peri-implant Mucositis: A Systematic Review.

Background: Considering that there is an increasing number of patients seeking dental implant treatments, the prevention and treatment of their associated complications illustrate a serious and relevant challenge. Peri-implant mucositis is a peri-implant inflammatory disease where it´s key diagnostic criteria is bleeding on probing. Over the years, both photothermal and antimicrobial photodynamic diode laser therapies were tested alongside mechanical debridement to evaluate their effects on inflammatory clinical parameters. It is documented that diode laser therapy is effective as an adjuvant in decreasing inflammatory clinical signs compared to conventional therapy alone. There is, however, a lack of studies comparing the efficacy of photothermal laser therapy to photodynamic laser therapy as adjuvants. Therefore, the present systematic review aims to compare the efficacy of both diode laser therapies by analyzing the Plaque Index (PI), Probing Pocket Depth (PPD) and Bleeding on Probing (BoP) at a 3-month follow-up period.

Methods: Both CRAI library Ducle Chacón and Elsevier's Scopus search engines were used to perform the search on February 10th, 2022. The databases included in CRAI library Ducle Chacón are the following: Medline Complete, Academic Search Ultimate, Dentistry & Oral Sciences Source, CINAHL and E-Journals. Studies were excluded based on the following exclusion criteria: 1) animal and in-vitro studies; 2) studies published in 2011 or before; 3) studies in languages other than English or Spanish. Studies were included based on the following inclusion criteria: 1) cohort study or randomized control trial (RCT); 2) population based on patients with peri-implant mucositis; 3) intervention used either photothermal diode laser therapy or photodynamic diode laser therapy as an adjuvant to conventional therapy; 4) clinical outcome measured includes the bleeding on probing index; 5) follow-up of at least 3 months. The risk of bias of each study was assessed with Cochrane Collaboration tool RoB 2.

Results: Seven randomized controlled trials (RCTs) were included in the systematic review ranging from 38-220 individuals per study. PI reduction was 18.6%, 9.2% and 2.5% greater in aPDT and 0.177%, 5.3% and 7.2% greater in PT compared to the control

groups. PPD reduction 0.072mm and 0.2mm greater than the control group in two studies for PT. Greater differences of 3.1mm and 0.5mm were noted for aPDT. The reductions observed in BoP 0.303%, 5.7% and 7.5% greater in PT than the control group. Reductions of 1.6% and 2.5% were observed in aPDT studies.

Discussion: aPDT studies demonstrated greater abilities in reducing the PI and PD however, PT studies demonstrated significant improvements of the BoP index. This is achieved not only through the decontamination of pathogenic bacteria but, especially through the biostimulation of peri-implant tissues. The seven articles have a risk of bias ranging from low risk to high risk of bias. For that reason, although the photodynamic laser therapy shows more promising results in terms of reducing PI and PD, those studies showed an overall higher risk of bias compared to the studies experimenting with photothermal laser therapy. Additional homogenous studies with a longer follow-up period are needed with the proper study design to accurately compare the results obtained. Future homogenous research should be guided towards determining whether one therapy is more useful in specific populations or clinical situations.

KEYWORDS

- Peri-implant mucositis
- Diode laser therapy
- Photothermal laser therapy
- Photodynamic laser therapy
- Bleeding on probing

1.INTRODUCTION

1.1 IMPLANTOLOGY

1.1.1 Background & Definition

Dating back to prehistoric times, anthropologists and paleontologists have brought forth several findings demonstrating human beings practicing dental replacement. The loss of tooth structure has been problematic since the dawn of humanity mainly because one's inability to sustain oneself. Henceforth, dental replacements have evolved tremendously into what is now known as modern dental implantology. Modern-day implantology encompasses great advancements in not only the materials used but also in their designs and maintenance. According to the U.S Food & Drug Administration, an implant is defined as a "medical [device] surgically implanted into the jaw to restore a person's ability to chew or their appearance. They provide support for artificial [...] teeth, such as crowns, bridges, or dentures" (1). Since the 1990s, the branches of dentistry have expanded to include that of dental implantology. Nowadays, dental implants are in great use, especially in totally or partially edentulous patients owing to their predictable and long-term surgical-prosthodontic nature (2). Considering that the use of implants is becoming more sought-after, it is crucial to recognize the criteria necessary for a successful dental implant treatment.

1.1.2 Survival Rate vs Success Rate of Implants

In the field of implantology, the most common way to study the performance of dental implants is to evaluate their survival and success rates. The best implant designs and techniques are characterized based on these rates. It is important to differentiate a dental implant's success rate from its survival rate. Mistakenly, many use these terms interchangeably. The survival rate of a dental implant refers to the amount of time the implant remains in the patient's mouth. The survival rate alone cannot determine the overall success of a dental implant. Dental implants have a high survival rate, with a mean survival rate of 94.6%, ranging from 73.4% to 100% in a 10-years follow-up. In contrast, dental implants have a much lower success rate, ranging from 34.9% to 100% with a mean success rate of 89.7% in a 15-year follow-up period (3). This is because the success of a dental implant takes into consideration both the health and functionality of the dental implant. Therefore, the difference between dental implant survival and success rates is the increasing incidence of complications. As the number of patients

receiving dental implants continues to increase every year, the complications derived from the treatment also increase accordingly (4)(5). Taking this into consideration, an implant that survives in the patient's mouth for a long period of time but with biological or mechanical complications is an unsuccessful dental implant treatment. Conversely, for an implant to be deemed successful, it must not only be able to survive in the patient's mouth but also meet additional criteria referred to as success criteria. The first and widely used success criteria of dental implants is that proposed by Albrektsson et al. in 1986 (6). These criteria are regarded as the basis of dental implant success. Over the years, different authors proposed the modification and/or addition of the criteria for a more complete overview. Table 1 enumerates the first established success criteria as well as the most recent criteria proposed.

Table 1: Evolution of Success Criteria for Dental Implant

Authors/Year	Criteria for implant success
Dr. Sanjay et al. (2019) (7)	1. Absence of pain, discomfort, or persistent infection 2. Lack of implant mobility 3. Lack of peri-implant radiolucency 4. Lack of marginal bone loss (normal bone loss is 1.5mm for the first year after implant placement then 0.1 mm every year afterwards). 5. Sulcus and Probing Depth ** 6. Gingival Status based on Mombelli et al. Gingival inflammation classification. 7. Absence of damage to adjacent teeth and anatomical structures *** 8. Implant must allow an esthetically pleasant restoration placement. 9. 5-year success rate between 87.5%- 96.5% and 10-year success rate at 93% at the mandibular symphysis. 81%- 82% success rate after 5-10 years in the maxilla. *
Albrektsson T et al. (1986) (6)	1. That an individual, unattached implant is immobile when tested clinically. 2. That a radiograph does not demonstrate any evidence of peri-implant radiolucency. 3. That vertical bone loss be less than 0.2mm annually following the implant's first year of service. 4. That individual implant performance be characterized by an absence of persistent and/ or irreversible signs and symptoms such as pain, infections, neuropathies, paresthesia, or violation of mandibular canal. 5. That, in the context of the above, a successful rate of 85% at the end of five-year observation period and 80% at the end on a ten-year period be minimum criterion for success. *

** Success criteria are not definite indications of implant success and numbers may change overtime.*

*** Success criterion suggests further research needed before including it as primary criteria.*

**** Success criterion indicates complication due to iatrogenic origin.*

1.1.3 Mechanical and Biological Complications

Considering that there is an increasing number of patients seeking dental implant treatments, the prevention and treatment of their associated complications illustrate a serious and relevant challenge (5). Despite great advancements in implant innovations, it is important to note both the presence of mechanical and biological complications. Mechanical complications are consequences that encompass the fracture of the implant body, abutment screw and/or prosthesis (8). Mechanical complications may happen either immediately after implant placement or at a later period. Early implant failure is due to the lack of osseointegration. Late implant failure, however, is the result of fractures that happen mainly due to material fatigue or biomechanical overloading (8). Consequently, patients report implant mobility, spontaneous gingival bleeding, large pocket depth, plaque accumulation and pain. On the other hand, biological complications refer to the late failure of a dental implant secondary to infections or peri-implant diseases. This results in the loss of biological structures needed to support the implant.

1.2 PERI-IMPLANT DISEASE

In 1993, peri-implant diseases were first defined and described at the First European Workshop on Periodontology held in Ittingen, Switzerland (9). Peri-implant disease was solely understood as an inflammatory reaction that occurs in the tissues surrounding a functional implant (10). At the most recent World Workshop in Periodontology held in 2017, however, it was proposed that to accurately define peri-implant diseases, the term “peri-implant health” should first be clarified. Peri-implant health is defined as the absence of clinical signs such as erythema, bleeding on probing and inflammation, in the peri-implant mucosa. Peri-implant diseases embody peri-implant mucositis, peri-implantitis and implant failure. According to the most recent consensus report from the World Workshop in Periodontology, peri-implant mucositis is defined as a reversible peri-implant mucosal inflammation in absence of continuous marginal peri-implant bone loss. Periimplantitis, however, is an irreversible inflammatory reaction that causes an additional loss of bone surrounding a functional

implant. Implant failure is an inflammatory reaction in soft tissues as well as the loss of bone integration and implant mobility (11).

1.3 PERI-IMPLANT MUCOSITIS

1.3.1 Definition, Prevalence, Etiology, and Mechanism of action

Although peri-implant pathologies are significantly prevalent and therefore a topic that should not be overlooked, the actual prevalence is oftentimes disputable. This is mainly due to the lack of homogeneity when it comes to the definition of peri-implant diseases as well as the methods used to assess them. This is seen in, for example, the systematic review published by Froum et al (12). There exists a wide range in figures when it comes to the prevalence of peri-implant mucositis, ranging between 20 and 80% of patients with dental implants after a minimum of 5 years with prosthetic rehabilitation in place (12). What is clear is that according to several scientific publications, the most frequent complication that may arise subsequent to implant placement is peri-implant mucositis. The definition of peri-implant mucositis from the latest World Workshop of Periodontology is currently valid for research purposes. Table 2 depicts how the definition of peri-implant mucositis changed over the years. The most recent definition defines peri-implant mucositis as “peri-implant mucosal inflammation in absence of continuous marginal peri-implant bone loss” (11). Based on a 2021 cross-sectional study carried out by Romandini et al., the prevalence of peri-implant mucositis is 31.9% while that of periimplantitis is 27.9% at implant-level (13). After implant placement, healthy conditions of the peri-implant mucosa are those considered to have a “barrier epithelium and the presence of scattered inflammatory cells [which] constitute the soft tissues seal separating the peri-implant attachment from the oral cavity” (14). Peri-implant mucositis is an unfavorable condition that arises due to the pathological transformation of healthy peri-implant mucosal tissue to one that is pathogenic. Notably, the surfaces of the titanium dental implant acquire a bacterial biofilm which then initiates an inflammatory response. A healthy peri-implant mucosa or a peri-implant mucosa suffering from peri-implant mucositis has a similar microbiota to that of natural teeth with healthy periodontium or gingivitis respectively. Peri-implant mucositis develops in healthy peri-implant mucosa after accumulation of bacterial

biofilm around osseointegrated dental implants. Evidence-based literature demonstrates the cause-effect relationship in humans between the experimental accumulation of biofilm and the development of an inflammatory response (14). Typical bacteria present in a peri-implant pocket suffering from peri-implant mucositis are cocci, motile bacilli, and spirochetes. There is a noticeable increase of F. nucleatum, P. intermedia and Eubacterium species while a decrease in Streptococci spp. and Actinomyces spp. (15). Scientific research shows not only the cause-effect relationship between biofilm bacterial accumulation and peri-implant mucositis, as it occurs in gingivitis, but also that the inflammatory response of peri-implant tissue is much greater than that observed in the periodontium under similar conditions. This indicates a greater susceptibility to inflammatory pathologies (16)(17).

Table 2: The Evolution of the Definition of Peri-implant Mucositis

Authors/Year	Definition of Peri-implant Mucositis	Diagnostic Criteria
Berglundh T, Armitage G, et al. **(2018)** (11)	Peri-implant mucosal inflammation in absence of continuous marginal peri-implant bone loss	○ Presence of bleeding and/or suppuration on gentle probing (0.25N). ○ Absence of bone loss beyond crestal bone level changes (<1 mm) resulting from initial bone remodeling. ○ May be accompanied by an increased periodontal probing depth compared to previous examinations. ○ Radiographs to assess bone level
Sanz M, Chapple IL **(2012)** (18)	Peri-implant mucositis describes an inflammatory lesion that resides in the mucosa. It does not affect the underlying bone. The pathology is reversible.	○ Presence of bleeding and/or suppuration on gentle probing (0.25N). ○ Absence of bone loss beyond crestal bone level changes (<1 mm) resulting from initial bone remodeling. ○ May be accompanied by increased periodontal probing depth compared to previous examinations. ○ Radiographs to assess bone level

Lang NP & Berglundh T (2011) (19)	Peri-implant mucositis describes an inflammatory lesion that resides in the mucosa. It does not affect the underlying bone. The pathology is reversible.	○ The key parameter for the diagnosis of peri-implant mucositis is bleeding on gentle probing (0.25 N).
Lindhe J & Meyle J. (2008) (20)	Peri-implant mucositis describes an inflammatory lesion that resides in the mucosa. It does not affect the underlying bone. The pathology is reversible.	○ Peri-implant mucositis may be identified clinically by redness and swelling of the soft tissue, but bleeding on probing is currently recognized as the important feature.

1.3.2 Clinical Manifestations

The main clinical manifestation of peri-implant mucositis is bleeding on gentle probing. Other signs and symptoms include erythema, swelling and/or suppuration. The different definitions of mucositis have evolved as the understanding of this disease advances, however, the element that remains stable over the years is that peri-implant mucositis is described as the inflammation of the peri-implant tissues with bleeding on probing being the main clinical sign. A lack of peri-implant inflammation indicates a lack of peri-implant mucositis. Similar to gingivitis, peri-implant mucositis is a reversible pathology, however, the inflammatory response is significantly more aggressive around the surface of the implant compared to the former. Due to its reversibility, it is important to stress prophylactic measures, early diagnosis, as well as early treatment to prevent its evolution into a much more aggressive pathology: peri-implantitis (11).

1.3.3 Risk Factors

Understanding the risk factors of peri-implant diseases can help one develop a prophylactic mechanism against the pathology. Although the accumulation of pathogenic bacterial on the biofilm is the main risk factor with the most scientific evidence involved in the development of peri-implant mucositis, other risk factors associated with this pathology have been documented as well. Some of the evidence-based risk factors include deficient oral hygiene, tobacco consummation and previous history of periodontitis or mucosal diseases. Particularly, bacterial plaque accumulation

is the most significant risk factor in the initiation of peri-implant diseases. Furthermore, the absence of keratinized mucosa influences hygiene levels and the health of peri-implant tissue causing its retraction. Table 3 enumerates local, systemic, and patient-related risk indicators of peri-implant mucositis. Controlling these risk factors is key in preventing peri-implant diseases. It is especially crucial to control and facilitate the patient's oral hygiene habits (21).

Table 3: Local, Systemic & Patient-Related Risk Indicators of Peri-implant Mucositis (21)

Local Risk Indicators	**Systemic Risk Indicators**	**Patient Related Risk Indicators**
→ Plaque accumulation	→ Tobacco*	→ Poor oral Hygiene
→ Implant surface characteristics	→ Radiation therapy*	→ Maintenance visits
	→ Diabetes Mellitus*	→ Function time of the implant
→ Residual cement		→ Genetics*
→ Keratinized tissue		→ Sex (male)*

** Indication of weak evidence or weak correlation between the risk factor and peri-implant mucositis.*

1.3.4 Diagnosis

Diagnosing peri-implant diseases is crucial since the pathology is time-dependent. Detecting peri-implant diseases in the initial phases favours one's ability to control the disease. To diagnose peri-implant mucositis, the clinical manifestations must be present. Peri-implant mucositis requires the "[p]resence of bleeding and/or suppuration on gentle probing with or without increased probing depth compared to previous examinations" and the "[a]bsence of bone loss beyond crestal bone level changes resulting from initial bone remodeling" (11). To detect the presence of inflammation, clinicians use a combination of the following three techniques: inspection, palpation, and probing. A peri-implant probe is used to measure the peri-implant pocket. It is important to note that there is no definitive pocket depth that indicates the presence or absence of peri-implant disease. What is important is to compare values obtained immediately after implant placement to the values obtained during follow-up revisions. Notably, a force of no more than 0.25N should be used to avoid damaging peri-implant tissues and possible iatrogenic peri-implant tissue loss (19). To objectively assess the level of inflammation, the following three indices depicted in Table 4A and Table 4B are used respectively: plaque index and modified gingival

bleeding index. More specifically, Loe & Silness' plaque index (1964) is used to evaluate the amount of biofilm (22). Mombelli's (1987) modified gingival bleeding index is a modification of Loe & Silness' classic gingival index but catered towards dental implants (23). This index is used to assess the clinical characteristics of the different levels of gingival inflammation. The probing depth is also used to objectively indicate peri-implant inflammation seen in peri-implant mucositis. As mentioned earlier, there is no definitive pocket depth that suggests pathogenicity, however, it is important to recognize increasing probing depth over a length of time. Alongside probing depth, periapical radiographs must be done to monitor the crestal bone levels. Bearing in mind that peri-implant mucositis is an inflammatory pathology with the absence of crestal bone loss, increasing probing depth must be strictly due to inflammation and not the reduction of bone level.

Table 4 Loe & Silness's Plaque Index (1994)

Score	Criteria
0	No Plaque
1	A film of plaque adhering to the free gingival margin and adjacent area of the tooth. They plaque may be seen in situ only after application of plaque revealing agents or by probing the tooth surface.
2	Moderate accumulation of soft deposits within the gingival pocket, or on the tooth and gingival margin which can be seen with the naked eye
3	Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

Silness J, Löe H. Periodontal Disease in Pregnancy II. Correlation Between Oral Hygiene and Periodontal Condition. Acta Odontol Scand. 1964 Feb;22:121-35. (22)

Table 5: Mombelli's Modified Gingival Bleeding Index (1987)

Score	Criteria
0	No bleeding when a periodontal probe is passed along the gingival margin adjacent to the implant.
1	Isolated bleeding spots visible
2	Blood forms a confluent red line on margin
3	Heavy or profuse bleeding

Mombelli A, van Oosten MA, Schurch E Jr, Land NP. The microbiota associated with successful or failing osseointegrated titanium implants. Oral Microbiol Immunol. 1987 Dec;2(4):145-51. (23)

1.4 TREATMENT OF PERI-IMPLANT MUCOSITIS

1.4.1 Conventional Therapy: Mechanical Debridement

Over the past couple of decades, there has been a surge of studies aimed towards providing patients with peri-implant diseases with the optimal treatment plan. Notably, effective treatment plans for peri-implant mucositis are being sought to avoid the evolution of the disease into peri-implantitis. Mechanical debridement, the most common professional non-surgical intervention, is the conventional treatment of peri-implant mucositis. It is a procedure that involves the utilization of curettes and ultrasounds to remove plaque, calculus, and debris. According to a randomized controlled clinical trial carried out by Javed et al., after treating peri-implant patients with mechanical debridement, there was a statistically significant reduction in the plaque index and periodontal pocket depth after 12 weeks (24). Unfortunately, complete destruction of bacteria is difficult to achieve with conventional therapy alone (21). This limiting outcome has been depicted in multiple studies including that carried out by Salvi et al. Their study demonstrated that despite mechanical debridement showing a reduction of gingival inflammation, there was still an elevated level of inflammatory host markers such as matrix-metalloproteinase-8 (16). Likewise, a study carried out by Heitz et al. demonstrated that the bleeding on probing index of 76% of dental implants improved after one month of mechanical debridement. After 3 months, 38% of implants have shown complete resolution. Microbiologically, however, there is no significant change. After 1 month of conventional therapy, there is a slight decrease in bacterial DNA, however, the bacterial load returns to baseline levels after 3 months (25). Similarly, Thöne-Mühling et al.'s pilot study depicted an insignificant change of bacterial load with conventional therapy since a decrease of the bacterial load was only seen immediately after treatment. These values returned to baseline levels after the 8-month follow-up revision (26). Moreover, accomplishing adequate mechanical debridement with curettes and ultrasonic scalers is difficult to achieve without damaging the implant (27). Due to these limitations in the conventional non-surgical treatment of peri-implant mucositis, adjuvant elements are being studied to improve the clinical outcomes. One of the most studied therapies today is the use of diode laser for phototherapy purposes.

1.4.2 Lasers and Diode Lasers: Definition and History

Light amplification by the stimulated emission of radiation, known as laser for short, is an electro-optic device that produces a narrow and highly energized monochromatic beam of radiation of a specific wavelength. When aimed at atoms or molecules, their stimulation and release of photons occur. Therefore, depending on the wavelength of the laser and the area where it is applied, different optical phenomena may occur (27).

Diode lasers are semiconductor lasers made up of a Gallium Arsenide (GaAs) or Aluminum Gallium Arsenide (AlGaAs). They emit a wavelength in the near-infrared spectrum between 800 and 1000nm. Since this cannot be detected by the human eye, it is oftentimes accompanied by a Helium (He) and Neon (Ne) marker laser. As it is a contact laser, a glass optical fiber with a specific handpiece as the transmission medium, of different diameters, depending on the applications, is necessary. The diode laser can be used at different powers up to a maximum of 10 W (27)(28)(29). In addition to the physical properties of laser operation, the reaction of the tissues to laser light must also be taken into consideration. Since the oral cavity has highly differentiated and specialized cells, applying laser therapy in this area is very complex. Hard and soft tissues in the oral cavity have different optical characteristics and therefore different response although the same laser and wavelength are used (30).

Periodontal phototherapy is a treatment employed in dentistry in order to improve periodontal health. Lasers are greatly employed due to their great ability to interact with soft tissues. The guide to use of lasers for therapeutic purposes depends on the type of laser used and the desired thermal effects on targeted tissues. To advance in the understanding of laser therapy in oral tissues, it is crucial to explore the main photobiological effects. These are the effects that the laser beam produces when it is absorbed by the oral tissues. The main photobiological effects are photothermal and photochemical effects. The most widely used diode laser therapies are based on these two effects (31).

1.4.3 Photothermal Therapy and Peri-implant Mucositis

Photothermal therapy (PT) is the first type of phototherapy studied. Beneficial thermal properties of photothermal therapy on tissues are very precise cuts, vaporization, and coagulation of small blood vessels. This therapy is based on the conversion of light energy into thermal energy which results in the increasing temperature of tissues (30)(27). Essentially, part of the emitting photon is transformed into heat at the tip of the laser. Consequently, a heated tip is formed enabling its ability to cut through soft tissues. Additionally, there arise both thermic and hemostatic side effects. Areas irradiated by lasers may cause various degrees of thermal denaturation. Since diode lasers are deep penetrating lasers, they are known to produce great amounts of coagulation and moderate amounts of carbonization (30). Thanks to their photothermal effects, lasers also have antimicrobial and detoxification effects. This is important in peri-implant diseases since it can help heal periodontal pockets as well as inhibit recurrent bacterial colonization on the biofilm. Moreover, laser therapy may act as a prophylactic measure for bacteremia (30). Therefore, depending on the temperature achieved, different photobiological effects are seen.

In essence, photothermal therapy functions due to an increase in local temperature induced by the action of the laser. The light energy is exposed to the tissue for a period of time inducing a thermal interaction. Thus, photothermal therapy is mainly used for tissue incision, excision, ablation, vaporization, hemostasis, and coagulation (32).

1.4.4 High-Intensity Laser Therapy vs Low-Level Laser Therapy

Photothermal laser therapy can be differentiated into the following two subcategories according to the power at which the diode laser is being used: high-intensity laser therapy (HILT) and low-level laser therapy (LLLT). In HILT, the laser emits a power greater than 0.5 W while in LLLT, the laser power should not exceed 0.5W. LLLT clinical effects can also be achieved at higher wattages but with tips of application that emit out of focus (33). Lasers' photobiomodulating characteristic depends heavily on the amount of energy applied. The objective of HILT is to destroy diseased tissues and to achieve an aseptic/detoxified zone. It also has the ability to scatter its energy into surrounding tissue and therefore, promote tissue healing and regeneration. On the

other hand, LLLT promotes cellular regeneration without producing irreversible thermal changes (30).

The main benefits of using diode laser in photothermal therapy are microbial decontamination and biostimulation of surrounding tissues. Experimental studies show that the main etiological factor involved in the development of mucositis is the accumulation of bacteria on the biofilm (29)(30). It is therefore vital that the diode laser acts against this bacterial load. Bacterial decontamination is achieved by using HILT. Studies including that of Moritz et al. show that the bactericidal effects of diode lasers include the destruction of the main aggressive pathogens: Actinobacillus actinomycetemcomitans, Prevotella intermedia and Porphyromonas gingivalis (34). Biostimulation of surrounding peri-implant tissues is the result of both bacterial decontamination and thermal effects. This can be achieved by using both high-intensity and low-level laser therapy. Applying HILT on the peri-implant surfaces also results in the penetration heat of lower intensity towards the deepest layers. This results in higher levels of heat on the external surface compared to deeper surfaces of peri-implant tissues. Thus, HILTs provide a combination of both bactericidal and biostimulator effects. On the other hand, LLLT is designed to uniquely provide biostimulator effects. The basis of LLLT is that its activity in tissues is due to the interaction of electromagnetic waves with cells rather than thermal effects (35). Hence, this therapy revolves around the use of solely light to directly stimulate host cells to reduce inflammation, relieve pain, and /or promote wound healing (30)(35).

1.4.5 Photodynamic therapy and Peri-implant mucositis

Antimicrobial Photodynamic therapy (aPDT) is a laser therapy based on a photochemical mechanism of action rather than a photothermal one. A photochemical mechanism of action is the interaction of light photons to initiate a chemical reaction. It involves the use of a photosensitizer, laser light source and tissue molecular oxygen. A pigment called a photosensitizer is used to selectively reach the targeted cell or microorganism aimed to be eliminated. In essence, photosensitizers are exposed to a light source at a wavelength specific to the selected pigment. This results in the photosensitizer to become energized to what is known as a highly energized triplet-state

photosensitizer. These energized photosensitizer molecules are then ultimately exposed to tissue oxygen in order to cause cellular damage (30)(36).

Antimicrobial Photodynamic therapy has only been recently introduced in dentistry for antimicrobial reasons. It is used to treat periodontal and peri-implant diseases. This therapy can successfully kill bacteria without altering the surfaces of implants. Although this is promising, one of the challenges about this type of therapy is finding a photosensitizing agent that targets pathogenic bacteria. It is important to keep in mind that these agents are not necessarily sensitive to all pathogenic bacteria species. Oftentimes, natural oral flora bacteria are targeted which will lead to other complications. For example, a common photosensitizer used is toluidine blue O. In a study published by Mattiello et al, when combining toluidine blue with a diode laser light source, the levels of both Aggregatibacter actinomycetemcomitans and Streptococcus sanguinis decreased (34). However, a systematic review published by Al Habashneh et al. illustrated that although this is true, the regrowth of P gingivalis, Prevotella intermedia, Tannerella forsythia, and Treponema denticola has been observed (38). Therefore, this supports the fact that the efficacy of aPDT depends heavily on the type of photosensitizer used. In aPDT, a photosensitizer should ideally possess the following properties: a high yield of singlet oxygen, high binding affinity for microorganisms, wide spectrum of action, low binding affinity for mammalian cells to avoid the risk of damage to host tissues, minimal risk of promoting mutagenic processes, and low chemical toxicity (39)(40). Most photosensitizers commercialized in dentistry are made from Methylene Blue, Toluidine Blue or their derivatives such as Tolonium. Commonly, these photosensitizers are available in low concentrations (> 0.1%), and the light, laser or Light-Emitting Diodes (LEDs), ranges in wavelength between 635 and 660nm with powers close to 50mW. It is important to note that other combinations of photosensitizers and wavelengths do exist (36).

The general indications of aPDT are to eliminate bacteria, fungi, viruses, and microbes resistant to other types of treatments. According to a randomized controlled clinical trial published by Javed et al., there is a greater statistically significant reduction in the plaque index, bleeding on probing index and periodontal pocket depth in patients who have undergone photodynamic therapy immediately after mechanical debridement compared to those who have only received mechanical debridement alone

(41). Similarly, in the clinical study published by Ramos et al., mechanical debridement alongside aPDT demonstrated a greater improvement in peri-implant parameters compared to mechanical debridement alongside systemic antibiotics and thus should be an alternative to systemic antibiotics (42).

As previously noted, both photothermal and photodynamic diode laser therapy have their benefits and limitations. Both therapies are used in conjunction with conventional mechanical therapies to improve their efficacies. There is, however, no data currently present comparing the efficacy of PT to aPDT. Hence, the present systematic review aims to compare the efficacy of both therapies.

2. JUSTIFICATION, HYPOTHESIS AND OBJECTIVES

2.1 JUSTIFICATION

Considering dental implants are becoming more widespread over the years, the increase of peri-implant diseases is anticipated. Peri-implant mucositis is the most prevalent peri-implant disease that arises from dental implant treatments. When left untreated, it can progress into a substantially more severe pathology known as periimplantitis. Peri-implantitis is an irreversible peri-implant disease that not only causes mucosal inflammation but also rapid and irreversible bone loss. Consequently, there is an increased risk of losing the dental implant at this stage considering that adequate bone support is a requisite for implant stability. Furthermore, periimplantitis can initiate or worsen systemic conditions. Due to the gravity of this pathology, researchers are invested in discovering the optimal treatment plan. Non-surgical techniques such as mechanical debridement is still used to control bacterial plaque accumulation on the biofilm. Inevitably, regenerative, and non-regenerative surgical techniques are also implemented to arrest and regenerate bone loss. Evidently, not only are the clinical manifestations considerably more complex in the case of periimplantitis, but so are the treatment plans. Generally, these treatment plans are over a longer period of time and are more costly. The additional complications, poor prognosis, and complex treatment plan of peri-implantitis are reasons to gear our focus towards its the prevention. Preventing peri-implant mucositis from progressing into periimplantitis is key in ensuring the best prognosis and simpler treatment plan.

As noted earlier, peri-implant mucositis is a reversible peri-implant pathology. It is not accompanied by bone loss hence, with adequate treatment, it is possible to reverse the disease. Through early diagnosis and intervention, the reversal of peri-implant mucositis is promising. Currently, there are numerous treatment strategies recommended to help manage peri-implant mucositis. Conventional therapy or mechanical debridement is a required intervention to initiate the initial steep reduction of bacterial biofilm accumulation. Adjuvant treatments are then recommended to further decrease the bacterial load and prevent its regrowth. In patients with peri-implant mucositis, it is documented that photothermal diode laser therapy is effective as an adjuvant in decreasing inflammatory clinical signs compared to conventional therapy alone. Similarly, studies show that antimicrobial photodynamic diode laser therapy is effective as an adjuvant in decreasing inflammatory clinical signs compared

to conventional therapy alone. There is, however, a lack of evidence comparing the efficacy of photothermal laser therapy to photodynamic laser therapy. The unknown is whether the former treatment is superior, inferior, or equal in efficacy compared to the latter. Therefore, the present systematic review aims to compare the efficacy of both therapies in order to make the most efficient choice when it comes to treating patients with peri-implant mucositis.

2.2 HYPOTHESIS

The null hypothesis for the following systematic review is that there is no statistically significant difference between using photothermal laser therapy compared to photodynamic laser therapy as an adjuvant in reducing clinical signs of patients with peri-implant mucositis.

2.3 OBJECTIVES

The **main objective** of this systematic review is to determine which laser therapy, photodynamic laser therapy or photothermal laser therapy, demonstrates greater improvement in clinical signs of peri-implant mucositis as an adjunct to mechanical debridement.

The **specific objectives** are the following:

1. To evaluate the clinical effect of diode laser therapies, as adjunctive treatment to conventional therapy for peri-implant mucositis, in reducing the plaque index.
2. To evaluate the clinical effect of diode laser therapies, as adjunctive treatment to conventional therapy for peri-implant mucositis, in reducing the bleeding on probing.
3. To evaluate the clinical effect of diode laser therapies, as adjunctive treatment to conventional therapy for peri-implant mucositis, in reducing the peri-implant probing depth.

3. MATERIALS AND METHODS

3.1 SELECTION CRITERIA

3.1.1 Protocol and Focus Question

The Preferred Reporting Items for Systematic Review and Meta- Analysis (PRISMA) guideline was followed to perform this systematic review (52). Based on the information mentioned in the introduction and justification, a clinical question was written according to the PICO structure to center the systematic review. The following focus question was employed according to the population, intervention, comparison, and outcome study design: **Among patients with peri-implant mucositis (P), does photothermic laser therapy (I) demonstrate greater improvement in clinical inflammatory signs (O) in comparison to photodynamic therapy (I) as an adjuvant to conventional therapy (C)?**

3.1.2 Inclusion and Exclusion Criteria

Studies were excluded based on the following exclusion criteria: 1) animal and in-vitro studies; 2) studies published in 2011 or before; 3) studies in languages other than English or Spanish. Studies were included based on the following inclusion criteria: 1) cohort study or randomized control trial (RCT); 2) population based on patients with peri-implant mucositis; 3) intervention used either photothermal diode laser therapy or photodynamic diode laser therapy as an adjuvant to conventional therapy; 4) clinical outcome measured includes the bleeding on probing index; 5) follow-up of at least 3 months.

3.2. INFORMATION SOURCES AND SEARCH STRATEGY

3.2.1 Databases

Both CRAI library Ducle Chacón and Elsevier's Scopus search engines were used to perform the search on February 10th, 2022. The databases included in CRAI library Ducle Chacón are the following: Medline Complete, Academic Search Ultimate, Dentistry & Oral Sciences Source, CINAHL and E-Journals.

3.2.2 Construction of the Search Algorithm

To carry out the search, the PICO question was broken down into key terms. Subsequently, the equivalence of these keywords was evaluated in the Medical Subject Heading (MeSH). Depicted in Table 6 were keywords and MeSH terms used to perform the search. Finally, in order not to exclude any relevant study, the search algorithm was constructed using the combinations of the following MeSH and keywords: **("Peri-implant mucositis" OR "Peri-implant disease" OR "Mucositis") AND ("Photothermic" OR "Photodynamic" OR "Diode laser" OR "Laser Therapy" OR "Photothermal Therapy" OR "Phototherapy" OR "Laser, Semiconductor/ therapeutic use" OR "Photochemotherapy") AND ("Conventional therapy" OR "Conventional non-surgical therapy" OR "Mechanical debridement" OR "Mechanical curettage" OR "Periodontal debridement" OR "Dental Scaling" OR "Dental prophylaxis") AND ("Clinical inflammatory signs" OR "Plaque index" OR "bleeding on probing index" OR "Gingival Index").** Table 7 summarizes the search results obtained from each search engine. No data and language filters were applied for the search. Additional studies were retrieved by reference cross-searching of relevant articles.

Table 6: Keywords and Medical Subject Heading Words Used to Construct the Search Algorithm

PICO Elements	Keywords	MeSH Words
P (Population)	"Peri-implant mucositis" ; "Peri-implant disease"	"Mucositis"
I (Intervention)	"Photothermic"; "Photodynamic"; "Diode laser"	"Laser Therapy; "Photothermal Therapy"; "Phototherapy"; "Laser, Semiconductor/ therapeutic use", "Photochemotherapy"
C (Comparison)	"Conventional therapy"; "Conventional non-surgical therapy"; "Mechanical debridement"; "Mechanical curettage"	"Periodontal debridement"; "Dental Scaling"; "Dental prophylaxis"
O (Outcome)	"Clinical inflammatory signs"; "Plaque index", "Bleeding on probing index"; "Gingival Index"	"Periodontal pocket depth"; "Oral Hygiene Index"; "Dental Plaque Index"; "Periodontal Index"

Table 7: Search Algorithm used for Each Search Engine

Search Engine	Search Algorithm	Filters	Date
University Europea's Dulce Chacón CRAI Library	((Peri-implant mucositis) OR (Peri-implant disease) OR (Mucositis)) AND ((Photothermic) OR (Photodynamic) OR (Diode laser) OR (Laser Therapy) OR (Photothermal Therapy) OR (Phototherapy) OR (Laser, Semiconductor/ therapeutic use) OR (Photochemotherapy)) AND ((Conventional therapy) OR (Conventional non-surgical therapy) OR (Mechanical debridement) OR (Mechanical curettage) OR (Periodontal debridement) OR (Dental Scaling) OR (Dental prophylaxis)) AND ((Clinical inflammatory signs) OR (Plaque index) OR (Bleeding on probing index) OR (Gingival Index))	N/A	February 10th, 2022
Scopus	("Peri-implant mucositis" OR "Peri-implant disease" OR "Mucositis") AND ("Photothermic" OR "Photodynamic" OR "Diode laser" OR "Laser Therapy" OR "Photothermal Therapy" OR "Phototherapy" OR "Laser, Semiconductor/ therapeutic use" OR "Photochemotherapy") AND ("Conventional therapy" OR "Conventional non-surgical therapy" OR "Mechanical debridement" OR "Mechanical curettage" OR "Periodontal debridement" OR "Dental Scaling" OR "Dental prophylaxis") AND ("Clinical inflammatory signs" OR "Plaque index" OR "bleeding on probing index" OR "Gingival Index").	N/A	February 10th, 2022

3.3 SELECTION PROCESS

Two impartial reviewers (NK and RS) independently performed the systematic review search. Once the duplicates between the two databases had been eliminated, two screening phases were performed to determine the eligibility of the studies.

The first screening phase consisted of selecting relevant articles based on their title and abstract. Relevant articles were then excluded based on the exclusion criteria. The remaining articles were therefore the total number of articles included after the first screening phase. The second screening phase consisted of reading the full texts of the articles included in the first screening phase. Articles were then excluded if they do not fit the inclusion criteria.

The bibliography of each article was then reviewed to perform a cross-search. Outside resources were also employed. Relevant studies were first selected based on their title and abstract. The full text was then read completely and only those satisfying the eligibility criteria were selected. The remaining articles were therefore the total number of articles included after performing a cross-search.

The studies selected in the second search phase and cross-search were included in the systematic review. Any disagreement in study eligibility was resolved by discussion between both reviewers until a consensus was reached. The level of agreement between the reviewers was calculated using the k-score according to the Landis & Koch criteria (43).

3.4 DATA COLLECTION PROCESS

The following was data collected from the included studies and can be seen in detailed in Table 9: Name of the authors, year of publication, country of the study, information of the sample and overall risk of bias. The information of the sample includes sample size, mean and age range in years, and male-to-female ratio. The diagnostic criteria for peri-implant mucositis, the number of participants in each study group and the follow-up time of the patients were also included. Likewise, data on the diode laser were also collected, such as the therapy and technical specifications used. Finally, data regarding the variables used in the studies to measure inflammatory signs were also collected. Table 9 specified which variables each study used as well as the unit of measurement.

3.5 STUDY RISK OF BIAS ASSESSMENT

The risk of bias was assessed independently and by the same reviewers who performed the search (NK and RS) according to the Cochrane collaborations' tool (44). A study was deemed to have a low risk of bias if it had a low risk of bias in all domains. If it was determined that the study raised some doubts in at least one domain, it was considered to have an unclear risk of bias. A study with a high risk of bias was one with a high risk of bias in at least one domain or doubtful specifications in more than one domain. Other sources of bias were also recorded and considered including internal and external validity, statistical analysis, assessment method, examiner calibration, data reproduction, validation of measurements, the use of a placebo, and the patient’s compliance.

4. RESULTS

4.1 STUDY SELECTION

As illustrated in the PRISMA flowchart (Figure 1), initially, a total of 167 studies were identified across the following databases via Universidad Europea of Madrid's Ducle Chacón CRAI Library and Elsevier's Scopus: MEDLINE complete (n=25), Academic Search Ultimate (n=6), Dentistry & Oral Sciences Source (n=4), CINAHL (n=3), E-Journals (n=1) and Scopus (n=128). Between all databases, 32 records were duplicated and hence removed resulting in a total of 135 records that underwent the first screening. The first screening consisted of selecting relevant articles based on their title and abstract. 121 out of 135 records were excluded based on the exclusion criteria. More specifically, 7 were excluded due to the year of publication (older than 2012) and 115 were excluded due to the lack of relevancy to the current topic. Hence, a total of 14 reports were sought for retrieval however, one report was not able to be retrieved. Therefore, a total of 13 reports were included at the end of the second screening and assessed in the second screening. The second screening consisted of reading the report in full and excluding those that do not meet the inclusion criteria. 4 articles were excluded since they were not Cohort/RCT studies while two were excluded since the population of focus were patients with periimplantitis rather than peri-implant mucositis. As a result, a total of five studies were identified via databases. Table 8 lists details of excluded studies including population characteristics, studied groups, follow-up time, studied variables and reason for exclusion.

A cross-search was also done to identify studies via other methods such as websites, organizations and citation searching. From the cross-search, three records were identified via citation searching due to its relevancy based on its title and abstract. The reports were retrieved and read in full. The eligibility of the reports was assessed based on the inclusion and exclusion criteria. One out of the three articles were excluded since the population of focus was patients with periimplantitis rather than peri-implant mucositis resulting in a total of two articles identified from the cross-search. As a result, a total of seven studies (45–51) were included in the present systematic review.

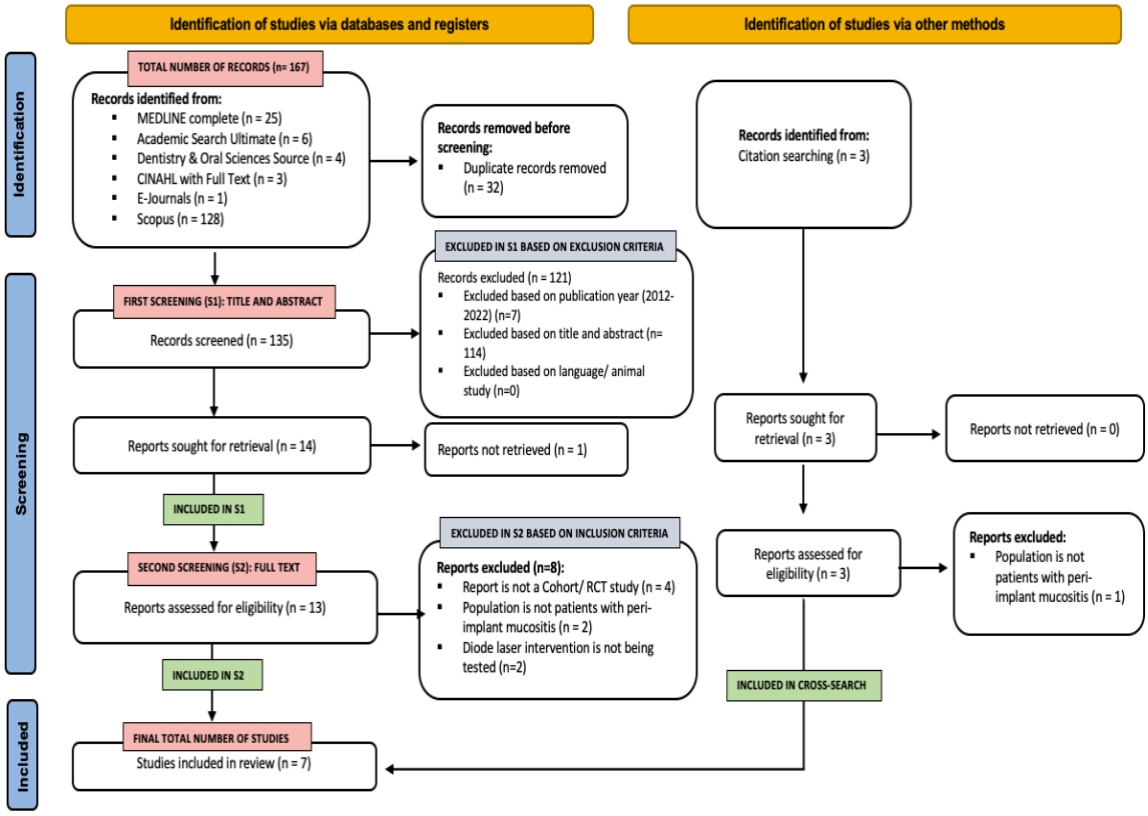

Figure 1: Study identification process and results of the literature search via databases and other methods according to PRISMA 2020 (5

4.2 STUDY CHARACTERISTICS

4.2.1 Excluded Studies

Portrayed in Table 8 are the 8 studies excluded from the present systematic review. Although all the studies expressed study variables that were interesting for the present systematic review, they were excluded for not meeting the eligibility criteria. Sanchez- Martos et al, Shahmohammadi et al. and Albaker et al. studies were excluded since they were a systematic review/ meta-analysis (53–55). This does not meet the inclusion criteria of the present systematic review. Lerario et al.'s study is not only a preliminary clinical study but also the patients included in the study are a mixture of patients with peri-implant mucositis and periimplantitis. The results of the study did not separate the two pathologies hence, the study cannot be used in the present systematic review (56). Karimi et al's RCT was also excluded for similar reasons (57). Alresayes et al's cohort study was excluded since the population of study only included patients with periimplantitis (58).

Table 8: Studies Excluded in the Present Systematic Review

Author/ Year	Country	Type of study	Sample			Study groups	Study variables	Reason for exclusion
			Sample size	Gender ratio (M: F)	Mean age (years)			
Shahmohammadi et al. 2021 (54)	Iran	SR & MA	NA	NA	NA	C: NA T: NA	PI (%mean) PPD (mean mm) BOP (%mean)	Not RCT/ Cohort study
AlDeeb et al. 2020 (48)	Saudi Arabia	RCT	71	71:0	Group 1: 29.5 ± 5.8 Group 2: 27.8 ± 3.1 Group 3: 30.2 ± 4.4	C: 46 T: 25	PI (mean %) BoP (mean %) PPD (mean mm) MMP-8 (mg/mL) TNF-α (pg/mL)	All groups received laser diode therapy. Study is evaluating risk factors,
Alresayes et al. 2020 (58)	Saudi Arabia	Cohort Study	Test:24 patients with 41 implants Control:25 npatients with 46 implants	T:10:14 C: 12:13	T: 49.4 C: 45.8	C:25 T: 24	PI (%mean ± SD) PD (mean mm) BOP (%mean ± SD) MBL (mean mm ± SD) PICF (mean ul ± SD) hsCRP (mean pg/ml ±SD) TNF-α (mean pg/ml ± SD) IL-6 (mean pg/ml ± SD)	Population included only patients with peri implantitis.
Al Hafez et al.2020 (38)	Saudi Arabia	Cross-sectional Cohort Study	60	50:10	Group 1: 51.6 ± 2.4 Group 2: 54.1 ± 1.6 Group 3: 55.4 ± 0.8 Group 4: 52.4 ±1.1	C; 30 T: 30	PI (mean %) BoP (mean %) PPD (mean mm)	All groups received laser diode therapy. Study is evaluating risk factors,
Sanchez-Martos et al. 2020 (53)	Spain	SR &MA	NA	NA	NA	C: NA T: NA	PI (%mean ± SD) PPD (mean mm) BOP (%mean ± SD)	Not RCT/ Cohort study
Albaker et al. 2018 (55)	Saudi Arabia	SR	NA	NA	NA	C: NA T: NA	PI (%mean) PPD (mean mm) BOP (%mean)	Not RCT/ Cohort study
Karimi et al. 2016 (57)	Iran	RCT	Patients: 10 Implants:30	2:8	52.8 ± 7.33	C:10 T:10	PPD (mm mean ± SD) CAL (mm mean ± SD) MR (mm mean ± SD) GI (mean %) BoP (mean %)	- Split-mouth clinical trial - Population group is a mixture of patients with peri-implant mucositis and peri-implantitis. The outcomes are not differentiated between the two.
Lerario et al. 2016 (56)	Italy	Preliminary clinical study	Patients: 27 Implants: 125	15:12	range (36-67)	C:6 T:21	PI (%mean ± SD) PPD (mean mm) BOP (%mean ± SD)	- Not RCT/ Cohort. - Population group is a mixture of patients with peri-implant mucositis and peri-implantitis. The outcomes are not differentiated between the two.

RCT: Randomized controlled clinical trial; SR: Systematic Review; MA: Meta-Analysis; C: Control; T: Test;PI: Plaque index; PPD: Probing pocket depth; GI: Gingival Index; BOP: Bleeding on probing; SD: Standard deviation; IL-6: Interleukin-6; (TGF)-α: Transforming growth factor α; MBL: Marginal bone level, PICF: peri-implant crevicular fluid, hsCRP: high sensitivity C-reactive protein NA: Not applicable/Not available

4.2.2 Included Studies

Outlined in Table 9 are the 7 studies included in the present systematic review. Details of the publication's author, year, country, type of study, population sample (including sample size, gender ratio and mean age), study groups, follow up time, study variables and risk of bias were listed. All the studies included were randomized controlled trials. The sample size of the population ranged from 38- 220 participants where Al Rifaiy et al.'s clinical study had the lowest number of participants while Aimetti et al.'s study had the most. When it came to the male-to-female gender ratio, there were generally more male participants. Aimetti et al.'s study and Mariani et al.'s study were the only studies where there were more female participants. The mean age of the participants ranged from 44.6 years (50) up to 69 years old (49). The number of individuals belonging to the control and test group were generally even for all the studies except for one where there was great a disparity (48). Mariani et al.'s had 3 more individuals in the test group compared to the control group. Deeb et al.'s study had 30 individuals in the control group and 15 in the test group (48). All the included studies had a follow-up period of 3 months except for Mariani et al.'s study that had a longer follow-up period of 12 months. All included studies measured bleeding on probing in mean percent. Other study variables included were plaque index, periodontal pocket depth, recession, and levels of MMP-8 and TNF-α. Regarding the risk of bias, 5 out of the 7 studies had a low risk of bias (45–49). The risk of bias was unclear for Javed et al's (51). Al-Sowygh et al.'s study, however, had a high risk of bias (50).

Table 9: Studies Included in the Present Systematic Review

Author Year	Country	Type of study	Sample			Study groups		Follow up	Study variables	Risk of bias
			Sample size	Gender ratio (M: F)	Mean age (years)	Control	Test			
Sanchez-Martos et al. 2020 (45)	Spain	RCT	68	40:28	56.9	34	34	3	PI (mean %) BoP (mean %) PD (mean mm) REC (mean mm)	Low
Mariani et al. 2020 (46)	Italy	RCT	73	26:47	Test: 62.1 ± 6.8 Control: 59.2 ± 9.3	35	38	12	PI (mean %) BoP (mean %) PD (mean mm) REC (mean mm)	Low
Aimetti et al. 2019 (47)	Italy	RCT	220	71:149	57.4	110	110	3	PI (mean %) BoP (mean %) PD (mm) REC (mm) FMPS (%) FMBS (%)	Low
Deeb et al. 2019 (48)	Saudi Arabia	RCT	45	45:0	Group A: 52.6 ± 0.9 Group B: 53.8 ± 0.7 Group C: 49.2 ± 0.13	30	15	3	PI (mean %) BoP (mean %) PD (mean mm)	Low
Al Rifaiy et al. 2018(49)	Saudi Arabia	RCT	38	38:0	69	18	20	3	BoP (mean %) PD (mean mm)	Low
Al-Sowygh et al 2017(50)	Saudi Arabia	RCT	48	48:0	44.6	24	24	3	BoP (mean %) PD (mean mm)	High
Javed et al. 2017 (51)	United States of America	RCT	54	54:0	51.4	26	28	3	BoP (mean %) PD (mean mm)	Unclear

RCT: Randomized controlled clinical trial; PI: Plaque index; PPD: Probing pocket depth; BOP: Bleeding on probing; REC: Recession, MMP-8: matrix metalloproteinase-8, (TGF)-α: Transforming growth factor α; FMPS: full mouth plaque score; FMBS: full-mouth bleeding score; NA: Not applicable/Not available

4.2.3 Characteristics of the Laser used in Included Studies

Table 10 summarizes the technical specifications of the laser therapy used in each study. In terms of the laser brand used to carry out the laser therapy, all the studies included their specification except for three (46,47,50). Sánchez-Martos et al, Aimetti et al. and Mariani et al.'s clinical trials employed photothermal diode laser therapy whereas the rest implemented photodynamic diode laser therapy. The wavelength of the laser used in photothermal diode laser therapy was much greater than that used in photodynamic diode laser therapy. The three photothermal diode laser therapy studies used a wavelength between 810-980nm while the photodynamic diode laser therapy studies used a wavelength ranging from 660 to 670 nm. Methylene-blue, also known as

methylthioninium chloride or phenothiazine chloride was the photosensitizer used at a concentration of 0.005% for photodynamic laser therapy. Photothermal diode laser therapy studies specifically stated the procedure of biostimulation in conjunction with the main laser therapy. This consists of the application of radiation either before or after the main laser therapy in order to promote soft tissue generation. A laser with a large optic fiber diameter tip (1cm) was employed in order to disperse the light beam and encourage low-intensity propagation. Both Aimetti et al's and Mariani's studies utilized a power of 0.7W irradiated for 60 seconds twice after the main photothermal laser therapy. Sanchez-Martos et al's clinical study, however, utilized a power of 1W irradiated for 30 seconds for an unspecified number of times before the main photothermal laser therapy. In terms of the main laser diode therapy, all 3 photothermal diode laser therapy studies utilized a smaller optical fibre diameter tip (0.3mm) in order to focalize the light beam. Both Aimetti et al's and Mariani's studies employed a power of 0.7W, irradiated for 30 seconds while Sanchez-Martos et al's study empoyed a power of 1W, irradiated for 30 seconds. Regarding the photodynamic diode laser therapy studies, a laser tip of 0.06mm with a power of 0.15W irradiated once for 60 seconds was used for 3 studies. Javed et al.'s and Deeb et al.'s clinical trial, however, employed a laser with an unspecified optic fibre diameter tip at a power of 0.1 W irradiated once for 10 seconds. It is important to note that Al-Sowygh et al's randomized clinical trial employed photodynamic diode laser therapy, however, it is the only article that lacked information pertaining to all technical specifications of the laser therapy used.

Table 10: Laser Specifications of Included Studies

Author/ Year	Diode laser brand	PT/ PDT	Photosensitizer	Biostimulation				
				Pre/ Post Irradiation	Power (W)	Irradiation time (s)	Optic fiber diameter (mm)	Number of sessions
Sánchez-Martos et al. 2020 (45)	Fox® diode laser (A.R.C. Laser GmbH, Nürnberg, Germany)	PT	NA	Pre-Irradiation	1	30	1	NA
Aimetti et al. 2019 (47)	NA	PT	NA	Post-Irradiation	0.7	60	1	2
Al Rifaiy et al. 2018 (49)	HELBO® (Ther- aLite Laser, Photodynamic Systems GmbH, Wels, Austria).	PDT	Methylene-blue 0.005%	NA	NA	NA	NA	NA
Javed et al. 2017 (51)	HELBO® (Ther- aLite Laser, Photodynamic Systems GmbH, Wels, Austria).	PDT	Methylene-blue 0.005%	NA	NA	NA	NA	NA
Al-Sowygh et al. 2017 (50)	NA	PDT	NA	NA	NA	NA	NA	NA
Mariani et al. 2020 (46)	NA	PT	NA	Post-irradiation	0.7	60	1	2
Deeb et al. 2020 (48)	HELBO® (Ther- aLite Laser, Photodynamic Systems GmbH, Wels, Austria).	PDT	Methylene-blue 0.005%	NA	NA	NA	NA	NA

Table 10 cont.: Laser Specifications of Included Studies

Author/ Year	Treatment				Wavelength (nm)
	Power (W)	Irradiation time (s)	Optic fiber diameter (mm)	Number of sessions	
Sánchez-Martos et al. 2020 (45)	1	30	0,3	1	810
Aimetti et al. 2019 (47)	2.5 W (average 0.7 W)	30	0.3	3	980
Al Rifaiy et al. 2018 (49)	0.15	60	0.06	1	670
Javed et al. 2017 (51)	0.1	10	NA	1	660
Al-Sowygh et al. 2017 (50)	NA	NA	NA	NA	NA
Mariani et al. 2020 (46)	2.5 W (average 0.7 W)	30	0.3	3	980
Deeb et al. 2020 (48)	0.1	10	NA	1	660

4.3 RISK OF BIAS ASSESSMENT

The risk-of-bias of each study included in the present systematic review was assessed using the Cochrane Collaboration tool RoB 2 (44). Answering specific signaling questions permits one to determine domain-level judgments about the risk of bias. An overall risk-of-bias judgement of each study independently as well as an overall risk-of-bias judgment across all included studies can be assessed based on the domain-level judgments. Illustrated in Figure 2 is the overall risk-of-bias assessment of each study as well as each domain across all studies. The first domain assessed was the risk of bias arising from the randomization process. This judgment depended on whether the allocation sequence was random and concealed. Additionally, it was crucial to note whether the results obtained suggested any problems with randomization. Four out of the seven included studies included (45–47,49) demonstrated a low risk of bias in this domain since the allocation sequence was random, concealed and the results did not suggest problems with randomization. The remaining three studies demonstrated some concerns in this domain since the studies did not mention whether the allocation sequence was concealed until participants were enrolled and assigned to the interventions (48,50,51). The randomization technique used in the studies included varied from coin tossing (49–51), stratified block randomization (45), permuted block randomization (47,48) and computer-generated randomization (46). The second domain assessed was the risk of bias due to deviations from the intended interventions. The signaling questions pertaining to this domain reflect patient blinding, operator blinding and whether failing to do so had affected the outcome of the study. In all included studies, the operator was not blinded while implementing the intervention. Only two studies (46,47) blinded the participants by not activating the laser tip when performing the laser therapy. Therefore, all studies included portrayed a low risk of bias in this domain. The third domain assessed was the risk-of-bias judgment due to missing outcome data. This domain explores whether there was any missing information that may affect the outcome of the study. This pertains to situations where there were missing measurements of the outcome due to the loss of participants from dropouts. The loss of participants may lead to bias in the intervention effect estimate. All the

studies included had a low risk of bias when it came to this domain except for two (50,51). This was since these two studies did not include any indication of how many participants were included initially and at the end of the experiment. Additionally, there was no evidence that the results were not biased by missing outcome data nor was there information about whether this lack of information depended on its true value. Hence, Javed et al‘s study and Al-Sowygh et al‘s study both yielded a high risk of bias in this domain. The fourth domain assessed was the risk of bias in measurement of the outcome. The signaling questions pertaining to this domain explored whether the methodology to measure the variables were appropriate or not, examiner blinding, and the influence these factors had with the results obtained. All the studies included used appropriate measuring methodology. The majority of the studies mentioned examiner blinding except for two (50,51). The examiner knowing which participant received what intervention can influence the outcome of the results, however, this was probably not the case for the two studies. Therefore, all the studies demonstrated a low risk of bias for this domain. Javed et al‘s and Al-Sowygh et al‘s studies, however, demonstrated some concerns of bias due to the lack of examiner blinding and the possible influence this may have on the outcome of the results. The last domain assessed was the risk of bias in selection of the reported results. The signaling questions for this domain revolved around the consistency of what was planned to the assessed at the beginning of the trial and what was decided to be assessed afterwards. It also takes into consideration whether the numerical values being examined have multiple eligible outcome measurements and analyses of the data. All the studies included produced results in accordance with the analysis plane prior to the start of the trial except for one (50). Al-Sowygh et al’s study did not include any numerical values of the variables studied, only a graph. All studies measured the variables at multiple times, that is at baseline, 3 months and sometimes many months afterwards. All these values were recorded in all studies except for one (50). All studies demonstrated a low risk of bias for this domain except for one (50) study due to the lack of pertinent information. The overall risk-of-bias judgment for each study included in the present systematic review was low except for two studies (50,51) which presented a high risk of bias overall. The overall risk-of-bias judgment across all studies for each domain assessed varies. Regarding the deviation from intended interventions, the present systematic review has

a low risk of bias. In terms of the randomization process and the measurement of the outcome, there are some concerns of bias. The domains related to missing outcome data and selection of the reported result, however, presented a high risk of bias.

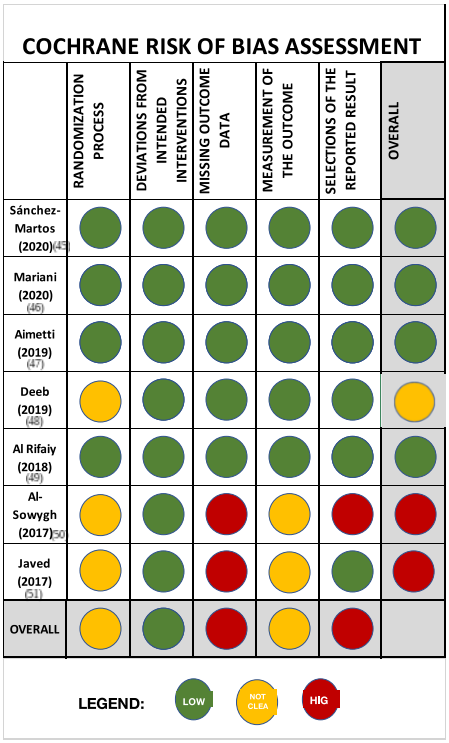

Figure 2: Cochrane Risk of Bias Assement

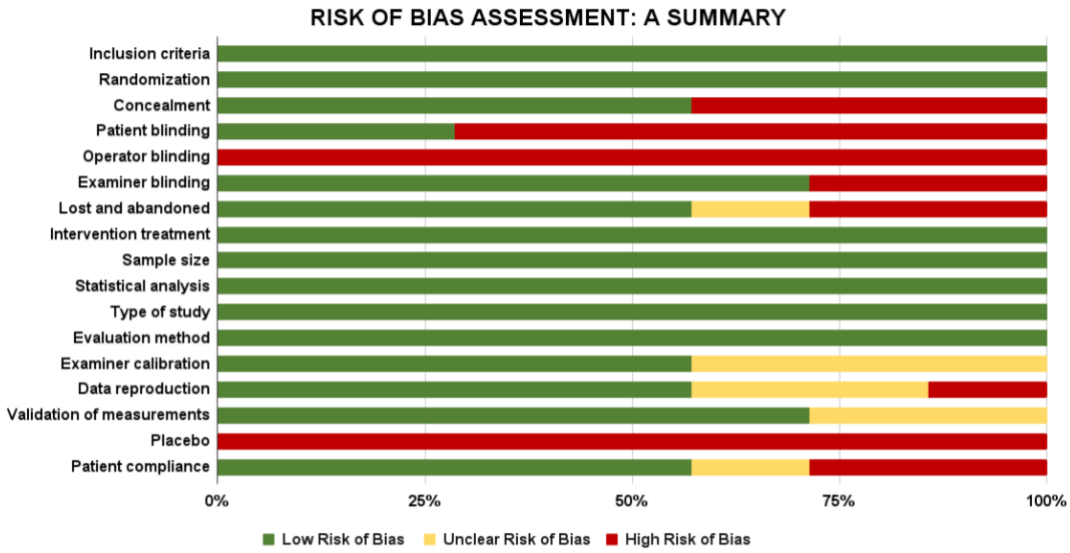

Figure 3: Risk of Bias: A summary. Depiction of the risk of bias of each factor presented as percentages across all studies included in the systematic

Illustrated in Figure 3 is a summary of the risk of bias of each factor across all studies based on the judgment of the reviewers. This permitted an analysis of the risk of bias of each publication included in the systematic review in greater detail. Each factor was analyzed and presented as percentages across all studies included in the systematic review. All included studies clearly specified the inclusion criteria, method of intervention, sample size, statistical analysis, type of study and evaluation method. All the included studies of the present systematic review were RCT and clearly mentioned the inclusion criteria of the trials. 57.1% of the studies (45–47,49) indicated the technique of concealment whilst 42.9% of the studies did not (48,50,51). Patient blinding was only present in two studies (46,47). None of the studies implemented operator blinding nor a placebo. All the studies mentioned examiner blinding except two studies (50,51). 57.1% of the studies included presented a flowchart to reference the lost and abandonment process and compliance of the participants (45–47,49). Deeb et al's study did not illustrate the flow of participants with a flowchart, however, it does mention selecting more patients to compensate for 20% dropout rate of each group. This resulted in the risk-of-bias to be unclear for this study. Javed et al's and Al-Sowghy et al's studies had a high risk of bias due to the lack of information about flow of participants throughout the trial. All studies scored a low risk of bias in terms of details pertaining to the intervention treatment, sample size, statistical analysis, type of study and evaluation method. The examiner calibration process was clearly specified with the process and kappa score in 57.1% of the included studies (45–47,49,50). The rest of the studies only provided the kappa score, however, lacked details about the calibration process. Therefore, the remaining studies have some concerns of bias. Most of the studies explained thoroughly the methodology of the clinical trial and hence eased the possibility of data reproduction except for one (50), while two were unclear (49,51) since they did not explicitly mention and explain the mechanical debridement treatment received by the control group. The majority of the studies clearly indicated the instrument's specification used to validate the measurements except for two (46,51). These two studies only mentioned that a probe was used to measure the study variables, however, the specific probe used was not included.

4.4 RESULTS OF INDIVIDUAL STUDIES

In order to assess the efficacy of each laser therapy, the plaque index, probing depth and bleeding on probing index of each included study were analyzed at baseline and at the 3-month follow-up (Table 11&12). The difference between baseline values and 3-month follow-up values were compared between the control and test groups of each included study. Depicted in Figure 4 is a graphical representation of the baseline values and values at the 3-month follow-up period of both the Pl and PPD. Similary, depicted in Figure 5 is a graphical representation of values obtained for BoP.

4.4.1 Photodynamic Laser Therapy

In Al Rifaiy et al, Javed et al., and Deeb et al's photodynamic laser therapy studies, the baseline values of the plaque index of the control groups were 46.8%, 51.2% and 45.3% while that of the test groups were 51.1%, 47.6% and 44.5% respectively (48,49,51). The reductions seen in the plaque index over a 3-month period when aPDT was used were 37.9%, 37.2% and 33% according to Al Rifaiy et al, Javed et al., and Deeb et al's studies respectively. The reductions seen in the plaque index over a 3-month period with mechanical debridement alone were 19.3%, 28% and 30.5%. As a result, there was a greater reduction in plaque in the test group in comparison to the control group. More specifically, the plaque index reduction was 18.6%, 9.2% and 2.5% greater in the test group.

In Al Rifaiy et al, Javed et al., and Deeb et al's studies, the baseline values of periodontal probing index of the control groups were 4.5mm, 6.6mm and 4.5mm while that of the test groups were 4.3mm, 7.4mm and 4.8mm respectively. The reductions seen in the periodontal probing depth over a 3-month period when aPDT was used were 2.2mm, 5.9mm and 0.9mm according to Al Rifaiy et al, Javed et al., and Deeb et al's studies respectively. The reductions seen in the periodontal probing depth over a 3-month period with mechanical debridement alone were 2.3 mm, 2.8mm and 0.4mm accordingly. As a result, two out of the three studies demonstrated a greater reduction in periodontal probing depth in the test group in comparison to the control group (48,51). More specifically, the probing depth reduction was 3.1mm and 0.5mm greater in the test group according to Javed et al., and Deeb et al's studies respectively.

However, in Al Rifaiy et al's study, the pocket depth reduction is greater in the control group by 0.1mm in comparison to the test group.

In Al Rifaiy et al, Javed et al., and Deeb et al's studies, the baseline values of bleeding on probing index of the control groups were 9.2%, 8.6% and 13.6% while that of the test groups were 14.6%, 10.2% and 12.3% respectively. The reductions seen in the bleeding on probing over a 3-month period when aPDT was used were 2.9%, 1.4% and 4.3% according to Al Rifaiy et al, Javed et al., and Deeb et al's studies respectively. The reductions seen in the bleeding on probing over a 3-month period with mechanical debridement alone were 1.3%, 1.7% and 1.8% respectively. As a result, two out of the three studies demonstrated a greater reduction in bleeding on probing index in the test group in comparison to the control group (48,49). More specifically, the bleeding on probing index reduction was greater in the test group by 1.6% and 2.5% according to Al Rifaiy et al and Deeb et al's studies respectively. However, in Javed et al's study, the bleeding on probing index reduction was greater in the control group by 0.3% in comparison to the test group.

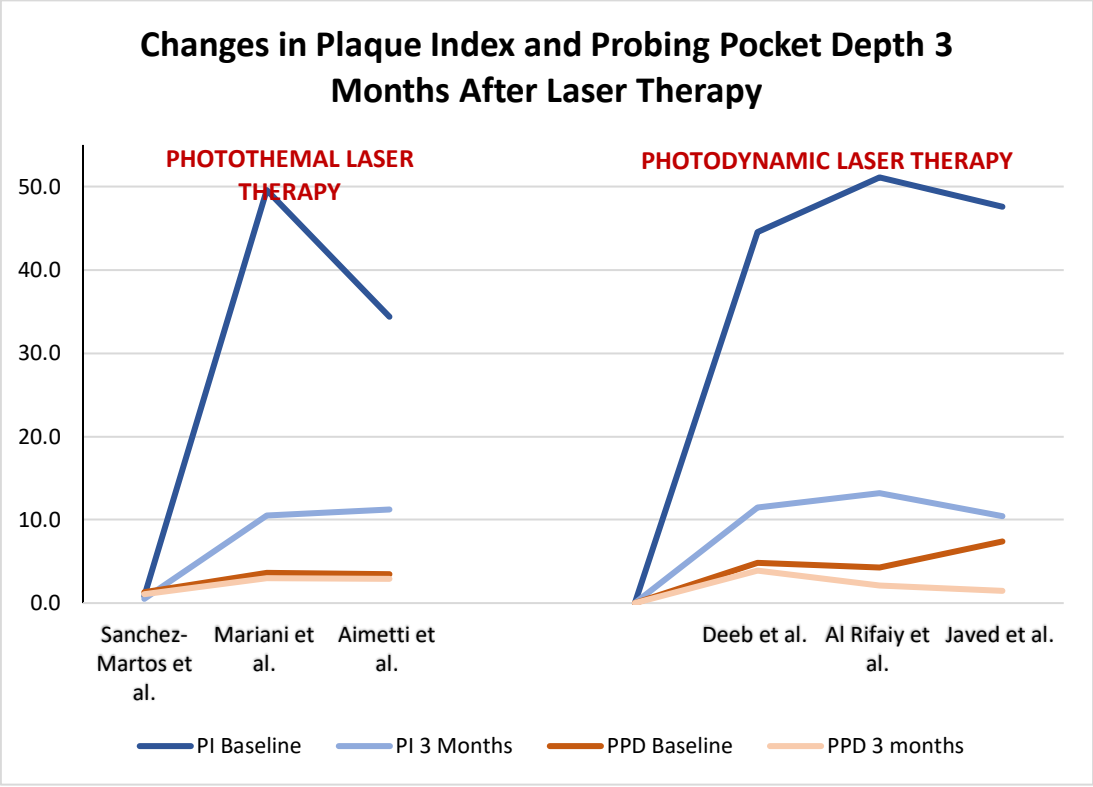

Figure 4: Graphical Representation of the Changes in Plaque Index and Probing Pocket Depth 3 Months After Laser Therapy

4.4.2 Photothermal Laser Therapy

In Sanchez-Martos et al, Aimetti et al., and Mariani et al's photothermal laser therapy studies, the baseline values of the plaque index of the control groups were 0.676%, 30.6% and 44.8% while that of the test groups were 0.824%, 34.4% and 49.6% respectively. The reductions seen in the plaque index over a 3-month period when PT was used were 0.344%, 23.2% and 39.1% according to Sanchez-Martos et al, Aimetti et al., and Mariani et al's studies respectively. The reductions seen in the plaque index over a 3-month period with mechanical debridement alone were 0.167%, 17.9% and 31.9% accordingly. As a result, there was a greater reduction in plaque in the test group in comparison to the control group. More specifically, the plaque index reduction was 0.177%, 5.3% and 7.2% greater in the test group.

In Sanchez-Martos et al, Aimetti et al., and Mariani et al's studies, the baseline values of the periodontal probing depth of the control groups were 1.303mm, 3.4mm and 3.8mm while that of the test groups were 1.277mm, 3.5mm and 3.6mm respectively. The reductions seen in the periodontal probing depth over a 3-month period when PT was used were 0.209mm, 0.6mm and 0.6mm according to Sanchez-Martos et al, Aimetti et al., and Mariani et al's studies respectively. The reductions seen in the periodontal probing depth over a 3-month period with mechanical debridement alone were 0.137mm, 0.4mm and 0.7mm respectively. As a result, two out of the three studies demonstrated a greater reduction in periodontal probing depth in the test group in comparison to the control group (45,47). More specifically, the periodontal pocket depth reduction was 0.072mm and 0.2mm greater in the test group according to Sanchez-Martos et al, Aimetti et al.'s studies respectively. However, in Mariani et al's study, the pocket depth reduction was greater in the control group by 0.1mm in comparison to the test group.

In Sanchez-Martos et al, Aimetti et al., and Mariani et al's studies, the baseline values of bleeding on probing index of the control groups were 1.176%, 46.2% and 59.5% while that of the test groups were 1.175%, 48.3% and 63.6% respectively. The reductions seen in the bleeding on probing over a 3-month period when aPDT was used were 0.911%, 25.1% and 40.3% according to Sanchez-Martos et al, Aimetti et al., and Mariani et al's studies respectively. The reductions seen in the bleeding on probing over a 3-month period with mechanical debridement alone were 0.608%, 19.4% and 32.8%

accordingly. As a result, there was a greater reduction in bleeding on probing index in the test group in comparison to the control group. More specifically, the bleeding on probing index reduction is greater in the test group by 0.303%, 5.7% and 7.5% (45–47).

Table 11: Changes in Plaque Index and Periodontal Probing Depth over a period of 3 months after Diode Laser Therapy.

Author/ Year	Laser Therapy	Variables	Groups	Baseline	3 months	Δ 0-3 months
Sanchez-Martos et al. (2020) (45)	PT	PI (%)	Control	0.676	0.509	0.167
			Test	0.824	0.480	0.344
		PPD (mm)	Control	1.303	1.166	0.137
			Test	1.277	1.068	0.209
Mariani et al. (2020) (46)	PT	PI (%)	Control	44.8	12.9	31.9
			Test	49.6	10.5	39.1
		PPD (mm)	Control	3.8	3.1	0.7
			Test	3.6	3.0	0.6
Aimetti et al. (2019) (47)	PT	PI (%)	Control	30.6	12.6	17.9
			Test	34.4	11.2	23.2
		PPD (mm)	Control	3.4	3.0	0.4
			Test	3.5	2.9	0.6
Deeb et al. (2019) (48)	PDT	PI (%)	Control	45.3	14.8	30.5
			Test	44.5	11.5	33
		PPD (mm)	Control	4.5	4.1	0.4
			Test	4.8	3.9	0.9
Al Rifaiy et al. (2018) (49)	PDT	PI (%)	Control	46.8	27.5	19.3
			Test	51.1	13.2	37.9
		PPD (mm)	Control	4.5	2.2	2.3
			Test	4.3	2.1	2.2
Javed et al. (2017) (51)	PDT	PI (%)	Control	51.2	23.2	28
			Test	47.6	10.4	37.2
		PPD (mm)	Control	6.6	3.8	2.8
			Test	7.4	1.5	5.9

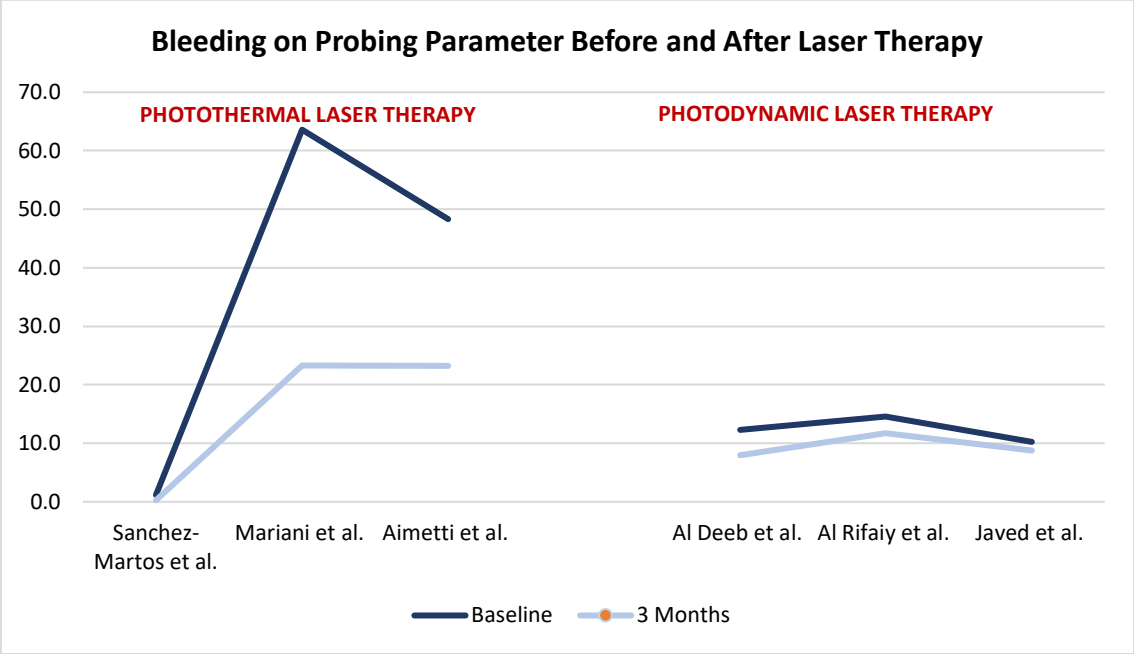

Figure 5: Graphical Representation of the Changes in Bleeding on Probing Index 3 Months After Laser Therapy

Table 12: Changes in Bleeding on Probing Index over a period of 3 months after Diode Laser Therapy.

Author/ Year	Laser Therapy	Variables	Group	Baseline	3 months	$\Delta_{0\text{-}3\ months}$
Sanchez-Martos et al. (2020) (45)	PT	BoP (%)	Control	1.176	0.568	0.608
			Test	1.175	0.264	0.911
Mariani et al. (2020) (46)	PT	BoP (%)	Control	59.5	26.7	32.8
			Test	63.6	23.3	40.3
Aimetti et al. (2019) (47)	PT	BoP (%)	Control	46.2	26.8	19.4
			Test	48.3	23.2	25.1
Al Deeb et al. (2019) (48)	PDT	BoP (%)	Control	13.6	11.8	1.8
			Test	12.3	8.0	4.3
Al Rifaiy et al. (2018) (49)	PDT	BoP (%)	Control	9.2	7.9	1.3
			Test	14.6	11.7	2.9
Javed et al. (2017) (50)	PDT	BoP (%)	Control	8.6	6.9	1.7
			Test	10.2	8.8	1.4

5. DISCUSSION

5.1 DESCRIPTION OF STUDY METHODOLOGY

The present systematic review aims to compare the efficacy of photothermal diode laser therapy to photodynamic diode laser therapy as a treatment for peri-implant mucositis. Although the clinical manifestations of peri-implant mucositis include increased level of plaque, probing pocket depth and the absence of bone loss, bleeding on gentle probing is the key factor when it comes to its diagnosis. Therefore, all studies included in the present systematic review are homogenous in terms of the key clinical sign for its diagnosis. The study variables for all studies vary slightly. At a minimum, the following variables were assessed in each study: plaque index, probing pocket depth and bleeding on probing. Other variables some authors included are the level of recession (45), Full-Mouth Plaque Score and Full Mouth Bleeding Score (47). Regarding the study population, study design and sample size there is a considerable amount of heterogeneity observed between the studies included.

The study population included in the present systematic review is heterogeneous. Most of the studies included test the intervention on population with a mix of the following characteristics: both males and females, non-smokers and light smokers, patients with and without non-influential systemic diseases, and patients with and without a history of periodontal disease (45–47). Some studies test the intervention on a population group of only tobacco smokers (48,51) smokeless tobacco users (50) and electronic tobacco smokers (49). Since tobacco is a crucial risk factor for peri-implant mucositis, the outcome of the intervention will also be affected if the study sample only includes tobacco users. Notably, the main objective of those studies is to determine the efficacy of laser therapy on tobacco users. However, for this present systematic review, using studies that do not have a general representative population makes it difficult to make general conclusive statements.

Furthermore, most of the studies included in the present systematic review only include males in their clinical trials (48–51). This disparity in biological sex representation is important due to the differences in the inflammatory response seen between men and women. The influence of estrogen in periodontology has been studied for decades. Systemic bone metabolism as well as vascular inflammation were known to alter when women reach menopause due to hormonal changes (59,60). In periodontal conditions, “women with early menopause… had higher clinical attachment loss… along with

increased sites with bleeding on probing" (59). Although the interactions seen in a natural tooth may differ than that of the implant, this concept should not be overlooked. In addition, since the mean age of participants for the studies included in the present systematic review is at least 44.6 years old, not incorporating females in this age group may lead to the outcomes of these studies not being reproducible in different populations. Balancing the number of both men and women in the trials may give rise to outcomes that may be more representative of the general population.

Although all the studies included are RCTs, the designs of the studies vary greatly. The aleatory process used in the studies includes coin tossing (49–51), computer-generated sequence (46), permuted block randomization (47,48) and stratified block randomization (45). Simple randomization is based on randomly assigning participants in a single sequence without considering certain characteristics such as age, gender or risk factors. Therefore, with this technique, it is possible to have a lot more participants in the control group, for example, compared to the test group. Since the participants' characteristics are also not accounted for, it can lead to uneven distribution of influential characteristics. For instance, there can be a significant number of tobacco smokers in the control group compared to the test group in a clinical trial testing peri-implant treatment efficacy. Inevitably, this can skew the results especially if an intervention is being tested and not the risk factors associated to the disease. For that reason, simple randomization is usually only used in larger sample sizes in order to ensure that the groups are split evenly by chance. The permuted block system, also known simply as block randomization, ensures the equal distribution of the number of participants in each group in a random manner. This technique consists of dividing an equal number of participants into blocks and noting all possible permutations. From these different arrangements, one specific combination is chosen randomly- usually done through electronic means. This aleatory method is beneficial for small sample sizes. Similar to the previous technique, this one does not bear in mind the study sample's characteristics. The stratified block randomization system is notably the best randomization method to implement for the studies included in the present systematic review. This aleatory process randomly assigns an equal number of participants to groups and addresses influential characteristics accordingly. It "requires identification of key prognostic characteristics that are measurable at the time of randomization and

are considered to be strongly associated with the primary outcome" (61). Therefore, it guarantees a homogenous distribution of participants and eliminates the risk of bias. It is essential to randomize participants well, since this is what gives RCTs the level of evidence and *prestige* when comparing to other types of studies. If the sample is already biased from the beginning, the results are difficult to replicate and therefore there is a lack of confidence in the studies.

Sanchez-Martos et al's study is the only study that implemented the stratified block technique. Judging by the sample size (n=68) and medical characteristics of the participants, this randomization technique guaranteed a balanced distribution of the participants in the most homogenous and non-bias manner. Since smoking tobacco is a known risk factor to initiate and aggravate peri-implant diseases, patients were randomized taking this into consideration. Aimetti et al. and Deeb et al.'s studies used the block randomized system to allocate their participants into the test and control groups. Aimetti et al's study included participants who were light smokers as well as participants with a history of treated periodontitis. Regardless, with the permuted block technique, the number of light smokers and patients with a history of periodontitis were distributed relatively evenly between the control and test groups. Similarly, the general characteristics of the study groups in Deeb et al's study show an even distribution in the number of individuals as well as influential characteristics. This is because all the participants included are long-term male smokers hence, there is no need to stratify the participants based on the risk factor. The remaining studies show similar allocation in terms of balancing the number of participants in each group as well as properly distributing the risk factors despite the utilization of simple randomizing techniques. Although the participants are allocated evenly, one cannot ensure that this was done in a non-bias manner. Great importance is given to the randomization technique used since this is what give RCTs relevant information with a high level of evidence. If the sample is already bias from the beginning, the results are difficult to replicate.

Homogeneity is seen amongst all the studies in terms of the minimum follow-up period. All the studies included in the present systematic review had a follow-up period of at least 3 months. Clinically, the follow-up period is relevant since it provides evidence of treatment efficacy, the duration of the effect and the level of compliance of the

participants in the maintenance phase (62). Immediately after mechanical debridement and laser therapy, there is a steep drop in bacterial load in the peri-implant pocket. Measuring the clinical parameters at earlier stages confirms the fact that the intervention used can eradicate pathogenic bacteria in the peri-implant pocket. This is especially important in terms of photodynamic laser therapy since its efficacy depends heavily on the ability of the characteristics of the photosensitizer. Additionally, regardless of the laser therapy implemented, there is a possibility of bacterial regrowth after a couple of weeks post-treatment. Therefore, measuring the clinical parameters only after months have elapsed is difficult to determine the course of action of the intervention. It is possible that intervention was able to target pathogenic bacteria initially, but a later bacterial regrowth has occurred. Contrary, it is also possible that there was no significant change in the pathogenic bacterial load at the initial stages and growth continued post-therapy. However, to reduce damage and promote healing of the peri-implant pocket, it is recommended to wait 6-8 weeks after non-surgical therapy for re-evaluation. Thus, to ensure the efficacy of the therapies at earlier stages, that is before the 6-8 timeframe, lesser invasive methods such as biochemical evaluations should be used (62). A 3-month follow-up is reasonable since there is sufficient time for the colonization of the natural oral microflora and healing of soft tissues. A longer follow-up period may have been useful to see if there were any pathogenic bacteria regrowth and the advancement of peri-implant mucositis into periimplantitis despite the patient undergoing laser therapy (50). Similarly, in Javed et al's study, it is thought that "the peri-implant parameters (PI, BOP and PPD) would have been comparable among both study groups in case these patients were followed up for a longer duration (at least 6-months)" (50,51). Indeed, the outcome would be different with a longer follow-up period, however the reasons as to why is important. At this stage, it is mostly the patient's responsibility to maintain a low pathogenic bacterial load through proper oral hygiene habits and eliminating risk factors. Therefore, an extended follow-up period would reflect more on the quality of the patient's oral hygiene habits and lifestyle rather than on the direct effect of the treatment applied (62,63). Although this is true, longer follow-up periods are still necessary since there is a need for treatments that are effective for longer periods of time. The growing interest in laser therapies is to offer patients better and longer lasting results. It is well known that the conventional

treatment, mechanical debridement, is effective but the results are very temporary. This is shown in Salvi et al's study where inflammatory cytokines, more specifically, mmp-8, increased after 8 weeks of conventional therapy (16). Therefore, in the case of laser therapy, longer follow-up periods are necessary to observe the longevity of the effects.

5.2 ANALSIS OF CLINICAL PARAMETERS

5.2.1 Plaque Index

The accumulation of pathogenic bacteria on the peri-implant pocket biofilm is strongly correlated to the appearance of peri-implant mucositis. The randomized clinical trials of the present systematic review demonstrate the benefits of both photothermal and photodynamic laser diode therapy as an adjuvant to mechanical debridement in reducing the overall plaque index. Figure 4 highlights the significant reduction of plaque after both types of laser therapies over a period of 3 months. It is, however, clear that the reduction seen in aPDT surpassed that seen in PT. The percentage of reduction of the plaque index over a 3-month period was higher in the studies implementing aPDT (48,49,51) compared to the studies utilizing PT (45–47). On average, the plaque reduction index was reduced after aPDT by 36.0% while that of PT was only reduced by 20.9% at 3 months follow-up. The importance of these values is dependent on various factors, the first being whether the differences observed were statistically significant or not. Regarding the plaque index, all the results included for the purpose of assessing aPDT were statistically significant at a 3-month follow-up, meaning the difference seen between the control and test group is less likely due to chance but more due to the intervention employed. On the contrary, in the case of PT, the results of all the studies concluded that the difference between the test and control group were not statistically significant at the 3-month follow-up period. Therefore, the difference in plaque index was most likely observed due to chance and cannot be confidently said to be due to photothermal diode laser therapy. Based on the statistical analysis, it is clear that aPDT does in fact yield a difference in the plaque index after 3 months while photothermal diode laser therapy does not. The results should not solely be based on the statistical analysis but also the level of bias these studies may have. All three studies used for the photothermal laser therapy analysis has a low risk of bias according to the Cochrane Collaboration tool RoB 2 (44). One out of the three studies

with available results used for the photodynamic laser therapy analysis had a low risk of bias (49), another had some concerns of risk of bias (48), while one had a high risk of bias (51). Deeb et al's study lacked pertinent information about the randomization process since it is unclear whether the allocation sequence was concealed until participants were enrolled and assigned to the laser therapy. Allocation concealment is crucial since "knowledge of the next assignment can enable selective enrolment of participants on the basis of prognostic factors" (44). Additionally, the overall randomization method used for the studies of photothermal diode laser therapy are more suitable compared to those used in the photodynamic laser therapy. Two out of the three aPDT studies employed coin-tossing (49,51) while one employed permuted block randomization (48). Studies used for the photothermal diode laser therapy, however, employed stratified block randomization (45), permuted block randomization and computer-generated randomization (46,53). Therefore, the outcome of overall risk of bias and randomization process for the studies pertaining to photothermal laser therapy depicts superior validity in comparison to the outcome of photodynamic laser therapy. Lastly, the outcome of the plaque index reduction is dependent on the initial baseline value. For any intervention, drastic changes are usually seen in cases with the worst initial conditions. Meaning, that initially, if a patient has a very high plaque index percentage, after mechanical and chemical cleaning, the changes observed will be more drastic in comparison to a case when the patient initially has very minimal plaque. In general, the baseline plaque index values of both therapies are similar across. This effect is only seen in the study of Sanchez-Martos et al. For that reason, the change seen after 3 months of therapy is very low (0.167%) giving the average plaque reduction for photothermal diode laser therapies to be much lower than that of photodynamic diode laser therapy. Similar reasonings were mentioned in a systematic review and meta-analysis published by Sanchez-Martos et al (53). Sanchez-Martos et al. stated that the sample population is also important since recruiting participants who are only smokers, for example, usually results in an overall higher baseline plaque index value and therefore the benefits of the treatment are more evident (53). This may be seen in four randomized control trials in the present systematic review (48–51).

Therefore, although the results of the present systematic review indicate photodynamic laser therapy in being superior as an adjuvant in reducing the plaque

index in comparison to photothermal laser therapy since statistically significant results were observed without any baseline values that may favor drastic results, the outcome still must be interpreted carefully due to some concerning and high risk of bias.

Additionally, the decrease in the plaque scores seen with both interventions may be due to multiple reasons. In the case of photodynamic diode laser therapy, the intervention influenced the level of plaque. According to an experiment carried out by Braham et al., aPDT promotes an antimicrobial environment through multiple mechanisms (64). This therapy rapidly selects and destroys targeted bacterial species, inactivating virulence-associate protease and detrimental host factors such as TNF-a and IL-1B. Additionally, the photosensitizers can flow deeply into the sulcus and thus maximize the effects of aPDT (64,65). It is, however, important to note that major differences seen in the plaque index are mainly due to the conventional therapy rather than the laser therapy. Although laser therapy can play a role in plaque control, its role is very minimal in comparison to mechanical debridement. As shown in Aoki et al. aticle, the most effective way to remove plaque is through physical means (30). Along with mechanical debridement, it is also possible that oral hygiene maintenance has improved over the course of the clinical trial. Not only have the participants been shown how to improve their oral hygiene habits, but they may have also upheld a strict regime simply because they know they will soon be examined at the follow-up appointment. Hence, the reduction of the plaque index seen in both diode laser therapies can be thanks to mechanical debridement, cooperation of the participants and very minimally, the laser therapy itself.

5.2.2 Probing pocket depth

The peri-implant pocket depth may vary greatly and is not always indicative of peri-implant mucositis. This variable is, however, still measured since it is possible to detect the presence of inflammation. An increasing probing depth without bone loss indicates possible inflammation and therefore peri-implant mucositis. Shown in Figure 4 are the benefits of both photothermal and photodynamic laser diode therapy as an adjuvant to mechanical debridement in reducing the overall probing pocket depth. In the case of aPDT, two out of the three studies demonstrated a greater reduction in probing pocket depth with the intervention after a 3-month follow-up. The reductions observed were 3.1mm (51) and 0.5mm

(48) greater when the intervention was implemented. Similarly, in the case of PT, two out of three studies also demonstrated a greater reduction in probing pocket with the intervention after a 3-month follow-up. More specifically, the results observed were 0.072mm (47,53) and 0.2mm greater than the control. One study from each type of intervention, however, showed a probing pocket depth reduction to be slightly higher, of 0.1mm, when using mechanical debridement alone in comparison to the additional adjuvant (46,49). The importance of these values is dependent on various factors, the first being whether the differences observed were statistically significant or not. Similar to the statistical outcome observed in the plaque index, all the results included for the purpose of assessing aPDT were statistically significant at a 3-month follow-up while those used for PT were not.

Amongst the clinical trials implementing photothermal laser therapy, the variations between the control and the test groups range from 0.072- 0.2 mm. In addition to these variations being very minute, the values are not statistically significant and therefore the variations seem more likely due to other factors unrelated to the intervention such as the method of mechanical debridement, oral hygiene habits and lifestyle choices of the participants or chance. Amongst the clinical trials implementing antibiotic photodynamic laser therapy, the variations between the control and test groups range from 0.1- 3.1 mm. The greater statistically significant variations observed may be due to variations in initial baseline values, photosensitizer placement methodology and patient compliance. As noted earlier, baseline values are in determining the changes seen at the follow-up appointment. The average baseline values for Javed et al's study was 7.4mm- the highest amongst all studies. 3 months after aPDT laser diode therapy, the probing pocket depth was reduced by 5.9mm. This is the highest reduction seen among all clinical trials. Although their results are statistically significant and therefore the difference seen is more likely due to the intervention employed and not by chance, it is important to note that the drastic decrease in probing pocket depth seen in this study is most likely due to the very large initial probing depth. It is therefore more useful to compare the results obtained from the other two photodynamic laser therapy studies since they both started with similar baseline values (48,49). Al Rifaiy et al's study demonstrates that the conventional therapy was slightly more effective while Deeb et al's study demonstrates otherwise. The former study show

that the conventional therapy reduced the pocket depth by 0.1mm more compared to the laser therapy implemented. The latter study, however, demonstrated that the laser therapy reduced the probing depth by 0.5mm more in comparison to the conventional therapy. Both results were statistically significant and yielded a low risk of bias. In terms of laser specifications, interestingly, Al Rifaiy et al's study used a laser of higher wavelength, power density and irradiation time (670nm of 0.15W for 60 seconds) compared to Deeb et al's study (660 nm of 0.1W for 10 seconds). Therefore, although Al Rifaiy et al's study employed laser specifications with higher values, their results demonstrated that conventional therapy alone yielded promising results. This allows one to conclude that using photodynamic laser therapy as an adjuvant to conventional therapy does not enhance probing pocket depth. The increased reduction seen in Deeb et al's study may possibly be due to the different methodology employed when inserting the photosensitizer. Both Deeb et al.'s and Javed et al.'s clinical trials had the photosensitizer placed in the deepest part of the periodontal pocket and left in place for 2 minutes before being irradiated for 10 seconds. In Rifaiy et al's study, however, the photosensitizer was only left in place for 10 seconds before being irradiated for 60 seconds. It is possible that leaving the photosensitizer in the pocket longer encourages it to reach into the deepest parts of the sulcus and therefore enhance the bactericidal action, especially in crevices with limited access. This may be the possible reason why better results were obtained when the photosensitizer was left in for 120 seconds instead of just 10 seconds. More research needs to be done to determine whether there is a plausible correlation between the technique used to place the photosensitizer and the probing pocket depth. It is also important to note that the decrease in probing pocket depth seen in these studies may simply be due to the improvement of the plaque index. There is a direct relationship between plaque accumulation and soft tissue inflammation. For this reason, it is safe to conclude that an improved plaque index also results in a decrease in inflammation and therefore probing depth. Further research is needed to consider all these factors in order to factually state the specific benefits of the laser in terms of probing depth.

5.2.3 Bleeding on Probing

Although the definitions of peri-implant mucositis have differed over the years, what has remained persistent is that the key diagnostic clinical manifestation of peri-implant mucositis is bleeding on gentle probing. Bleeding on gentle probing has a low positive predictive value but a high negative one. Implants have a higher tendency to bleed than natural teeth due to their higher risk for early inflammation and longer healing period time (30,31). Therefore, an implant that bleeds does not bring significant value compared to an implant that does not bleed. It is said that negative bleeding of gentle probing has a high negative predictive value since it shows that the implant is healthy. For that reason, the efficacy of both types of therapies will be dependent on the results obtained from this clinical parameter. The randomized clinical trials of the present systematic review demonstrated the benefits of both photothermal and photodynamic laser diode therapy as an adjuvant to mechanical debridement in reducing the overall bleeding on gentle probing index. As depicted in Figure 5, photothermal diode laser therapy resulted in a greater significant change in the BoP index in comparison to the photodynamic diode laser therapy. In regard to photothermal diode laser therapy, the reductions seen in the bleeding on probing over a 3-month period were 0.911%, 25.1% (47) and 40.3% . The reductions seen in the bleeding on probing over a 3-month period when aPDT was used were 2.9% (3), 1.4% (4) and 4.3% (7). The statistical significance of the results obtained for photothermal studies were only statistically significant at the 3-month follow-up for Sanchez-Martos et al's trial (45). This may be due to the variation of baseline characteristics of the participants of each study. In Aimetti et al.'s and Mariani et al's studies, a significant number of participants has a history of treated periodontitis. Although periodontitis may arise from genetic factors or factors beyond the patient's control, it is safe to say that the oral hygiene habit of the patient plays a crucial role. If the sample population is composed of patients who had a history of periodontal disease, one can conclude that the microbial composition, as well as the oral hygiene habits, may influence the results. This is because patients with a history of periodontal diseases have a higher risk of developing peri-implant diseases (66,67). As stated in Alhakeem et al.'s retrospective cohort study, "partially edentulous patients with the history of severe periodontitis… expressed higher probability of peri-implantitis. In addition, inadequate frequency of brushing (at most once daily) and irregular visits were associated with

greater chance of peri-implant BOP" (68). More specifically, a history of periodontal disease increases the risk of peri-implantitis by 2.2 times (69). Hence, this may be the reason why the results were not significant with adjuvant laser diode therapy. Additionally, the sample population size, notably Aimetti et al.'s study, is much larger compared to Sanchez-Martos et al.'s study. Perhaps a longer follow-up period is necessary to appreciate the efficacy of each laser therapy in order to compare them to each other.

One of the main benefits of diode laser therapy is biostimulation. In laser therapy, biostimulation is the promotion of cellular regeneration in the deepest layers of soft tissue through the use of a laser. For that reason, it is generally used in order to have regenerative effects on wound healing (30,70). Both photothermal and photodynamic laser therapies encompasses biostimulation with the use of Low-Level Laser Therapy. The general theory is that laser irradiation causes an intrinsic mechanism resulting in the increased synthesis of various proliferative factors. LLLT promotes and activates cellular proliferation, collagen synthesis, mitochondrial respiration and ATP synthesis (30,31,71). This is done through the release of various cells and factors such as growth factors, periodontal ligament cells, gingival fibroblasts, osteoblasts and mesenchymal stem cells. When used in periodontal therapy, it is beneficial since early wound healing is achieved through rapid proliferation and differentiation. In Sanchez-Martos et al.'s study, a statistically significant difference was seen between both groups. This may be thanks to the combination of biostimulatory and bactericidal properties of photothermal laser therapy. Biostimulation is one of the most important aspects of photothermal laser therapy that has yet to be studied. Diode lasers exhibit their bactericidal properties through direct heat or with the help of a photosensitizer. Low-level lasers are designed to inactive bacterial endotoxins involved in peri-implant diseases (72). According to a two-year clinical outcomes follow-up study carried out by Mettraux et al., low-level laser irradiation has a biostimulatory effect that promotes would healing and reduces inflammation. More specifically, BoP decreased drastically from 100% to 43% at the 2-year follow-up of patients with peri-implantitis (72). As far as research shows, biostimulation aids at a cellular level not only by eradicating bacteria superficially but also by favoring cellular regeneration at deeper levels of the soft tissue. As previously noted, the anti-inflammatory effect of bacterial decontamination is very

temporary. A stable peri-implant tissue allows the anti-inflammatory effect to remain for longer periods of time and improves its health and therefore clinical parameters. This can only be done through the regeneration of peri-implant soft tissues at a cellular level. Therefore, in terms of the efficacy of the laser treatments, biostimulation is the key to predicting the therapies' worthiness.

The statistical significance of the results obtained for photodynamic studies were only statistically significant for Deeb et al's study (48). Al Rifaiy et al. and Javed et al.'s studies showed that the intervention had no effect and the differences seen may be due to other factors. The control and test groups both noted a decrease in the Bleeding on Probing index not due to the intervention but possibly due to the characteristics of the sample population. Their studies compared the efficacy of the therapies in e-cigarette smokers and tobacco smokers (49,51). Vasoconstriction due to smoking, whether tobacco smoking or e-cigarette smoke, can be seen due to the pathophysiological mechanism of nicotine. In addition to reduced cellular healing ability, nicotine has also been reported to reduce the tendency of bleeding (73). Increased consumption of nicotine results in the vasoconstriction of blood vessels and therefore a decrease of blood flow in the cardiovascular system (74). Hence, if smokers continue to consume nicotine throughout the clinical trial, the decrease in blood flow in gingival blood vessels results in lower BoP scores regardless of the intervention used. Interestingly, Deeb et al.'s study showed statistically significant results despite the sample population being composed of smokers. It is important to note that for this specific study, all the participants were educated about the effects of nicotine and instructed to refrain from smoking throughout the duration of the clinical trial through motivational sessions. Therefore, there is a possibility that statistically significant results were obtained since the participants refrained from smoking during the trial. It is important to note that there is no mention of the methodology used to ensure that the participants were cooperating in terms of smoking habits.

In all, in terms of BoP, it is important to highlight its high predictive negative value. Therefore, while assessing the efficacy of a treatment, an implant that shows negative signs of BoP is indicative of peri-implant health. In terms of laser therapy, this is achieved not only through the decontamination of pathogenic bacteria but, especially

through the biostimulation of peri-implant tissues. This is thanks to the fact that biostimulation results in the regeneration of cellular peri-implant tissues and consequently creates peri-implant stability.

5.3 LMITATIONS OF THE PRESENT SYSTEMATIC REVIEW

Although the present systematic review demonstrates the combination of diode laser therapy and mechanical debridement to be more effective in reducing clinical signs of peri-implant mucositis, there are some limitations that must not be overlooked. Firstly, the number of studies included in the present systematic review is limited. After an extensive search in multiple databases, seven articles fit the eligibility criteria but only six had sufficient amount of information to do comparison. The seven articles also have a variation of risk of bias ranging from low risk to high risk of bias. For that reason, although the photodynamic laser therapy seems to show more promising results in terms of the reduction of clinical parameter signs such as PI and PD, one must take into consideration that those studies show an overall higher risk of bias compared to the studies experimenting with photothermal laser therapy. Future researchers should therefore consider carrying out more studies, specifically, randomized-controlled trials where there is adequate and non-bias randomization and a larger sample population size. Additionally, due to the heterogeneity amongst the studies, including the definition of peri-implant mucositis as well as sample population size and characteristics, it is quite difficult to merge the results and expect homogenized conclusions. This systematic review is also limited in the minimum follow-up period used to compare the results is 3 months. Longer follow-up periods are necessary to appreciate the efficacy of the laser therapy since oftentimes the reduction of clinical inflammatory signs is temporary. Although the main objective of the present systematic review is to determine whether one laser therapy is more effective than the other, it is important to reconsider that both therapies can coexist. Between both therapies, it is not fair to say that since one therapy is more effective, the other one is useless. It is more interesting to point to the possibility that therapies can be more effective depending on different indications. Laser therapy is versatile. The specifications such as the power, wavelength, time of irradiation and

number of laser sessions can be altered and depending on their values, they can be used for different purposes. Thus, longer evaluations and specifications are needed in order to not only compare the effectiveness of each laser therapy but also whether one laser therapy serves better for different populations and/or indications in the treatments of peri-implant mucositis. There is still a long way to go to determine the true role of diode laser therapies in the treatment of peri-implant diseases.

6. CONCLUSIONS

The present systematic review aimed to compare the efficacy of diode laser therapies with the intention of concluding whether one therapy combination surpasses the other through the analysis of the change in plaque index, probing pocket depth and bleeding on gentle probing. The null hypothesis for the following systematic review was rejected. There is statistically significant difference between using photothermal laser therapy compared to photodynamic laser therapy as an adjuvant in reducing clinical signs of patients with peri-implant mucositis.

Based on the main objective, antimicrobial photodynamic laser therapy demonstrated a greater improvement in clinical signs of peri-implant mucositis, especially in the reduction of bleeding on probing, as an adjunct to mechanical debridement.

Firstly, antimicrobial photodynamic laser therapy is more effective as adjunctive treatment to conventional therapy for peri-implant mucositis in reducing the plaque index possibly due to the chemical properties of the photosensitizer.

Secondly, antimicrobial photodynamic laser therapy is more effective as adjunctive treatment to conventional therapy for peri-implant mucositis, in reducing the peri-implant probing depth. This may be because of the reduced plaque index rather than the laser therapy itself.

Thirdly, photothermal laser therapy is more effective as adjunctive treatment to conventional therapy for peri-implant mucositis, in reducing the bleeding on probing. This is achieved not only through the decontamination of pathogenic bacteria but, especially through the biostimulation of peri-implant tissues.

The randomized clinical trials of the present systematic review illustrated that the mentioned conclusions are dependent on multiple factors that should not be overlooked. Moreover, additional homogenous studies with a longer follow-up period are needed with the proper study design to accurately compare the results obtained. Furthermore, future research should be guided towards that the fact that both laser therapies can coexist and not necessarily need to be superior to one another.

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ANNEX

ANNEX 1: MANUSCRIPT

TITLE: "Comparison of Photothermal and Photodynamic Diode Laser Therapy in Patients with Peri-implant Mucositis: A Systematic Review"

RUNNING TITLE: Diode laser and peri-implant mucositis

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ABSTRACT

Background: Peri-implant mucositis is a peri-implant inflammatory disease where it´s key diagnostic criteria is bleeding on probing. It is documented that diode laser therapy is effective as an adjuvant in decreasing inflammatory clinical signs compared to conventional therapy alone.

Objective: The present systematic review aims to compare the efficacy of both diode laser therapies in hopes of guiding clinicians make the best choice when it comes to treating patients with peri-implant mucositis.

Material and methods: Electronic databases were used to select articles. The following clinical question was written according to the PICO structure to center the systematic review: Among patients with peri-implant mucositis (P), does photothermic (PT) laser therapy (I) demonstrate greater improvement in clinical inflammatory signs (O) in comparison to antimicrobial photodynamic therapy (aPDT) (I) as an adjuvant to conventional therapy (C)? The risk of bias of each study was assessed with Cochrane Collaboration tool RoB 2.

Results: Seven randomized controlled trials (RCTs) were included in the systematic review. Characteristics of the study design, population and laser specifications were noted. The following clinical parameters were compared amongst all studies at baseline and 3-month follow-up values: Plaque Index (PI), Probing Pocket Depth (PPD) and Bleeding on Probing (BoP).

Conclusion: Antimicrobial photodynamic laser therapy alongside mechanical debridement demonstrated a greater improvement in clinical signs of peri-implant mucositis, especially in BoP. Future research should be guided towards determining whether one therapy is more useful in specific populations or clinical situations.

Keywords*: "peri-implant mucositis", "diode laser therapy", "Photothermal", "Photodynamic" and ¨Bleeding on probing".*

1. INTRODUCTION:

Peri-implant mucositis develops in healthy peri-implant mucosa after accumulation of bacterial biofilm around osseointegrated dental implants. The main clinical manifestation of peri-implant mucositis is bleeding on gentle probing. The accumulation of pathogenic bacterial on the biofilm is the main risk factor (1). Peri-implant mucositis is the most prevalent peri-implant disease that arises from dental implant treatments. Due to its reversibility, it is important to stress prophylactic measures, early diagnosis, as well as early treatment in order to prevent its evolution into a much more aggressive pathology: peri-implantitis. Currently, the most widely used treatment for peri-implant mucositis is to perform a non-surgical approach based on mechanical debridement, however, it has been observed that the bacterial load returns to baseline counts at 3 months (2). Due to these limitations, adjuvant elements are being studied to improve the clinical outcomes. One of the most studied therapies today is the use of diode laser for phototherapy purposes. The main photobiological effects periodontal phototherapy of are photothermal and photochemical effects. Currently, there are no systematic reviews comparing the efficacy of photodynamic to photothermal diode laser therapies in combination with mechanical debridement. Therefore, the purpose of this systematic review is to determine which laser therapy, photodynamic (aPDT) or photothermal (PT), demonstrates greater improvement in clinical signs of peri-implant mucositis as an adjunct to mechanical debridement through the evaluation of the plaque index, probing depth, and bleeding on probing index.

2. MATERIAL AND METHOD

2.1 Protocol and focused question

The Preferred Reporting Items for Systematic Review and Meta- Analysis (PRISMA) guideline was followed to perform this systematic review (3). The following clinical question, written according to the PICO structure: **Among patients with peri-implant mucositis (P), does photothermic laser therapy (I) demonstrate greater improvement in clinical inflammatory signs (O) in comparison to photodynamic therapy (I) as an adjuvant to conventional therapy (C)?**

2.2 Selection criteria:

Studies were excluded based on the following exclusion criteria: 1) animal and in-vitro studies; 2) studies published in 2011 or before; 3) studies in languages other than English or Spanish. Studies were included based on the following inclusion criteria: 1) cohort study or randomized control trial (RCT); 2) population based on patients with peri-implant mucositis; 3) intervention used either PT diode laser therapy or aPDT diode laser therapy as an adjuvant to conventional therapy; 4) clinical outcome measured includes the bleeding on probing index; 5) follow-up of at least 3 months.

2.3. Search strategy:

Both CRAI library Ducle Chacón and Elsevier's Scopus search engines were used to perform the search on February 10th, 2022. The databases included can be seen in Figure 1. Keywords and Medical Subject Heading (MeSH) terms were used to construct the following search algorithm: ("Peri-implant mucositis" OR "Peri-implant disease" OR "Mucositis") AND ("Photothermic" OR "Photodynamic" OR "Diode laser" OR "Laser Therapy" OR "Photothermal Therapy" OR "Phototherapy" OR "Laser, Semiconductor/ therapeutic use" OR "Photochemotherapy") AND ("Conventional therapy" OR "Conventional non-surgical therapy" OR "Mechanical debridement" OR "Mechanical curettage" OR "Periodontal debridement" OR "Dental Scaling" OR "Dental prophylaxis") AND ("Clinical inflammatory signs" OR "Plaque index" OR "bleeding on probing index" OR "Gingival Index").

2.4. Screening methods and data abstraction:

Two impartial reviewers (NK and RS) independently performed the systematic review search. Depicted in Figure 1 is the metholodology of the screening. Any disagreement in study eligibility was resolved by discussion between both reviewers until a consensus was reached. The level of agreement between the reviewers was calculated using the k-score according to the Landis & Koch criteria (4).

2.5. Risk of bias in individual studies:

The risk of bias was assessed independently and by the same reviewers who performed the search (NK and RS) according to the Cochrane collaborations' tool (5).

Other sources of bias, seen in Figure 3 were also recorded.

2.6. Case definitions

Peri-implant mucositis: The most recent definition of peri-implant mucositis is included within the New Classification of Periodontal and Peri-Implant Diseases and Conditions, 2018 (6). The following definition will be taken as the current definition of peri-implant mucositits in our review: Presence of bleeding and/or suppuration on gentle probing with or without increased probing depth compared to previous examinations and absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling.

Conventional non-surgical treatment of peri-implant diseases: Currently there is no gold standard in the treatment of peri-implant mucositis, several protocols have been described over the years based on the experience of treating gingivitis (7). The treatment is based on the non-surgical removal of plaque deposits and calculus by using plastic or teflon curettes and establishing good plaque control with proper oral hygiene instructions.

Diode laser therapies: There is no consensus on a gold standard protocol for laser treatment for peri-implant diseases. Two types of diode laser therapy will be considered in this review (8,9).

- Photothermal Laser therapy (PT): This therapy is based on the conversion of light energy into thermal energy, increasing the temperature in the tissues and producing injuries that will depend on the degrees reached. Depending on the power at which the laser is used in this therapy, bactericidal, cutting and coagulation effects as well as cellular biostimulation will be obtained (10,11).
- Photodynamic therapy (PDT): Photodynamic therapy is based on a non-thermal photochemical mechanism. A pigment is used, called a photosensitizer, which selectively reaches the cell or microorganism to be eliminated and is irradiated with a wavelength according to the selected pigment. This therapy seeks to obtain bactericidal and bacteriostatic effects (12,13).

2.7. Data analysis

The articles were compared, and the mean values of the primary variables were directly grouped and analysed using standardised mean difference (SMD) and 95% confidence intervals (CI). All analyses were performed with the IBM® SPSS® Statistics version 21.00 software. Statistical significance was defined for a value of $p < 0.05$.

3. RESULTS

3.1 Study selection:

As illustrated in the PRISMA flowchart (Figure 1), a total of seven studies were included. Table 1 lists details of the excluded studies.

3.2 Characteristics of included studies:

Outlined in Table 2 are the characteristics of the seven studies included in the present systematic review.

3.3 Laser and photochemotherapy related parameters:

Table 3 summarizes the technical specifications of the laser therapy used in each study.

3.4 Risk of bias across studies

The risk-of-bias of each study included in the present systematic review was assessed using the Cochrane Collaboration tool RoB 2 (5). Illustrated in Fig. 2 is the overall risk-of-bias assessment of each study as well as each domain across all studies. The overall risk-of-bias judgment for each study included in the present systematic review was low except for two studies (14,15) which presented a high risk of bias overall. The overall risk-of-bias judgment across all studies for each domain assessed varies. Illustrated in Figure 3 is a summary of the risk of bias of each factor across all studies based on the judgment of the reviewers.

Synthesis of the results:

The difference between baseline values and 3-month follow-up values were compared between the control and test groups of each included study (Table 3 & 4).

Antimicrobial Photodynamic Therapy: In Al Rifaiy et al, Javed et al., and Deeb et al's aPDT studies yeilded a reduction in the plaque index (15–17). The reductions seen in the PD over a 3-month period with mechanical debridement alone were 2.3 mm, 2.8mm and 0.4mm accordingly. 2 out of the 3 studies demonstrated a greater

reduction in PD in the test group in comparison to the control group. 2 out of the 3 studies demonstrated a greater reduction in BoP in the test group in comparison to the control group (16,17).

Photothermal Laser Therapy: All PT studies demonstrated a PI reduction (18–20). 2 out of the 3 studies demonstrated a greater reduction in PD in the test group in comparison to the control group (18,19). All studies demonstrated a reduction in BoP index.

4. DISCUSSION

All studies included in the present systematic review are homogenous in terms of the key clinical sign for its diagnosis: BoP. The study population included in the present systematic review is heterogeneous. Some studies test the intervention on a population group of only tobacco consumers. Since tobacco is a crucial risk factor for peri-implant mucositis, the outcome of the intervention will also be affected if the study sample only includes tobacco users. The aleatory process used were also heterogenous. The stratified block randomization system is notably the best randomization method to implement for the studies included in the present systematic review since this process randomly assigns an equal number of participants to groups and addresses influential characteristics accordingly (21). Longer follow-up period would have been useful to see if there were any pathogenic bacteria regrowth and the advancement of peri-implant mucositis into periimplantitis despite the patient undergoing laser therapy (14). On the other hand, it is also important to note that at this stage, it is mostly the patient's responsibility to maintain a low pathogenic bacterial load through oral hygiene habits and eliminating risk factors (22).

Regarding the outcome variables, PI is dependent on the initial baseline value. Initially, if a patient has a very high PI, after mechanical and chemical cleaning, the changes observed will be more drastic in comparison to a case when the patient initially has very minimal plaque. Similar correlations were mentioned in a similar systematic review (23). Additionally, the decrease in the plaque scores seen with both interventions may be due the laser therapy itself. aPDT promotes an

antimicrobial environment by rapidly selecting and destroying targeted bacterial species, inactivating virulence-associate protease and detrimental host factors (24). The photosensitizers are also able to flow deeply into the sulcus and thus maximize the effects of aPDT (24,25). It is also possible that oral hygiene maintenance has improved over the course of the clinical trial. Hence, the reduction of the plaque index seen in both diode laser therapies can be thanks to mechanical debridement, cooperation of the participants and very minimally, the laser therapy itself.

Regarding the probing depth, the peri-implant pocket depth may vary greatly but it helps detect the presence of inflammation. Amongst the clinical trials implementing antibiotic aPDT, the variations had greater statistically maybe due to initial baseline values, photosensitizer placement methodology and patient compliance. It is also important to note that the decrease in probing pocket depth seen in these studies may simply be due to the improvement of the plaque index.

With regards to the bleeding on probing index, although the definitions of peri-implant mucositis had differed over the years, what has remained persistent is that the key diagnostic clinical manifestation of peri-implant mucositis is bleeding on gentle probing. Bleeding on gentle probing has a low positive predictive value but a high negative one. In essence, implants have a higher tendency to bleed than natural teeth due to their higher risk for early inflammation and longer healing period time (9,26). Therefore, an implant that bleeds does not bring significant value compared to an implant that does not bleed. For that reason, the efficacy of both types of therapies will be dependent on the results obtained from this clinical parameter. Photothermal diode laser therapy resulted in a greater significant change in the BoP index in comparison to the photodynamic diode laser therapy. In Aimetti et al.'s and Mariani et al's studies, a significant number of participants has a history of treated periodontitis. If the sample population is composed of patients who had a history of periodontal disease, one can conclude that the microbial composition, as well as the oral hygiene habits, may influence the results (27). Al Rifaiy et al. and Javed et al.'s studies showed that the intervention had no effect. Their studies compared the efficacy of the therapies in e-cigarette smokers and tobacco smokers (15,16).

Vasoconstriction due to smoking, whether tobacco smoking or e-cigarette smoke, can be seen due to the pathophysiological mechanism of nicotine. In addition to reduced cellular healing ability, nicotine has also been reported to reduce the tendency of bleeding (28)(29). Hence, if smokers continue to consume nicotine throughout the clinical trial, the decrease in blood flow in gingival blood vessels results in lower BoP scores regardless of the intervention used.

One of the main benefits of diode laser therapy is biostimulation. Biostimulation is one of the most important aspects of photothermal laser therapy that has yet to be studied. In laser therapy, biostimulation is the promotion of cellular regeneration in the deepest layers of soft tissue through the use of a laser. Lasers promote and activate cellular proliferation, collagen synthesis, mitochondrial respiration and ATP synthesis (26). Low intensity lasers have a biostimulatory effect that promotes would healing and reduces inflammation. More specifically, BoP decreased drastically from 100% to 43% at the 2-year follow-up of patients with peri-implantitis (30). A stable peri-implant tissue allows the anti-inflammatory effect to remain for longer periods of time and generally improves its health and therefore clinical parameters.

The limitations of the present systematic review include the fact the number of studies and follow-up period are limited. They also have a variation of risk of bias. For that reason, although the photodynamic laser therapy seems to show more promising results in terms of the reduction of clinical parameter signs such as PI and PD, one must take into consideration that those studies showed an overall higher risk of bias compared to the studies experimenting with photothermal laser therapy. Future researchers should therefore consider carrying out more studies, specifically, randomized-controlled trials where there is adequate and non-bias randomization and a larger sample population size. In conclusion, aPDT alongside mechanical debridement demonstrates a greater improvement in PI and PD while PT demonstrates greater improvements of BoP index. Future research should be guided towards determining whether one therapy is more useful in specific populations or clinical situations.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in this study. The study was designed, conducted and analyzed by researchers belonging to the Official master's in advanced Oral Implantology (European University of Valencia, Valencia, Spain).

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TABLES AND FIGURES

Table 1. Methodology of excluded studies.

Author/ Year	Country	Type of study	Sample			Study groups	Study variables	Reason for exclusion
			Sample size	Gender ratio (M:F)	Mean age (years)			
Shahmohammadi et al. 2021	Iran	SR & MA	NA	NA	NA	C: NA T: NA	PI (%mean) PPD (mean mm) BOP (%mean)	Not RCT
AlDeeb et al. 2020	Saudi Arabia	RCT	71	71:0	Group 1: 29.5 ± 5.8 Group 2: 27.8 ± 3.1 Group 3: 30.2 ± 4.4	C: 46 T: 25	PI (mean %) BoP (mean %) PPD (mean mm) MMP-8 (mg/mL) TNF-α (pg/mL)	All groups received laser diode therapy. Study is evaluating risk factors,
Alresayes et al. 2020	Saudi Arabia	Cohort Study	Test:24 patients with 41 implants Control:25npatients with 46 implants	T:10:14 C: 12:13	T: 49.4 C: 45.8	C:25 T: 24	PI (%mean ± SD) PD (mean mm) BOP (%mean ± SD) MBL (mean mm ± SD) PICF (mean ul ± SD) hsCRP (mean pg/ml ±SD) TNF-α (mean pg/ml ± SD) IL-6 (mean pg/ml ± SD)	Population included only patients with peri implantitis.
Al Hafez et al.2020	Saudi Arabia	Cross-sectional Cohort Study	60	50:10	Group 1: 51.6 ± 2.4 Group 2: 54.1 ± 1.6 Group 3: 55.4 ± 0.8 Group 4: 52.4 ±1.1	C; 30 T: 30	PI (mean %) BoP (mean %) PPD (mean mm)	All groups received laser diode therapy. Study is evaluating risk factors,
Sanchez-Martos et al. 2020	Spain	SR &MA	NA	NA	NA	C: NA T: NA	PI (%mean ± SD) PPD (mean mm) BOP (%mean ± SD)	Not RCT/ Cohort study
Albaker et al. 2018	Saudi Arabia	SR	NA	NA	NA	C: NA T: NA	PI (%mean) PPD (mean mm) BOP (%mean)	Not RCT/ Cohort study
Karimi et al. 2016	Iran	RCT	Patients: 10 Implants:30	2:8	52.8 ± 7.33	C:10 T:10	PPD (mm mean ± SD) CAL (mm mean ± SD) MR (mm mean ± SD) GI (mean %) BoP (mean %)	- Split-mouth clinical trial - Population group is a mixture of patients with peri-implant mucositis and peri-implantitis. The outcomes are not differentiated between the two.
Lerario et al. 2016	Italy	Preliminary clinical study	Patients: 27 Implants: 125	15:12	range (36-67)	C:6 T:21	PI (%mean ± SD) PPD (mean mm) BOP (%mean ± SD)	- Not RCT/ Cohort. - Population group is a mixture of patients with peri-implant mucositis and peri-implantitis. The outcomes are not differentiated between the two.

RCT: Randomized controlled clinical trial; SR: Systematic Review; MA: Meta-Analysis; C: Control; T: Test;PI: Plaque index; PPD: Probing pocket depth; GI: Gingival Index; BOP: Bleeding on probing; SD: Standard deviation; IL-6: Interleukin-6; (TGF)-α: Transforming growth factor α;; MBL: Marginal bone level, PICF: peri-implant crevicular fluid, hsCRP: high sensitivity C-reactive protein NA: Not applicable/Not available

Table 2. Methodology of included studies

Author Year	Country	Type of study	Sample			Study groups		Follow up	Study variables	Risk of bias
			Sample size	Gender ratio (M:F)	Mean age (years)	Control	Test			
Sanchez-Martos et al. 2020	Spain	RCT	68	40:28	56.9	34	34	3	PI (mean %) BoP (mean %) PD (mean mm) REC (mean mm)	Low
Mariani et al. 2020	Italy	RCT	73	26:47	Test: 62.1 ± 6.8 Control: 59.2 ± 9.3	35	38	12	PI (mean %) BoP (mean %) PD (mean mm) REC (mean mm)	Low
Aimetti et al. 2019	Italy	RCT	220	71:149	57.4	110	110	3	PI (mean %) BoP (mean %) PD (mm) REC (mm) FMPS (%) FMBS(%)	Low
Deeb et al. 2019	Saudi Arabia	RCT	45	45:0	Group A: 52.6 ± 0.9 Group B: 53.8 ± 0.7 Group C: 49.2 ± 0.13	30	15	3	PI (mean %) BoP (mean %) PD (mean mm)	Low
Al Rifaiy et al. 2018	Saudi Arabia	RCT	38	38:0	69	18	20	3	BoP (mean %) PD (mean mm)	Low
Al-Sowygh et al 2017	Saudi Arabia	RCT	48	48:0	44.6	24	24	3	BoP (mean %) PD (mean mm)	High
Javed et al. 2017	United States of America	RCT	54	54:0	51.4	26	28	3	BoP (mean %) PD (mean mm)	Unclear

RCT: Randomized controlled clinical trial; PI: Plaque index; PPD: Probing pocket depth; BOP: Bleeding on probing; REC: Recession, MMP-8: matrix metalloproteinase-8, (TGF)-α: Transforming growth factor α; FMPS: full mouth plaque score; FMBS: full-mouth bleeding score; NA: Not applicable/Not available

Table 3. Laser and photosensitizer parameters of included studies.

Author/ Year	Diode laser brand	PT/ PDT	Photosensitizer	Biostimulation					Treatment				Wavelength (nm)
				Pre/Post Irradiation	Power (W)	Irradiation time (s)	Optic fiber diameter (mm)	Number sessions	Power (W)	Irradiation time (s)	Optic fiber diameter (mm)	Number sessions	
Sánchez-Martos et al. 2020	Fox® diode laser (A.R.C. Laser GmbH, Nürnberg, Germany)	PT	NA	Pre-Irradiation	1	30	1	NA	1	30	0,3	1	810
Aimetti et al. 2019	NA	PT	NA	Post-Irradiation	0.7	60	1	2	2.5 W (average 0.7 W)	30	0.3	3	980
Al Rifaiy et al. 2018	HELBO® (Ther- aLite Laser, Photodynamic Systems GmbH, Wels, Austria).	PDT	Methylene-blue 0.005%	NA	NA	NA	NA	NA	0.15	60	0.06	1	670
Javed et al. 2017	HELBO® (Ther- aLite Laser, Photodynamic Systems GmbH, Wels, Austria).	PDT	Methylene-blue 0.005%	NA	NA	NA	NA	NA	0.1	10	NA	1	660
Al-Sowygh et al. 2017	NA	PDT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mariani et al. 2020	NA	PT	NA	Post-irradiation	0.7	60	1	2	2.5 W (average 0.7 W)	30	0.3	3	980
Deeb et al. 2020	HELBO® (Ther- aLite Laser, Photodynamic Systems GmbH, Wels, Austria).	PDT	Methylene-blue 0.005%	NA	NA	NA	NA	NA	0.1	10	NA	1	660

PT: Photohtermic therapy; PDT: Photodinamic therapy; W: Wattios; s: Seconds; cm: Centimeters; nm: Nanometers; mm: Millimeters; NA: Not available

Table 4. Main results of included studies.

Author/ Year	Laser Therapy	Variables	Groups	Baseline	3 months	Δ 0-3 months
Sanchez-Martos et al. (2020)	PT	PI (%)	Control	0.676	0.509	0.167
			Test	0.824	0.480	0.344
		PPD (mm)	Control	1.303	1.166	0.137
			Test	1.277	1.068	0.209
		BoP (%)	Control	1.176	0.568	0.608
			Test	1.175	0.264	0.911
Mariani et al. (2020)	PT	PI (%)	Control	44.8	12.9	31.9
			Test	49.6	10.5	39.1
		PPD (mm)	Control	3.8	3.1	0.7
			Test	3.6	3.0	0.6
		BoP (%)	Control	59.5	26.7	32.8
			Test	63.6	23.3	40.3
Aimetti et al. (2019)	PT	PI (%)	Control	30.6	12.6	17.9
			Test	34.4	11.2	23.2
		PPD (mm)	Control	3.4	3.0	0.4
			Test	3.5	2.9	0.6
		BoP (%)	Control	46.2	26.8	19.4
			Test	48.3	23.2	25.1
Deeb et al. (2019)	PDT	PI (%)	Control	45.3	14.8	30.5
			Test	44.5	11.5	33
		PPD (mm)	Control	4.5	4.1	0.4
			Test	4.8	3.9	0.9
		BoP (%)	Control	13.6	11.8	1.8
			Test	12.3	8.0	4.3
Al Rifaiy et al. (2018)	PDT	PI (%)	Control	46.8	27.5	19.3
			Test	51.1	13.2	37.9
		PPD (mm)	Control	4.5	2.2	2.3
			Test	4.3	2.1	2.2
		BoP (%)	Control	9.2	7.9	1.3

			Test	**14.6**	**11.7**	**2.9**
Javed et al. (2017)	PDT	PI (%)	Control	51.2	23.2	28
			Test	47.6	10.4	37.2
		PPD (mm)	Control	6.6	3.8	2.8
			Test	7.4	1.5	5.9
		BoP (%)	Control	8.6	6.9	1.7
			Test	10.2	8.8	1.4

Figure 1. Study identification process and results of the literature search via databases and other methods according to PRISMA 2020

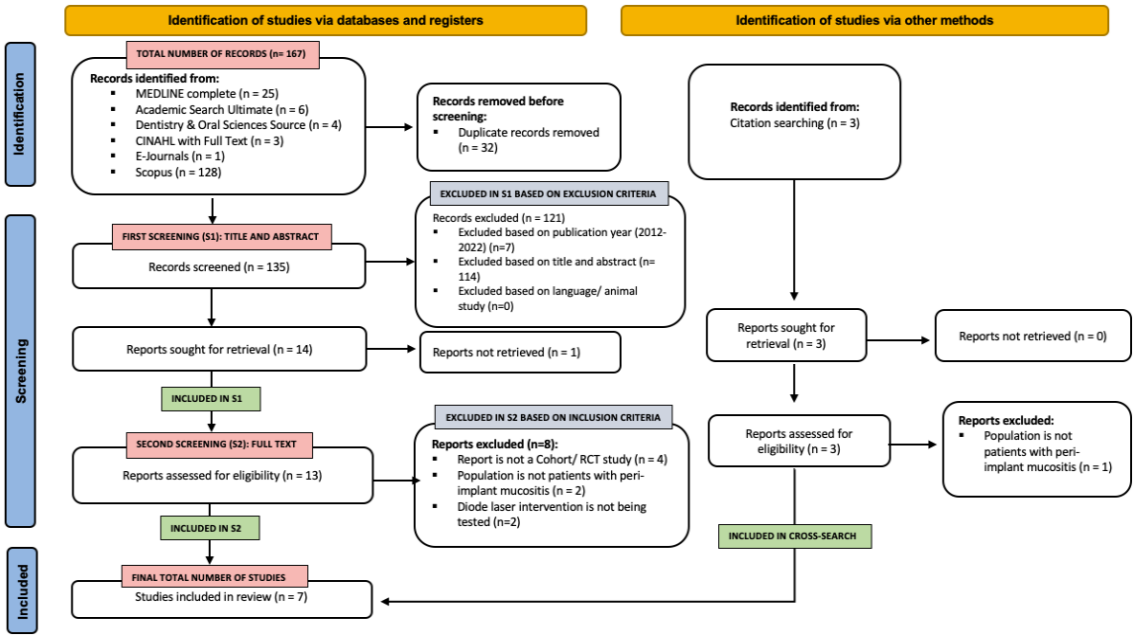


Figure 2. A) Risk of bias according to the Cochrane system. B) Risk of bias summary, review authors' judgments about each risk of bias item presented as percentages across all included studies.

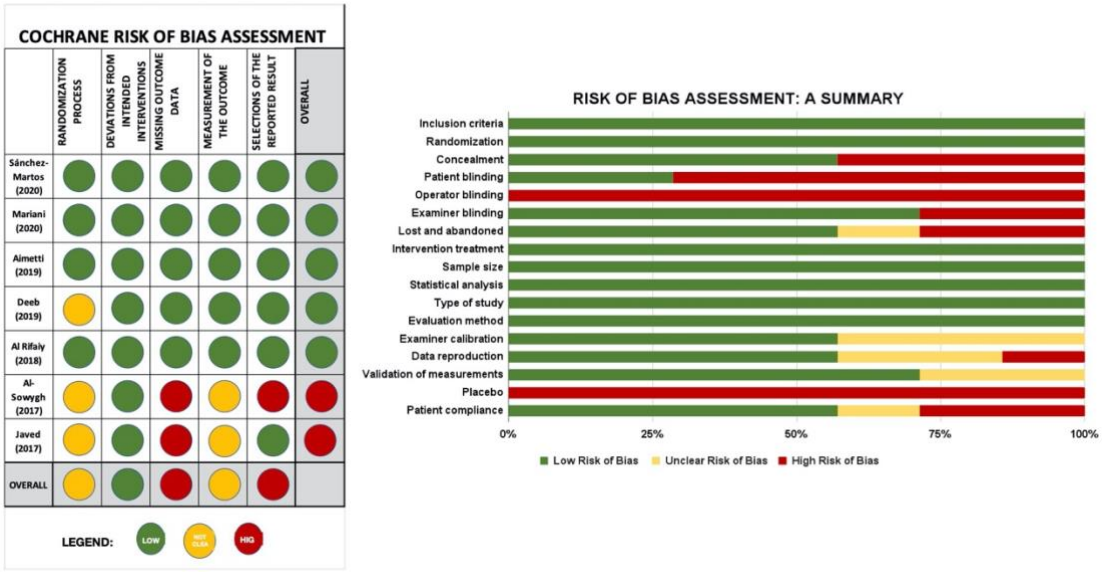
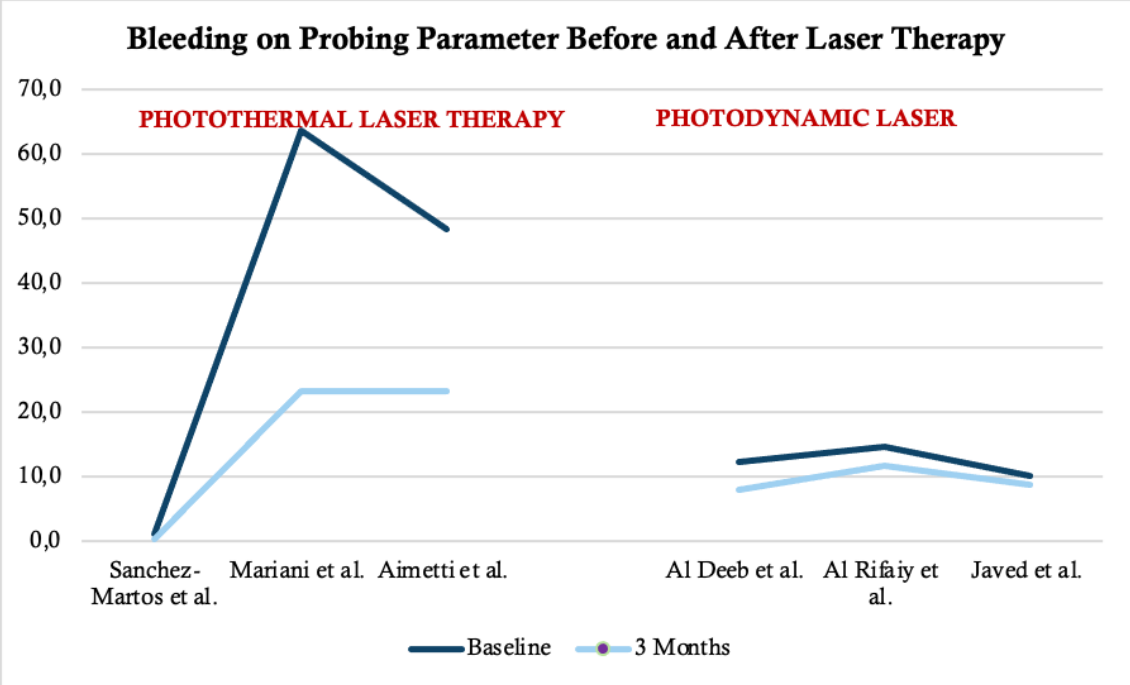


Figure 3. Graphical Representation of the Changes in Bleeding on Probing Index 3 Months After Laser 5 Therapy



ANNEX

ANNEX 2: PRISMA CHECKLIST

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	YES
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	YES
Registration	12	Provide the register name and registration number.	PENDING

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Cover
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	20
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	21
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	24
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	24
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	25
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	26
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	27
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	N/A
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	27
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	34
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	28-29
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	28-34
Study characteristics	17	Cite each included study and present its characteristics.	32.33
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	36-39
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	34
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	33
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	40-44
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	42
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	42
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	38
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	38
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	51-59
	23b	Discuss any limitations of the evidence included in the review.	47-51

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	59-60
	23d	Discuss implications of the results for practice, policy, and future research.	60
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pending: Information available after Prospero registration completion
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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