International Journal Dental and Medical Sciences Research
Volume 4, Issue 3, May-June 2022 pp 291-303 www.ijdmsrjournal.com ISSN: 2582-6018

Photodynamic Therapy in Periodontal Disease: A Novel Therapeutic Approach

Dr Sucharita Banerjee [1], Dr Amrita Dutta [2], Dr Surbhi Gautam[3],Dr Priyanka Bit [4], Dr Ashit Pal[5], Dr Pradip Kumar Giri[6]

[1](MDSPost graduate trainee,Dr R Ahmed Dental College& Hospital)
[2](MDSPost graduate trainee , Dr R Ahmed Dental College & Hospital)
[3] (MDS Post graduate trainee , Dr R Ahmed Dental College & Hospital)
[4] (MDS Post graduate trainee, Dr R Ahmed Dental College & Hospital)
[5] (Professor & Head of the Department,Dr R Ahmed Dental College & Hospital)
[6] (Professor,Dr R Ahmed Dental College & Hospital)

Submitted: 20-05-2022 Accepted: 30-05-2022

ABSTRACT: Human oral cavity is areservoir of different microorganism. Among them some microorganismfrequentlycolonizes in the dental biofilm and they are commonly known as periodontopathic bacteria. These bacteriaaffect tooth supporting structureswhich mayultimately causes periodontal diseases.For long time,different chemical antimicrobial agents are used to destroy this microorganism. As these agents are difficult to maintain at therapeutic concentrations in the oral cavity and can be rendered ineffective by resistance development in target organisms, there is a need for an alternative antimicrobial approach. A novel approach, photodynamic therapy (PDT), could be a solution to these problems. The use of aPDT requires a non-toxic photosensitizer, harmless visible light and oxygen. The photosensitizer binds to targeted bacteria and then can be activated by light of the appropriate wavelength in the presence of oxygen. The advantage of this new approach includes rapid bacterial elimination, minimal chance of resistance development and safety of adjacent host tissue and normal microflora. Thus, the available knowledge of photodynamic therapy should encourage a more clinically oriented application of this technique.

KEYWORDS: Photodynamic therapy, Laser, Bactericidal effect,Photosensitizer.

I. INTRODUCTION:

Periodontitis is a chronic inflammatory multifactorial disease involving the supporting structures of the teeth. It is triggered by periodontopathogens, while the clinical outcome is greatly influenced by the local host immune response.[1] Removal of the etiological agents i.e dental biofilm and mineralized deposits from the tooth surface are the fundamental aspects of periodontal therapy.[2,3]Therefore the conventional therapy includes non-surgical mechanical debridement including supra and subgingival scaling and/or root planning.[4]However, completeness of periodontal debridement procedures may decrease with increasing probing depth (PD) and other tooth related anatomic factors such as furcation involvement, cervical enamel projection, concavities etc.[5,6,7] Thus, bacterial reservoirs can remain on the root surface and affect periodontal healing following treatment.

In order to additionally facilitate bacterial reduction, in the 1990s, the application of light energy (in other words, phototherapy) has been considered as a novel treatment approach in periodontics.[8,9] Amongst which Laser therapy is being widely used till now and is an effective means of decontamination of periodontal pockets. Lasers possess high bactericidal properties and they have demonstrated effective killing of oral pathogenic bacteria associated with periodontitis and peri-implantitis.[10,11,12] Most high-level lasers exhibit bactericidal effects by thermal denaturation or direct ablation or destruction of bacterial cells.[9,13]Also, the use of high-level lasers usually results in irreversible thermal damage to the surrounding periodontal tissues and there is a concern of unexpected side effects, such as excessive ablation or thermal coagulation, carbonization or necrosis of the root, the gingival connective tissue, the bone and the pulp tissues, depending on the type of laser employed.[8,9,14]

International Journal Dental and Medical Sciences Research
Volume 4, Issue 3, May-June 2022 pp 291-303 www.ijdmsrjournal.com ISSN: 2582-6018

In recent times, a new type of non-invasive phototherapy for bacterial elimination, called photodynamic therapy (PDT), has been introduced, which uses low-level laser light.[15,16] Unlike high-level lasers, photodynamic therapy can selectively target the bacteria without potentially damaging the host tissues.[17,18,19] It can be defined as eradication of target cells by reactive oxygen species, predominantly singlet oxygen, produced by means of a photosensitizing compound and light of an appropriate wavelength.[20,21]. It also minimizes the occurrence of bacterial resistance.[15,22] Therefore, PDT represents an alternative antibacterial, antifungal, and antiviral treatment against drug – resistant organisms.[15] Allison et al. described PDT as a therapy that ''is truly the marriage of a drug and a light''.[23]

- HISTORICAL BACKGROUND:

Phototherapy was popular in ancient Greece, Egypt, and India, but disappeared for many centuries, only being rediscovered by the Western civilization at the beginning of the 20th century.[25] The use of contemporary photodynamic therapy was first reported by the Danish physician, Niels Finsen. He successfully demonstrated photodynamic therapy by employing heat filtered light from a carbon arc lamp (The Finsen Lamp) in the treatment of a tubercular condition of the skin known as Lupus Vulgaris.[25]

Subsequent work in the laboratory of Von Tappeiner coined the term "Photodynamic action" and showed that oxygen was essential.[26] Much later, Thomas Dougherty and Co-workers at Roswell Park cancer institute, Buffalo, New York, clinically tested PDT. It was John Toth, who renamed it as PDT.[28]

PDT was approved by the Food and Drug Administration in 1999 to treat pre-cancerous skin lesions of the face or scalp.[30] Ongoing investigations demonstrated practical usefulness of photosensitization in the broad field of different sciences including virology, microbiology, immunology and dermatology.

- PRINCIPLES AND MECHANISM OF ACTION:

PDT involves three components: photosensitizer, light and oxygen. When a photosensitizer is irradiated with light of specific wavelength it undergoes a transition from a low-energy ground state to an excited singlet state. Subsequently, the photosensitizer may decay back to its ground state, with emission of fluorescence, or may undergo a transition to a higher-energy triplet state. The longer lifetime of the triplet state enables the interaction of the excited photosensitizer with the surrounding molecules, and it is generally accepted that the generation of cytotoxic species produced during photodynamic therapy occurs in this state.[21] (Fig. 1). The triplet-state photosensitizer reacts with biomolecules by two mechanisms.

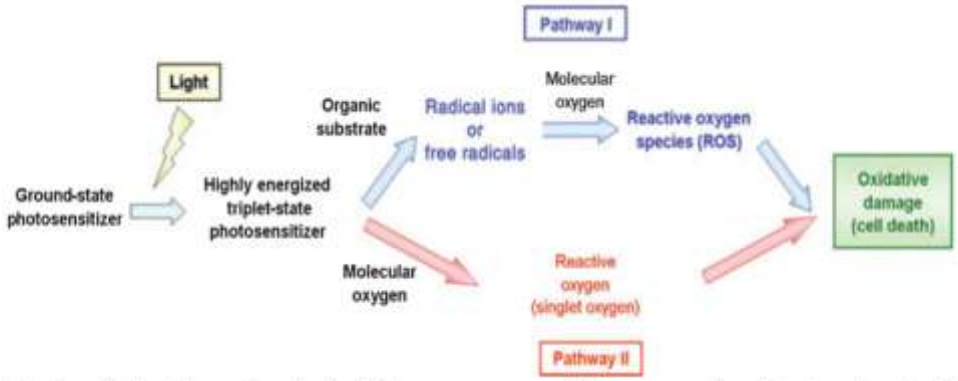


Fig. 1. Mechanism of photodynamic antimicrobial reactions at the molecular level. After irradiation with light of a specific wavelength, the photosensitizer in the ground state is converted to a highly-energized triplet state. The triplet-state photosensitizer follows two different pathways (I and II) to react with biomolecules. Pathway I involves the production of ions or electron / hydrogen removal from an organic substrate molecule of the cells to form free radicals. Pathway II involves the production of a highly reactive state of oxygen, known as singlet oxygen ($^1O_2$), which reacts with the surroundings as a result of its high chemical reactivity. The free radicals and the singlet oxygen convey toxic or lethal effects to the bacterial cell by damaging the cell membrane and the cell wall (111, 13

International Journal Dental and Medical Sciences Research
Volume 4, Issue 3, May-June 2022 pp 291-303 www.ijdmsrjournal.com ISSN: 2582-6018

The Type I reaction involves electron / hydrogen transfer directly from the photosensitizer, producing ions or electron / hydrogen removal from a substance, molecules to form free radicals. These radicals react rapidly with oxygen resulting in the production of highly reactive oxygen species (superoxide, hydroxyl radicals, hydrogen peroxide), which are harmful to cell membrane integrity, causing irreparable biological damage.[32,33]

In the type II reaction, the triplet-state photosensitizer reacts with oxygen to produce an electronically excited and highly reactive state of oxygen, known as singlet oxygen ($^1O2$), which can interact with a large number of biological substrates as a result of its high chemical reactivity, inducing oxidative damage and ultimately lethal effects upon the bacterial cell by damaging the cell membrane and cell wall.[32,33] Microorganisms that are killed by singlet oxygen include viruses, bacteria, protozoa and fungi. It seems that the primary cytotoxic agent responsible for the biological effects of the photo-oxidative process is singlet oxygen.

It is difficult to distinguish between the two reaction mechanisms. Though contributions from both Types I and II processes indicate that the mechanism of damage is dependent on both oxygen tension and photosensitizer concentration,[31] the process of antimicrobial photodynamic therapy is generally mediated by type II reaction, which is accepted as the major pathway in microbial cell damage.[15,33]

(a) PHOTOSENSITIZERS:

PDT uses several photoactive components. The first approved photosensitizer was Hematoporphyrin derivative for the treatment of refractory superficial bladder cancer.[38] An ideal photosensitizer should be non-toxic and activated only upon illumination. In general, the optimal photosensitizer should have a number of photo-physical, chemical and biological characteristics (Table 1).[31]

Table 1. Optimal properties of a photosensitizer

1.	Highly selective;
2.	Low toxicity and fast elimination from skin and epithelium;
3.	Absorption peaks in the low-loss transmission window of biological tissues;
4.	Optimum ratio of the fluorescence quantum yield to the inter-conversion quantum yield;
5.	High quantum yield of singlet oxygen production in vivo
6.	High solubility in water, injection solutions and blood substitutes
7.	Storage and application light stability

In addition, for treatment of periodontal infections, the photosensitizer should bind with bacteria and plaque without causing any cosmetic issues, such as unwanted staining of gingiva and other soft tissues. Furthermore, it should be acceptable to patients and personnel and is capable of easily accessing pathogens present in deeper periodontal pockets.[24]

Types of photosensitizers

Most of the photosensitizers used for medical purposes belong to the Tricyclic dyes, Tetrapyrroles and Furocoumarins.

In antimicrobial PDT, photosensitizers used are toluidine blue O and methylene blue. Both have similar chemical and physicochemical characteristics. Toluidine blue O is a solution that is blue – violet in color. It stains granules within mast cells and proteoglycans/glycosaminoglycans within connective tissues. Methylene blue is a redox indicator that is blue in an oxidizing environment and becomes colorless upon reduction. Methylene blue combined with light has been reported to be beneficial in killing the influenza virus, Helicobacter pylori, and C. albicans[39,40] and also because of its photocatalytic action of methylene blue, it has been utilized for virus inactivation in blood plasma before blood transfusions, using a white fluorescent lamp.[39]

With respect to antimicrobial photodynamic therapy, it has been demonstrated that methylene blue and toluidine blue O are

very effective photosensitizing agents for the inactivation of both gram-positive and gram-negative periodontopathic bacteria and therefore have been the photosensitizers of choice in the treatment of periodontitis and peri-implantitis..[29,41] There is, however, a difference in susceptibility, toluidine blue O seems to exhibit a greater ability for killing gram-positive and gram-negative bacteria than methylene blue. Elimination of A. actinomycetemcomitans, P. gingivalis and Fusobacterium nucleatum has been demonstrated to be more effectively achieved whilst using toluidine blue O than methylene blue.[29] It has been shown in vitro that toluidine blue O interacts with lipopolysaccharide more effectively than does methylene blue.[42] Thus a greater photobactericidal effect of toluidine blue O against gram-negative bacteria can be expected than for methylene blue.[42]

Tetracyclines used as antibiotics in periodontal diseases are also effective photosensitizers producing singlet oxygen.[43] The various photosensitizers and their clinically used treatment kits have been elaborated in Table 2.[44]

Photosensitizer	**Commercially available treatment kit**
Methylene blue	Periowave
Phenothiazine chloride	Helbo, photodynamic system GmbH and Co. KG, Grieskirchen, Austria.
Toluidine blue O	Denfotex Ltd, Dexcel pharma technologies Ltd.

Table 2: The Various Photosensitizer In Clinical Use Along With their Treatment Kit.

(b) LIGHTSOURCES:

PDT requires a source of light that activates the photosensitizer by exposure to low-power visible light at a specific wavelength.[31]Most of the photosensitizers used in aPDT are resonant with a red light source, corresponding to a light penetration depth from 0.5 cm (at 630 nm) to 1.5 cm (at ~ 700 nm).[45,46] as shown in table 3.

This limits the depth of necrosis and/or apoptosis and defines the therapeutic effect. The total light dose, dose rates, and the depth of destruction vary with each tissue treated and photosensitizer used.[46]

Table 3. photosensitizer and their respective maximum absorption wavelength

Photosensitizer	**λmax**
Methylene Blue	656 nm
Dimetil Methylene Blue	648 nm
Toluidine Blue O	625 nm
Malaquite Green	654 nm

Currently, the light sources of a specific wavelength mostly applied in photodynamic therapy are those of helium–neon lasers (633 nm), gallium-aluminum-arsenide diode lasers (630–690, 830 or 906 nm) and argon lasers (488–514 nm), the wavelengths of which range from visible light to the blue of argon lasers, or from the red of helium–neon and gallium–aluminum–arsenide lasers to the infrared area of some diode lasers.[47] Several types of laser devices have been applied during in vitro research studies. However, in the case of in vivo and clinical investigations, the diode lasers are the light source predominantly applied. More recently, non-laser light sources are used, such as light-emitting diodes (LED) that are less expensive, small, lightweight and highly flexible.[48] The use of a visible light source is beneficial in visualizing the target area, localization of the photo inactivation

International Journal Dental and Medical Sciences Research
Volume 4, Issue 3, May-June 2022 pp 291-303 www.ijdmsrjournal.com ISSN: 2582-6018

without damaging host tissue and presenting little damage to the operator.[29]

Sources of light delivery vary depending on the location and morphology of the lesion. The light should be uniform and should deliver precise calculation of the delivered dose. Fibre-optic catheters with terminal cylindrical diffusers or lenses are often used. The tip of the fibre can be formed into various shapes allowing for diffusion in all directions or for focus. Currently, the use of fibre optics is very expensive and not FDA approved. Only diffusing fibres (1–5 cm) are commercially available.[5]

(c) OXYGEN:

Photodynamic reactions, as described above, require a photosensitizer, light and oxygen at the same localization to induce a response. The extent of this response is modulated by both the concentration of photosensitizer, as well as the number of captured photons (fluence). Several studies have shown that PDT efficacy is oxygen dependent.[49] This oxygen dependence is generally believed to be mediated by singlet oxygen, the reactive oxygen species responsible for most photodynamic processes in biological systems.[27] Other reactive oxygen species such as hydroxyl radicals and superoxide anions may well be equally important players.

The bactericidal effect of singlet oxygen and other reactive oxygen radicals can be explained by two potential, but different, mechanisms. One is DNA damage[34] and the other is the damage caused to the cytoplasmic membrane of the bacteria,[35] leading to events such as inactivation of the membrane transport system, inhibition of plasma membrane enzyme activities, lipid peroxidation and others.[36,37] It seems that bacterial killing is mainly caused by damage to the bacterial cytoplasmic membrane.[22,35] It also produces cytotoxic effects on subcellular organelles and molecular level. Its effects are targeted on mitochondria, lysosomes, cell membranes and nuclei of tumor cells.

- PHYSICAL AND CHEMICAL PARAMETERS:

Photosensitization Efficacy

The capacity to eradicate bacterial cells depends on the ability to generate cytotoxic effects. The quantum liberation is the parameter that measures this ability. This characteristic can be modified and optimized by a change on the molecule structure. An example is the methylation of the molecule.

Photobleaching

Photo bleaching, also called photo degradation, is the degradation process of the chromosphere by the light. The exposure of MB and TBO to light can cause photo degradation and, as consequence, the formation of leuco molecules (reduced dye molecules), that are not resonant to the light source, reducing the photodynamic efficacy.

Hydrophilic / Lypophilic Balance

The hydrophilic character is determined by a logarithmic mathematical formula (Fig 4). Compounds like MB and TBO have LogP< 0, characterizing a hydrophilic compound. Species with LogP> 1.5 are considered lipophilic and compounds with LogP between 0 and 1.5 are considered amphiphilic.

$$\text{Log}\,P = \text{Log}\left\{\frac{(A - A^{1})}{A^{1}} \times \frac{V_{w}}{V_{o}}\right\}$$

Fig 2. LogP. A and A1 are intensity of absorption before and after of the partition; Vw and Vo are the volume of the respectives on water and 1-octanol. LogP measure the hydrophilic/lipophilic balance of a compound.

Planarity

Planarity is affected by the special distribution of the atom on the molecule, affecting its three dimensional aspect. The addition or exclusion of a radical can change the molecule specially, changing its binding site and cellular entrance.

- MICROBIOLOGICAL PARAMETERS:

Bacteria are grouped in two mean groups in accordance to response to Gram staining process, being gram positive (G+) or gram negative (G-). These bacterial groups show structural differences between them. The effectiveness of antimicrobial Photo-Dynamic Therapy (aPDT) is dependent of the bacterial group. Gram positive bacteria are more susceptible to photodynamic inactivation than Gram negative.[16] The outer membrane seems to have great importance in this resistance difference. It has high permeability to

International Journal Dental and Medical Sciences Research
Volume 4, Issue 3, May-June 2022 pp 291-303 www.ijdmsrjournal.com ISSN: 2582-6018

hydrophilic molecules. Lipopolysaccharides and porin channels seem to work as a selectivity barrier (Fig. 5).

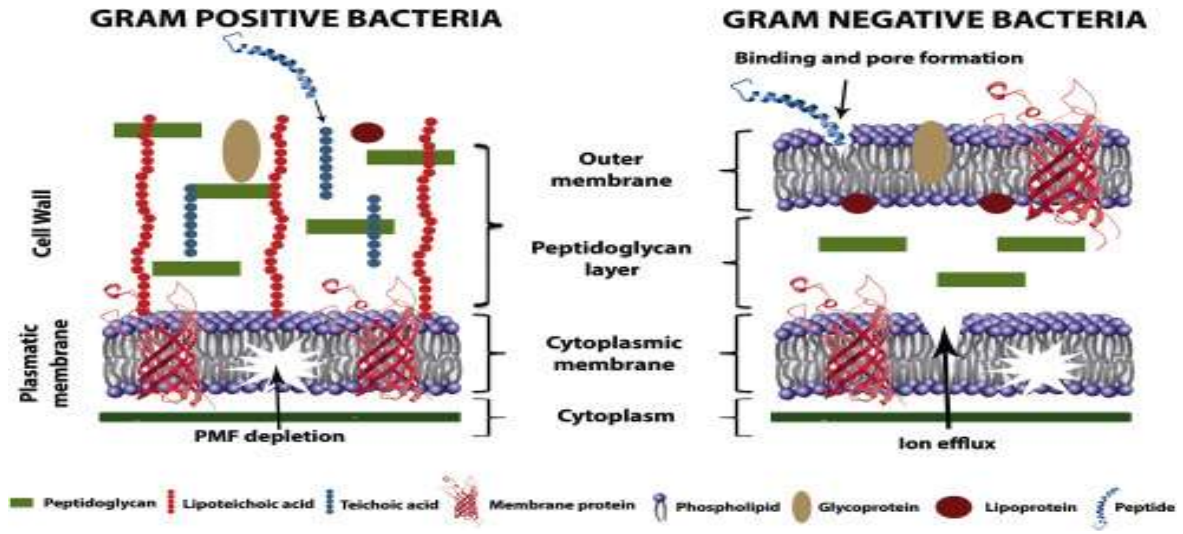


Fig 3. Structural difference between gram +ve and gram –ve bacterial cell membrane.

aPDT is equally effective against antibiotic-resistant and antibiotic-susceptible bacteria, and repeated photosensitization has not induced the selection of resistant strains.[50] Antioxidant enzymes, such as superoxide dismutase and catalase, protect against some oxygen radicals, but not against singlet oxygen. The photosensitizer can be delivered to infected areas by topical application, instillation, interstitial injection, or aerosol delivery. Several publications have summarized the photobiology of aPDT, and its potential for the treatment of localized infections.[15,22,50]

Although the differences between bacterial groups, we need to highlight that, when dealing with Periodontal Disease, we are confronting a polymicrobial infection with no planktonic bacteria, but a well formed dental biofilm.

- STRATEGIES OF OPTIMIZATION:

An attempt to improve photodynamic damage was made adding a photomechanical wave while irradiating. The result showed a 2 fold increased penetrance on oral biofilm in vitro, after 10 photomechanical pulses and a 99% of bacterial death.[52] The explanation to this phenomenon could be an deformation on biofilm micro colonies and alteration of the micro channels, improving dye penetration and photodynamic action on target sites.

Another strategy proposed is the conjugation of long chain molecule to the dye structure.[52]

The use of EDTA as a pretreatment has potential to improve photodynamic action. Adoption of EDTA can improve dye penetration on bacterial cell.[52]

Linkage of dye-target was improve by conjugation of monoclonal antibodies for P. gingivalisand TBO. The test was performed in vitro on presence of fibroblasts and S. sanguis, achieving substantial and preferential killing of periodontopathogens.[51]

- PHOTODYNAMIC THERAPY IN THE TREATMENT OF ORAL DISEASES:

Application of photodynamic therapy has led to significant advances in dentistry because the delivery of light is more accessible and topical application of the photosensitizer is more feasible in the oral cavity. Photodynamic therapy is used in the treatment of different types of oral solid tumors, and investigations into the application of photodynamic therapy to treat superficial precancerous oral lesions, such as oral leukoplakia, oral erythroleukoplakia and oral verrucous hyperplasia, have been widely performed, with some success.[53] In addition, photodynamic therapy has been effectively applied in the treatment of lichen planus.[54]

Furthermore, the antimicrobial properties of photodynamic therapy make it a

International Journal Dental and Medical Sciences Research
Volume 4, Issue 3, May-June 2022 pp 291-303 www.ijdmsrjournal.com ISSN: 2582-6018

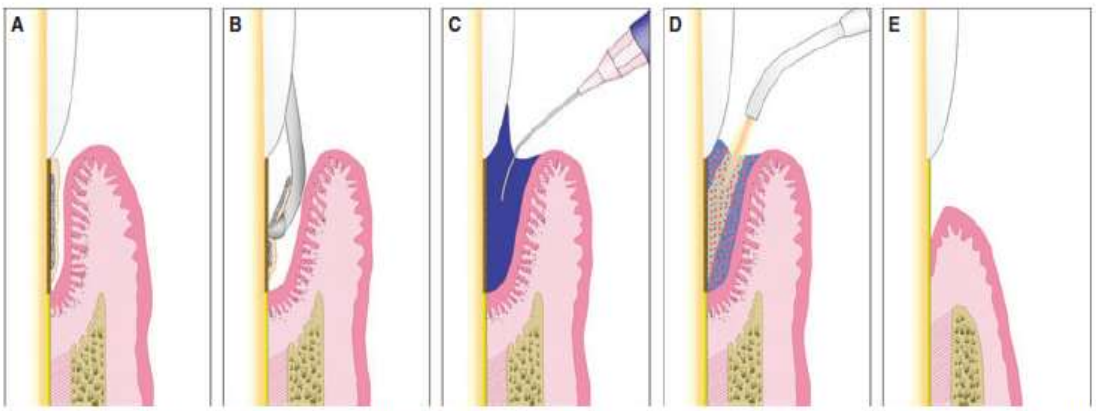
potential candidate for the treatment of bacterial, fungal and viral infections of the oral cavity. In operative dentistry, it has been well proven that the antimicrobial photodynamic therapy technique is effective for the treatment and prevention of dental caries. Several in vitro studies have demonstrated a strong bactericidal action of antimicrobial photodynamic therapy against gram-positive bacteria such as Streptococcus sorbinus, Streptococcus mutans and Streptococcus sanguinis, which play an important role in the etiology of dental caries.[55] Clinical trials of antimicrobial photodynamic therapy have been performed to eliminate the bacteria in softened carious dentine, thus intervening in the step-wise excavation techniques that may reduce the risk of pulpal exposure and necrosis, as well as the need for pulp capping.[56]

In endodontics, antimicrobial photodynamic therapy has been reported to be effective as an adjunct to conventional endodontic disinfection treatment to destroy the bacteria that remain even after irrigation with sodium hypochlorite.[56]

- ANTIMICROBIAL PDT IN THE TREATMENT OF PERIODONTAL AND PERI-IMPLANT DISEASES:

Based on the advantages and characteristics of antimicrobial photodynamic therapy, it has been proposed that periodontal and peri-implant diseases are potential targets of this novel antimicrobial photochemotherapy. Antimicrobial photodynamic therapy is expected to resolve the difficulties and problems of conventional antimicrobial therapy and can work as an adjunct to conventional mechanical treatments.

The photosensitizer is placed directly in the periodontal and peri-implant pocket and the liquid agent can easily access the whole root or implant surface before activation by the laser light through placement of the optical fiber directly in the pocket (Fig. 6). As a result of the technical simplicity of the method and the high effectiveness of bacterial killing, the application of antimicrobial photodynamic therapy in the treatment of periodontal and peri-implant diseases has recently been studied extensively.



4 g. 2. Diagram showing the steps of application of antimicrobial photodynamic therapy in the treatment of periodontitis. (A) Periodontally diseased site before treatment. (B) Mechanical debridement using hand curettes. (C) Application of the photosensitizer via syringe at the diseased site that contains residual bacteria. Occasionally, excess dye solution is removed using water spray. (D) Photosensitization is performed using an intensive light by a special tip applied in the pocket. Singlet oxygen and other very reactive agents that are toxic to bacteria are produced, resulting in photochemical disinfection of the periodontal pocket. (E) Improved wound healing in the treated site.

- PRECLINICAL STUDIES:

In this section the results of preclinical studies will be presented. Most of them are the basis for the rationale use of Antimicrobial Photodynamic Therapy, thus an important step to understanding the science behind this novel treatment.

In vitro studies

The bactericidal effect of antimicrobial photodynamic therapy on periodontal pathogens has been demonstrated in several basic studies. In the early 1990s, Dobson & Wilson[29] showed that low-level helium–neon laser irradiation

was effective for killing P. gingivalis, F. nucleatum, A. actinomycetemcomitans and S. sanguinis. Bhatti et al.[51]demonstrated that the bactericidal effect of light-activated toluidine blue O against P. gingivalis was caused by disruption of the outer membrane proteins of those bacteria.

Moreover, the bactericidal effect of antimicrobial photodynamic therapy was demonstrated not only on pure cultures of bacteria but also on the plaque biofilm. Sarkar & Wilson[57] reported that helium– neon laser irradiation combined with toluidine blue O killed oral bacteria within samples of subgingival plaque obtained from patients with chronic periodontitis. O_Neil et al.[58] also demonstrated the same.

Recently, Qin et al.[59] investigated the optimal parameters required for effective antimicrobial photodynamic therapy-induced killing of supragingival periodontal pathogens and reported that diode laser and toluidine blue O was the most effective option.

In black-pigmented bacteria such as P. gingivalis and Prevotella spp., the endogenous porphyrins present on the bacteria may also act as a photosensitizer.[60,61]

In vivo studies

Some animal studies have reported a reduction in the microbial load in ligature-induced periodontitis following the application of photodynamic therapy.[18,41,62]
Qin et al.[59] reported a significant reduction in the total bacterial flora and, histologically, a large reduction in inflammatory cell infiltration after application of antimicrobial photodynamic therapy (toluidine blue O + diode laser) in the treatment of experimentally induced periodontitis in rats.

- CLINICAL STUDIES:

There is number of clinical publication regarding the use of aPDT in periodontics. The first clinical publication was a split mouth design study comparing SRP, aPDT, SRP+aPDT and Oral Hygiene Instructions. Ten patients with one tooth with 4mm pocket depth per quadrant were recruited. The results showed significant reduction of F. nucleatumand E. nodatumat three month analysis and t. denticolaat six month analysis. There were no relevant differences between changes in pocket depth and clinical attachment levels. Despite, bleeding on probing showed greater reductions on aPDT group.[64]Similar results were also seen in other split mouth studies.[65,66]

The short-term effect of aPDT on diabetic uncontrolled patient was compared with two different therapies, with aPDT giving superioro results.[67]

Antimicrobial photodynamic therapy was firstly propose as a novel therapeutic strategy to treat aggressive periodontitis in a pilot split mouth study design as a single therapy, being compared to SRP. The clinical parameters were measured at baseline and 3 months after treatment and inter and intragroup results were compared.[68] Both therapies resulted in improvement of clinical parameters at 3 month evaluation.While another similar study proved the superiority of aPDT asan adjunct.[69]

- APPLICATION OF aPDT IN THE TREATMENT OF PERI-IMPLANT DISEASE:

Treatment of peri-implantitis has become an interesting topic among clinicians and researchers. With the extensive increase in placement of dental implants, the number of implants affected by peri-implantitis has also been increasing in clinical practice. Recently, several studies have demonstrated bactericidal and detoxification effects of high-level lasers on contaminated dental implant surfaces.[48,70,71] High-level lasers have been used successfully in the surgical management of peri-implantitis.[48] However, in nonsurgical therapy, high-level lasers have shown limited clinical efficacy.[72] Moreover, following the application of some lasers, surface alterations (such as melting and carbonization) have been observed on the treated titanium surface.[73] Antimicrobial photodynamic therapy was recently proposed as an adjunctive for bacterial elimination in the treatment of periimplantitis, based on its successful application in the treatment of periodontitis. Currently, one in vitro[74], few animal and clinical[17,75,76,74] studies are available reporting the various effects of application of antimicrobial photodynamic therapy as an adjunctive to the treatment of peri-implantitis.

- RISKS AND SIDE EFFECTS OF aPDT THERAPY:

A critical issue when applying novel techniques relates to their clinical safety. The risks and side effects of antimicrobial photodynamic therapy are basically classified into two categories: one relates to the effect of

light energy itself; and the other is related to the photosensitizer and the photochemical reaction (lethal photosensitization).

Regarding the light source itself, potential inadvertent irradiation of the patient's eyes must be strictly avoided during treatment, even though the laser power employed is very low.[77]Second, thermogenesis occurring as a result of the interaction of the laser with the tissues must be addressed and well controlled.

With respect to the photosensitizers and photochemical reactions, the safety of antimicrobial photodynamic therapy in the host periodontal tissues has been demonstrated by several animal and clinical studies,[19,65]

Nevertheless, it should be pointed out that the photosensitizer may be toxic to some extent and the effect on the periodontal tissues and cells should be precisely clarified. Also, most of the dyes adhere strongly to the soft tissue surface of the pocket, and retention of the dyes in the pocket, even for a short period of time, may affect periodontal tissue attachment during wound healing. It seems that removal of the dye solution has not been routinely performed clinically after photosensitization procedures. Further studies should be performed to investigate the longevity and the effects of remaining dyes. In addition, the use of photosensitizers can compromise the patients' esthetics by producing temporary pigmentation of the periodontal tissues. Thus, the use of photosensitizers with a paste base instead of liquids has been suggested, because pastes can be easily removed following treatment.[17]

In addition, it still remains to be clarified whether selective killing of periodontal pathogens by antimicrobial photodynamic therapy really occurs without affecting the normal oral microflora. A recent study has shown that, in the treatment of infections, a specific bacterium can be targeted and killed using photosensitizers conjugated to specific antibodies,[51] thus without affecting the hosts normal microbial flora. Further studies are necessary to develop and improve the current photosensitizers in order to assure safety and to optimize efficiency.

- NEW FRONTIERS IN ORAL ANTIMICROBIAL PHOTODYNAMIC THERAPY -

Since complex oral biofilms have limited susceptibility to antimicrobial photodynamic therapy the development of novel delivery and targeting approaches is essential. Recent innovations in the field of antimicrobial photodynamic therapy have been discussed below.

1. Phototherapy

In the oral black–pigmented species, the application of photosensitizer may not be required because photosensitizer occurs naturally in this species. Studies have shown that visible light ranging from 380 to 520 nm was able to achieve a threefold reduction in the growth of P. gingivalis, P. intermedia, P. nigrescens and P. melangencia in dental plaque samples obtained from human subjects diagnosed with chronic periodontitis.[44] Inactivation of black-pigmented bacteria by visible light has also been reported by other investigators.[78]

2. Antibody-targeted antibacterial approaches using photodynamic therapy

Antibodies conjugated with photosensitizer have been used to target staphylococcus aureus.[125] Recently gold nanoparticles were used as photo-thermal sensitizer which were conjugated to antibodies.[63]Selective killing of Red complex periodontopathogens can be achieved by this method.

3. Nanoparticle –based antimicrobial photodynamic therapy

To overcome the incomplete penetration of methylene blue in oral biofilms has led to the development of new delivery systems that significantly improve the pharmacological characteristics of methylene blue.

Researchers recently proposed the encapsulation of methylene blue within poly D,L-lactide-co-glycolide [PLGA] nanoparticle [150-200 nm in diameter] that may offer a novel design of nano-platform for enhanced drug delivery and photodestruction of oral biofilm.[44]

II. CONCLUSION:

Antimicrobial photodynamic therapy seems to be a promising tool in the treatment of periodontal disease. The results of a number of in-vitro studies clearly demonstrate the significant bactericidal effect of antimicrobial photodynamic therapy. However, sufficient clinical and microbiological data that support the superior effects of the adjunctive use of photodynamic therapy have not been demonstrated clinically in either periodontal or peri-implant therapies. The discrepancies in the results obtained from previous clinical studies are being speculated to be due to a number of reasons. However recent innovations in photodynamic therapy seem to be promising. Further, randomized long-term clinical trials and meta-analyses are necessary to demonstrate the role of photodynamic therapy in the management of chronic periodontitis.

BIBLIOGRAPHY

[1]. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS (1997) Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. Periodontol 2000 14:216–248

[2]. Westfelt, E. (1996) Rationale of mechanical plaque control. Journal of Clinical Periodontology 23, 263–267.

[3]. Bernimoulin, J. P. (2003) Recent concepts in plaque formation. Journal of Clinical Periodontology 30 (Suppl. 5), 7–9.

[4]. Cobb CM (1996) Non-surgical pocket therapy: mechanical. Ann Periodontol 1:443–490

[5]. Rabbani, G. M., Ash, M. M. Jr. &Caffesse, R.G. (1981) The effectiveness of subgingival scaling and root planing in calculus removal. Journal of Periodontology 52, 119–123.

[6]. Brayer, W. K., Mellonig, J. T., Dunlap, R. M., Marinak, K. W. & Carson, R. E. (1989) Scaling and root planing effectiveness: the effect of root surface access and operator experience. Journal of Periodontology 60, 67–72.

[7]. Adriaens PA, Adriaens LM. Effects of nonsurgical periodontal therapy on hard and soft tissues. Periodontol 2000. 2004;36:121–145.

[8]. Aoki A, Sasaki KM, Watanabe H, Ishikawa I. Lasers in nonsurgical periodontal therapy. Periodontol 2000 2004: 36: 59–97.

[9]. Ishikawa I, Aoki A, Takasaki AA, Mizutani K, Sasaki KM, Izumi Y. Application of lasers in periodontics – True Innovation or Myth? Periodontol 2000 2009: 50: 90–126.

[10]. Cobb CM, McCawley TK, Killoy WJ. A preliminary study on the effects of the Nd:YAG laser on root surfaces and subgingival microflora in vivo. J Periodontol 1992: 63: 701–707.

[11]. Ando Y, Aoki A, Watanabe H, Ishikawa I. Bactericidal effect of erbium YAG laser on periodontopathic bacteria. Lasers Surg Med 1996: 19: 190–200.

[12]. Moritz A, Gutknecht N, Doertbudak O, Goharkhay K, Schoop U, Schauer P, Sperr W. Bacterial reduction in periodontal pockets through irradiation with a diode laser: a pilot study. J Clin Laser Med Surg 1997: 15: 33–37.

[13]. Aoki A, Mizutani K, Takasaki AA, Sasaki KM, Nagai S, Schwarz F, Yoshida I, Eguro T, Zeredo JL, Izumi Y. Current status of clinical laser applications in periodontal therapy. Gen Dent 2008: 56: 674–687.

[14]. Wigdor H, Abt E, Ashrafi S, Walsh JT Jr. The effect of lasers on dental hard tissues. J Am Dent Assoc 1993: 124: 65–70.

[15]. Wainwright M. Photodynamic antimicrobial chemotherapy (PACT). J AntimicrobChemother 1998: 42: 13–28.

[16]. Meisel P, Kocher T. Photodynamic therapy for periodontal diseases: state of the art. J PhotochemPhotobiol B 2005: 79: 159–170.

[17]. Hayek RR, Araujo NS, Gioso MA, Ferreira J, Baptista-Sobrinho CA, Yamada AM, Ribeiro MS. Comparative study between the effects of photodynamic therapy and conventional therapy on microbial reduction in ligature induced peri-implantitis in dogs. J Periodontol 2005: 76: 1275–1281.

[18]. Sigusch BW, Pfitzner A, Albrecht V, Glockmann E. Efficacy of photodynamic therapy on inflammatory signs and two selected periodontopathogenic species in a beagle dog model. J Periodontol 2005: 76: 1100–1105.

[19]. Luan XL, Qin YL, Bi LJ, Hu CY, Zhang ZG, Lin J, Zhou CN. Histological evaluation of the safety of toluidine blue mediated photosensitization to periodontal tissues in mice. Lasers Med Sci 2009: 24: 162–166.
[20]. Raab O. The effect of fluorescent agents on infusoria. Z Biol 1900;39:524–526.
[21]. Ochsner M. Photophysical and Photobiological processes in the photodynamic therapy of tumors J PhotochemPhotobiol B 1997;39:1‐18.
[22]. Hamblin MR, Hasan T. Photodynamic therapy: A new antimicrobial approach to infectious diseases? PhotochemPhotobiol Sci 2004;3:436‐50.
[23]. Allison RR, Baganto VS, Cuenca R, Downie GH, Sibata CH. The future of photodynamic therapy in oncology. Future Oncol 2006;2:53–71.
[24]. M Raghavendra, A Koregol, S Bhola (2009) Photodynamic therapy: a targeted therapy in periodontics. Australian Dental Journal 2009; 54:(1 Suppl): S102–S109
[25]. Deniell MD, Hill JS. A history of Photodynamic therapy. Aust N Z J Surg 1991;61:34‐8.
[26]. Jodlbauer A, von Tappeiner H. U¨ ber die wirkungphotodynamischer (fluoreszierender) stoffe auf Bakterien. Munch Med Wochenschr1904;51:1096–1097.
[27]. Dougherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittleman A. Photoradiation therapy for the treatment of malignant tumors. Cancer Res 1978;38:2628–2635.
[28]. Dougherlg TJ, Marcus SL. Photodynamic therapy. Eur J Cancer 1992;28:1734‐42.
[29]. Wilson M, Dobson J, Sarker S. Sensitization of periodontopathogenic bacteria to killing by light from a low-power laser. Oral Microbiol Immunol 1993;8:182–187.
[30]. Lui H, Anderson RR. Photodynamic therapy in dermatology: Shedding a different light on Skin disease. Arch Dermatol 1992;128:1631‐6.
[31]. Konopka K, Goslinski T. Photodynamic therapy in dentistry. J Dent Res 2007;86:694‐707
[32]. Foote CS. Definition of type I and type II photosensitized oxidation. PhotochemPhotobiol 1991: 54: 659.
[33]. Sharman WM, Allen CM, van Lier JE. Photodynamic therapeutics: basic principles and clinical applications. Drug Discov Today 1999: 4: 507–517.
[34]. Fiel RJ, Datta-Gupta N, Mark EH, Howard JC. Induction of DNA damage by porphyrin photosensitizers. Cancer Res 1981: 41: 3543–3545.
[35]. Bertoloni G, Lauro FM, Cortella G, Merchat M. Photosensitizing activity of hematoporphyrin on Staphylococcus aureus cells. BiochimBiophys Acta 2000: 1475: 169–174.
[36]. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J PhotochemPhotobiol B 1990: 6: 143–148.
[37]. Mohr H, Lambrecht B, Schmitt H. Photo-inactivation of viruses in therapeutical plasma. Dev Biol Stand 1993: 81: 177–183
[38]. Triesscheijn M, Baas P, Schellens JH, Stewart FA. Photodynamic therapy in oncology. Oncologist. 2006;11: 1034–1044.
[39]. Lambrecht B, Mohr H, Knuver‐.Hopf J, Schmitt H. Photoinactivation of viruses in human fresh plasma by phenothiazine dyes in Combination with visible light. Vox Sang 1991;60:207‐13.
[40]. Millson CE, Wilson M, Macrobert AJ, Bedwell J, Brown SG. The killing of helicobacter pylori by low‐power laser light in the presence of a photosensitizer. J Med Microbiol1996;44:245‐52.
[41]. Komerik N, Nakanishi H, MacRobert AJ, Henderson B, Speight P, Wilson M. In vivo killing of Porphyromonas gingivalis by toluidine blue-mediated photosensitization in an animal model. Antimicrob Agents Chemother 2003: 47: 932–940.
[42]. Usacheva MN, Teichert MC, Biel MA. Comparison of the methylene blue and toluidine blue photobactericidal efficacy against gram-positive and gram-negative microorganisms. Lasers Surg Med 2001: 29: 165–173.
[43]. Miskoski S, Sanchez E, Garavano M, Lopez M, Soltermann AT, Garcia NA. Singlet Molecular oxygen ‐.mediated photo ‐oxidation of tetracyclines

kinetics, mechanism and microbiological implications. J PhotochemPhtobiol B – Biol 1998;43:164‑71.

[44]. Nikolaos S. Soukos and J. Max Goodson et al. Photodynamic therapy in the control of oral biofilms. Periodontal 2000. 2011;55:143-166.

[45]. Salva KA. Photodynamic therapy: Unapproved uses, dosages or indications. Clin Dermatol 2002;20:571‑81.

[46]. Grant WE, Hopper C, Speight PM, Bown SG. Photodynamic therapy, an effective, but non‑selective treatment for superficial cancers of the oral cavity. Int J Cancer 1997;71:937‑42.

[47]. Juzeniene A, Juzenas P, Ma LW, Iani V, Moan J. Effectiveness of different light Sources for 5 ‑.aminolevulinic acid photodynamic therapy. Lasers Med Sci 2004;19:139‑49.

[48]. Takasaki AA, Aoki A, Mizutani K, Schwarz F, Sculean A, Wang CY, et al. Application of antimicrobial photodynamic therapy in periodontal and peri‑implant diseases Periodontol 2000 2009;51:109‑40.

[49]. T.M. Sitnik, B.W. Henderson (1998). The effect of fluence rate on tumor and normal tissue responses to photodynamic therapy. Photochem. Photobiol. , 67, 462-466.

[50]. Wainwright M, Crossley KB (2004). Photosensitizing agents—circumventing resistance and breaking down biofilms: a review. Int BiodeteriorBiodegrad53:119-126.

[51]. Bhatti M, MacRobert A, Meghji S, Henderson B, Wilson M. Effect of Dosimetric and Physiological Factors on the Lethal Photosensitization of Porphyromonas gingivalis in vitro. Phochem. Photobiol. 1997; 65: 1026-1031.

[52]. Soukos NS, Mulholland SE, Socransky SS, Doukas AG. Photodestruction of Human Dental Plaque Bacteria: Enhancement of The Photodynamic Effect by Photomechanical Waves on an Oral Biofilm Model. Lasers Surg. Me. 2003; 33: 161-168.

[53]. Yu CH, Chen HM, Hung HY, Cheng SJ, Tsai T, Chiang CP. Photodynamic therapy outcome for oral verrucous hyperplasia depends on the clinical appearance, size, color, epithelial dysplasia, and surface keratin thickness of the lesion. Oral Oncol 2008: 44: 595–600.

[54]. van der Meij EH, Schepman KP, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective study. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2003: 96: 164–171.

[55]. Williams J, Pearson G, Colles M, Wilson M. The photoactivated antibacterial action of toluidine blue O in a collagen matrix and in carious dentine. Caries Res 2004: 38: 530–536.

[56]. Bonsor S, Pearson G. Current clinical applications of photo-activated disinfection in restorative dentistry. Dent Update 2006: 150: 153.

[57]. Sarkar S, Wilson M. Lethal photosensitization of bacteria in subgingival plaque from patients with chronic periodontitis. J Periodontal Res 1993: 28: 204–210.

[58]. O_Neill JF, Hope CK, Wilson M. Oral bacteria in multispecies biofilms can be killed by red light in the presence of toluidine blue. Lasers Surg Med 2002: 31: 86–90.

[59]. Qin Y, Luan X, Bi L, He G, Bai X, Zhou C, Zhang Z. Toluidine blue-mediated photoinactivation of periodontal pathogens from supragingival plaques. Lasers Med Sci 2008: 23: 49–54.

[60]. Henry CA, Judy M, Dyer B, Wagner M, Matthews JL. Sensitivity of Porphyromonas and Prevotella species in liquid media to argon laser. PhotochemPhotobiol 1995: 61: 410–413.

[61]. Soukos NS, Som S, Abernethy AD, Ruggiero K, Dunham J, Lee C, Doukas AG, Goodson JM. Phototargeting oral black pigmented bacteria. Antimicrob Agents Chemother 2005: 49: 1391–1396.

[62]. de Almeida JM, Theodoro LH, Bosco AF, Nagata MJ, Oshiiwa M, Garcia VG. In vivo effect of photodynamic therapy on periodontal bone loss in dental furcations. J Periodontol 2008: 79: 1081–1088.

[63]. Yilmaz A, Kuru B, Kuru L, Noyan Ü, Argun D, Kadir T. Effect of Galium Arsenide Diode Laser on Human Periodontal Disease: A Microbiological and Clinical Study. Lasers Sug. Med. 2002; 30:60-66.

[64]. Chondros P, Nikolidakis D, Christoulides N, Rössler R, Gutknecht N, Sculean A.

Photodynamic therapy as an adjunct to non-surgical periodontal treatment in patients on periodontal maintenance: a randomized controlled clinical trial. Lasers Med. Sci. 2008

[65]. Christodoulides N, Nikolidakis D, Chondros P, Becker J, Scharwz F, Rössler E, et al. Photodynamic Therapy as Adjunct to Nonsurgical Periodontal Treatment. A Randomized Controlled Clinical Trial. J. Periodontol. 2008; 79: 1638-1644.

[66]. Braun A, Dehn C, Krause F, Jepsen S. Short-term clinical effects of adjunctive antimicrobial photodynamic therapy in periodontal treatment: a randomized clinical trial. J. Clin. Periodontol. 2008; 35: 877–884.

[67]. Al-Zahrani MS, Bamshmous SO, Alhassani AA, Al-Sherbini MM. Short-term Effects of Photodynamic Therapy on Periodontal Status and Glycemic Control of Patients With Diabetes. J. Periodontol. 2009; 80; 1568-1573.

[68]. Oliveira RA, Novaes Jr. AB, Garlet GP, Souza RF, Taba Jr. MT, Sato S, Souza SLS, et al. The effect of a single episode of antimicrobial photodynamic therapy in the treatment of experimental periodontitis. Microbiological profile and cytokine pattern in dogs mandible. Lasers Med. Sci. 2011; 26: 359-367.

[69]. Novaes Jr., AB, Schwartz-Filho HO, Oliveira RR, Feres M, Sato S, Figueiredo LC. Antimicrobial photodynamic therapy in the non-surgical treatment of aggressive periodontitis: microbiological profile. Lasers Med. Sci. 2011 DOI 10.1007/s10103-011- 0901-6.

[70]. Schwarz F, Sculean A, Romanos G, Herten M, Horn N, Scherbaum W, Becker J. Influence of different treatment approaches on the removal of early plaque biofilms and the viability of SAOS2 osteoblasts grown on titanium implants. Clin Oral Investig 2005: 9: 111–117.

[71]. Kreisler M, Kohnen W, Marinello C, Gotz H, Duschner H, Jansen B, d_Hoedt B. Bactericidal effect of the Er:YAG laser on dental implant surfaces: an in vitro study. J Periodontol 2002: 73: 1292–1298.

[72]. Schwarz F, Bieling K, Nuesry E, Sculean A, Becker J. Clinical and histological healing pattern of peri-implantitis lesions following non-surgical treatment with an Er:YAG laser. Lasers Surg Med 2006: 38: 663–671.

[73]. Romanos GE, Everts H, Nentwig GH. Effects of diode and Nd:YAG laser irradiation on titanium discs: a scanning electron microscope examination. J Periodontol 2000: 71: 810–815.

[74]. Haas R, Dortbudak O, Mensdorff-Pouilly N, Mailath G. Elimination of bacteria on different implant surfaces through photosensitization and soft laser. An in vitro study. Clin Oral Implants Res 1997: 8: 249–254.

[75]. Shibli JA, Martins MC, Theodoro LH, Lotufo RF, Garcia VG, Marcantonio EJ. Lethal photosensitization in microbiological treatment of ligature-induced periimplantitis: a preliminary study in dogs. J Oral Sci 2003: 45: 17–23.

[76]. Shibli JA, Martins MC, Ribeiro FS, Garcia VG, Nociti FH Jr, Marcantonio E Jr. Lethal photosensitization and guided bone regeneration in treatment of peri-implantitis: an experimental study in dogs. Clin Oral Implants Res 2006: 17: 273–281.

[77]. AAP. The Research, Science and Therapy Committee of the American Academy of Periodontology. Lasers in periodontics (Academy report), authored by Cohen RE and Ammons WF, revised by Rossman JA. J Periodontol 2002: 73: 1231–1239.

[78]. Redmond RW, Gamlin JN. A compilation of singlet oxygen yields from biologically relevant molecules. PhotochemPhotobiol. 1999;70:391–475.