

# Photodynamic Therapy: A View through Light

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## ABSTRACT

The removal of biofilm and mineralized deposits from the tooth surface are the fundamental aspects of periodontal therapy. Using antimicrobial agents to treat periodontitis without disruption of the biofilm ultimately results in treatment failures. It is difficult to maintain therapeutic concentrations at the target sites and target organisms may develop resistance to drugs. Photodynamic therapy (PDT) is a mechanism which destroys target cells by reactive oxygen species produced by photosensitizing compounds and light of an appropriate wavelength. 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, Photosensitizer, Biofilms, Periimplantitis, Periodontitis.

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## INTRODUCTION

Following history, therapeutic use of ultraviolet light begins in 1900 when Raab<sup>1</sup> reported that combination of archidine orange and ultraviolet light could destroy living organisms (paramecium). In 1920s Policard<sup>2</sup> noted that tumor tissue was inherently more fluorescent than healthy tissue. In 1950s Ronchese<sup>3</sup> attempted to activate endogenous fluorescent molecules in tumor tissue to delineate its boundaries more accurately. In the 1960s Winkelman<sup>4</sup> used synthetic porphyrins (tetraphenylporphines) to detect tumor tissue. Throughout 20th century few attempts were made to treat tumor tissues mainly with nonporphyrin photosensitizers. In the 1970s Dougherty rediscovered that fluorescein diacetate could photodynamically destroy T A-3 cells *in vitro*.<sup>5</sup> Dougherty then began treating tumor-bearing animals with fluorescein and found that it could work as a photosensitizer.<sup>6</sup> In 1976; Weisshaupt et al<sup>7</sup> identified the cytotoxic product of photochemical reaction to be singlet oxygen. Porphyrin photosensitizers were then examined as they are efficient singlet oxygen generators and have absorption maxima in the red portion of electromagnetic spectrum. After several years spent isolating and identifying the active fractions of hematoporphyrin derivatives (HpDs), a purified version name Photofrin was produced. In following years Photofrin was approved for use in United States against early and late stage lung cancers and esophageal cancers

and dysplasia. Photodynamic therapy (PDT) has been used against bladder cancers, brain cancers, breast cancers, gynecological malignancies and colorectal cancers.<sup>8</sup>

Photodynamic therapy (PDT) is a medical treatment modality that utilizes light to activate a photosensitizing agent (photosensitizer) in the presence of oxygen. Photodynamic therapy (PDT), also known as photoradiation therapy, phototherapy, or photochemotherapy, involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen.<sup>8</sup>

## Mechanism of Action (Fig. 1)

Photodynamic therapy comprises of three components: Light, photosensitizer and oxygen. The exposure of the photo sensitizer to light results in the formation of oxygen species, such as singlet oxygen and free radicals, causing localized photo damage and cell death. Clinically, this reaction is cytotoxic and vasculotoxic.<sup>8</sup>

Depending on the type of agent, photosensitizers may be injected intravenously, ingested orally or applied topically.<sup>8</sup>

When administered to patients upon irradiation with specific wavelength photosensitizer goes to low-energy ground state to excited singlet state. Subsequently then goes to ground state with decay and there is emission of fluorescence or goes directly to high level- triplet state. The triplet state can react with endogenous oxygen to produce singlet oxygen and other radical species, causing a rapid and selective destruction of the target tissue.<sup>9</sup>

There are two mechanisms by which the triplet-state photosensitizer can react with biomolecules. First

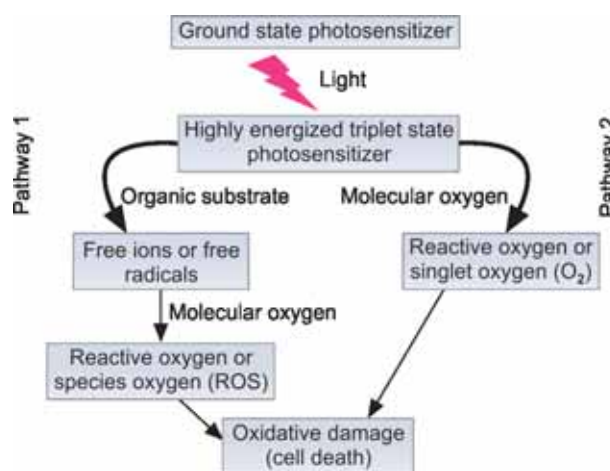


Fig. 1: Mechanism of action

mechanism involves electron/hydrogen transfer directly from the photosensitizer, producing ions or electron/hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species (superoxide, hydroxyl radicals and hydrogen peroxide). The other mechanism produces the electronically excited and highly reactive state of oxygen known as singlet oxygen. In PDT, it is difficult to distinguish between the two reactions mechanisms. A contribution from both types of processes indicates that the mechanism of damage is dependent on both oxygen tension and photosensitizer concentration.<sup>9</sup>

### Types of Photosensitizers

In antimicrobial photodynamic therapy, various types of photosensitizers are used (Table 1).

According through their evolution again they are subdivided into first, second and third generation photosensitizers (Table 2). Currently, only four photosensitizers are commercially available: Photofrin, ALA, Visudyne™ (Verteporfin) and Foscan.<sup>9,10</sup>

### Laser Sources

Human tissue transmits red light efficiently, and the longer activation wavelength of the photosensitizer results in deeper light penetration. Consequently, most photosensitizers are activated by red light between 630 and 700 nm.<sup>11</sup>

**Table 1:** Types of photosensitizers

Photosensitizers	Examples
Phenothiazine dyes	Methylene blue (MB) and toluidine Blue O (TBO; Tolonium chloride)
Phthalocyanine dyes	Aluminum disulphonated phthalocyanine, cationic Zn(II)-phthalocyanine, naphthalocyanine
Chlorophyll platform Porphyrins	Chlorins_Purpurins_Bacteriochlorins HPD (hematoporphyrin derivative), Photofrin® and ALA (5-aminolevulinic acid), texaphyrins, BPD (benzoporphyrin derivative)
Xanthenes	Erythrosin
Monoterpene	Azulene

**Table 2:** Generations of photosensitizers

Generation	Photosensitizers
First generation	Photofrin, hematoporphyrin derivatives (HPDs)
Second generation	5-aminolevulinic acid (ALA), benzoporphyrin derivative (BPD), lutetium texaphyrin, temoporfin (mTHPC), tinethyletiopurpurin (SnET2), talaporfin sodium (LS11) and Foscan® (mTHPC)
Third generation	Biologic conjugates (e.g. Antibody conjugate, liposome conjugate)

There are three light systems for the photodynamic therapy:<sup>12</sup>

1. Diode laser systems.
2. Noncoherent light sources: Preferred for treatment of larger areas and include tungsten filament, quartz halogen, xenon arc, metal halide and phosphor-coated sodium lamps.
3. Nonlaser light sources include light emitting diodes (LED).

### APPLICATION OF PHOTODYNAMIC THERAPY

Photodynamic therapy has been applied in many oral conditions like superficial precancerous oral lesions, such as oral leukoplakia, oral erythroleukoplakia, oral verrucous hyperplasia, lichen planus as well various bacterial, fungal and viral infections of the oral cavity.<sup>34</sup>

Use of photodynamic therapy in periodontitis and peri-implantitis:

#### As an Adjunct to Scaling and Root Planning

Research on plaque development has shown that oral bacteria colonize nonshedding hard surfaces and shedding soft tissue surfaces. The physical and morphologic characteristics of these surfaces create different ecosystems or niches with distinct bacterial plaque.<sup>13</sup>

Wide ranges of persistent human infections are due to microbial biofilms. Microorganisms grow in biofilms stuck to a solid surface where they multiply and form micro colonies embedded in extracellular polymeric matrix, which includes water and nutrient channels. Periodontal diseases result from accumulation of subgingival bacterial biofilms on tooth surfaces. There is reduced susceptibility of these biofilms to antimicrobial agents.<sup>15,16</sup>

Mechanical removal of the periodontal biofilms is currently the most frequently used method of periodontal disease treatment.<sup>14</sup>

Various studies have been done with combination antimicrobial therapy which has shown significant improvement in clinical as well as microbiological aspects.<sup>17-21</sup>

The combination of systematically administered amoxicillin and metronidazole for the treatment of certain periodontal infections has been quite effective.<sup>19-21</sup>

But certain biofilm species exhibit several antibiotic-resistance mechanisms, such as quorum sensing.<sup>22,23</sup>

Recently, a new type of noninvasive phototherapy for bacterial elimination, called photodynamic therapy, has been introduced, which uses low-level laser.<sup>24,25</sup> Unlike high-level lasers, photodynamic therapy can selectively target the bacteria without potentially damaging the host tissues.<sup>26,27</sup>

As depicted in Table 3. Various studies were done with different time period like 3 and 6 months and they used clinical

**Table 3:** Human studies on application of photodynamic therapy as an adjunct to scaling and root planning

Author and year (reference)	Type of study (number of subjects)	Light (wavelength)	Photosensitizer concentration, time of application	Light parameters and time of exposure method of irradiation	Purpose of application (period of observation)	Findings
Yilmaz et al 2002 <sup>29</sup>	RCT, SMD (10)	Diode laser (685 nm)	MB 0.005% (w/v), 1 min	Pulsed, 30 mW (5 Hz) 71s per each papillary region over gingiva	Initial therapy for chronic periodontitis (32 days)	Significant clinical and microbiological improvements were only observed in the SRP + PDT and SRP groups
Andersen et al 2007 <sup>30</sup>	RCT (33)	Diode laser (670 nm)	Phenazathionium chloride (MB) 0.005% (w/v)	CW, 150 mW 60s per site into periodontal pockets	Initial therapy for chronic periodontitis (3 months)	SRP + PDT resulted in significant clinical improvements over SRP
Chondros et al 2008 <sup>31</sup>	RCT (24)	Diode laser (670 nm)	Phenotiazine chloride (MB) 10 mg/ml, 3 min	CW, 75 mW 60s per tooth into periodontal pockets	Maintenance therapy for chronic periodontitis (6 months)	SRP + PDT resulted in PD reduction and CAL gain comparable to SRP, but significantly higher reduction in mean bleeding scores than SRP
Christodoulides et al 2008 <sup>32</sup>					Initial therapy for chronic periodontitis (6 months)	

**Table 4:** Animal studies on the application of photodynamic therapy in the treatment of periimplantitis

Author and year (reference)	Type of study	Light (wavelength)	Photosensitizer (concentration)	Light parameters and time of exposure	Purpose of application	Findings
Haas et al 1997	<i>In vitro</i> (titanium plates)	Diode laser (905 nm)	TBO (100 µg/ml)	CW, total power of 7.3 mW 60s each plate	Investigate the microbiological effects of PDT against A.a., P.g. and P.i. adhered to titanium plates	No bacterial growth of any of the microorganisms on the smear taken from the plates treated with PDT, in contrast to that of the nontreated plates in which all bacteria were detected
Shibli et al 2003	<i>In vivo</i> (six dogs)	Diode laser (685 nm)	TBO (100 µg/ml)	CW, 50 mW 80s per implant	Examine the microbiological effects of PDT against A.a., P.g. and P.i. on the surface of implants affected by ligature-induced peri-implantitis	PDT reduced the bacterial count of P.i., P.n., Fusobacterium spp. and beta-hemolytic <i>Streptococcus</i> on the implant surface

CAL: Clinical attachment level; OHI: Oral hygiene instruction; PPD: Probing pocket depth; RAL: Relative attachment level; RCT: Randomized clinical trial; SMD: Split mouth design; SRP: Scaling and root planning; w/v: Weight/volume

**Table 5:** Human studies on the application of photodynamic therapy in the treatment periimplantitis

Author and year (reference)	Type of study	Light (wavelength)	Photosensitizer (concentration)	Light parameters and time of exposure	Purpose of application	Findings
Haas et al 2000	Clinical study, case series (17 subjects)	Diode laser (906 nm)	TBO (100 µg/ml)	CW, NA 120s per implant	Disinfect the contaminated implant surface in the treatment of periimplantitis	Combination of PDT, autogenous bone grafts and membrane placement could reduce bone defects
Dörtbudak et al 2001	Clinical study, case series (15 subjects)	Diode laser (690 nm)	TBO (100 µg/ml)	CW, NA 60s per implant	Examine the microbiological effects of PDT against A.a., P.g. and P.i. on the surface of implants affected by peri-implantitis	PDT significantly decreased all bacterial counts, but TBO alone could also reduce the bacterial counts to some extent

CW: Continuous wave; NA: Not available; PDT: Photodynamic therapy; TBO: Toluidine blue O; w/v: weight/volume; A.a.: Aggregatibacter actinomycetemcomitans; P.g.: Porphyromonas gingivalis; P.i.: Prevotella intermedia

parameters like probing depth, clinical attachment level and bleeding on probing and showed clinically significant improvement in all parameters using photodynamic therapy as an adjunct to scaling and root planing.<sup>29-32</sup>

### As an Adjunct to Periimplantitis

Periimplantitis is described as destructive inflammatory process affecting the soft and hard tissues around osseointegrated implants, leading to the formation of a peri-implant pocket and loss of supporting bone (1st European Workshop on Periodontology, Ittingen, Switzerland, 1993).<sup>33</sup>

Conventional mechanical methods are apparently ineffective for complete debridement of the bone defect as well as of the contaminated microstructured implant surface.<sup>34</sup>

Due to unfavorable periimplant tissue morphology after therapy, implant surfaces exposed to bacterial contamination sometimes cannot be kept plaque free by the patient with conventional means of oral hygiene.<sup>34</sup>

Antimicrobial photodynamic therapy overcomes the difficulties and problems of conventional antimicrobial therapy and work as an adjunctive to conventional periodontal therapy.

However, *in vivo* and clinical studies are very limited and significant clinical effects of antimicrobial photodynamic therapy have not yet been demonstrated<sup>28</sup> (Tables 4 and 5).

From our limited clinical experience, adjunctive application of antimicrobial photodynamic therapy during nonsurgical treatment of periimplantitis did not provide significant clinical improvements. Therefore, further animal and clinical studies to establish the optimal conditions and procedures for antimicrobial photodynamic therapy in the nonsurgical or surgical treatment of periimplantitis, and to demonstrate the advantages of antimicrobial photodynamic therapy over conventional chemical methods for implant surface decontamination, should be encouraged.

### Disadvantages of Photodynamic Therapy

In photodynamic therapy, Laser power employed is very low. But during treatment procedures, irradiation of the patient's eyes must be avoided by wearing protective glasses. 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.<sup>34</sup>

### Current Status of Antimicrobial Photodynamic Therapy and What is its Future

With combination of dyes and light application regarding clinical application, whilst the manufacturer recommends that antimicrobial photodynamic therapy treatment should

be performed repeatedly during the first week of healing to enhance the antimicrobial effect. Some says single application for example; the new periowave photo-disinfection technology is a simple two-step clinical procedure, which, within 60 seconds, destroys the cells of specifically targeted Gram-negative anaerobic microorganisms in a selected periodontal defect.<sup>35,36</sup>

While others says multiple application which, within 60 seconds gives better results, however, it has not been established how often photodynamic therapy should be applied for the effective elimination of bacteria, as well as prevention of recolonization by the bacteria of sites previously treated by nonsurgical periodontal therapy.<sup>37</sup>

Future studies are needed to elucidate, if multiple courses of antimicrobial photodynamic therapy may enhance treatment outcomes.

### CONCLUSION

Antimicrobial photodynamic therapy seems to be a unique and interesting therapeutic approach toward the treatment of periodontitis and periimplantitis. However, the wavelengths of diode lasers exhibiting deep-tissue penetration basically do not interact with the periodontal tissues within the pocket or tooth crown. Therefore, photodynamic therapy as a low-level therapy, using a diode laser with a short irradiation time, is considered not to produce any thermal changes within the gingival tissues and root surfaces, or destruction of the intact attachment apparatus at the base of pockets. Furthermore, the liquid of the photosensitizer solution applied may minimize thermal generation within the pockets. However, an extended period of irradiation at the same spot must be avoided to prevent any thermal accumulation or injury to the deeper tissues, such as bone or dental pulp. Thus, in order for lasers to be used safely within the clinical environment, the practitioner should have precise knowledge of the characteristics and effects of the laser system and its performance during application, and should exercise appropriate caution during use.

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