Periodontology 2000

Periodontology 2000, Vol. 68, 2015, 217–269

PERIODONTOLOGY 2000

Periodontal and peri-implant wound healing following laser therapy

Akira Aoki, Koji Mizutani, Frank Schwarz, Anton Sculean, Raymond A. Yukna, Aristeo A. Takasaki, Georgios E. Romanos, Yoichi Taniguchi, Katia M. Sasaki, Jorge L. Zeredo, Geena Koshy, Donald J. Coluzzi, Joel M. White, Yoshimitsu Abiko, Isao Ishikawa & Yuichi Izumi

To date, mechanical therapy has been the mainstream treatment for plaque-induced periodontal disease. However, complete eradication of bacteria and/or optimal wound healing may not necessarily be achieved with conventional mechanical therapy alone. Therefore, chemotherapy using antimicrobial agents as an adjunct to mechanical therapy has been advocated to increase bacterial eradication as well as to enhance wound healing/tissue regeneration following debridement. Mechano-chemotherapy has also been accepted and partly employed for the treatment of aggressive or severely advanced forms of periodontitis. In addition to conventional mechanical therapy and chemotherapy, periodontal phototherapy using lasers/light-emitting diodes has generated attention in periodontology because of various beneficial effects in terms of clinical performance, treatment procedures and reported outcomes. Thus, mechano-chemo-phototherapy is gradually becoming more popular. This article deals with the outcome of laser therapy, focusing on postoperative wound healing of periodontal and peri-implant tissues following treatment, based on scientific evidence from currently available *in vitro*, *in vivo* and clinical studies, as well as case reports.

Periodontal phototherapy

A large number of studies have reported the use of lasers/lights in the field of periodontal therapy (22, 116, 246, 264). The term "phototherapy" basically encompasses treatment modalities that employ lasers or incoherent light at low- or high-energy levels. In particular, laser therapy has been gradually introduced in dentistry and successfully applied clinically since the early 1990s.

Lasers have numerous tissue interactions, such as ablation or vaporization, hemostasis, microbial inhibition and destruction, as well as biological effects, such as biostimulation (photo-bio-modulation), which induce various beneficial therapeutic effects and biological responses. Thus, the use of lasers is considered effective and suitable for treating a variety of inflammatory and infectious conditions, such as periodontal and peri-implant diseases (22, 115, 116, 122, 264). In addition, laser therapy may alleviate a patient's physical and mental stress as well as intraoperative and postoperative pain.

Various dental laser instruments have been used for soft-tissue periodontal therapy. Development of the erbium-doped yttrium-aluminium-garnet (Er:YAG) laser (2,940 nm) and the erbium, chromium-doped yttrium-scandium-gallium-garnet (Er,Cr:YSGG) laser (2,780 nm), which can be applied on hard tissues with an extremely low thermal effect when used with water cooling, meant that periodontal tissues (such as gingiva, tooth roots and bone tissue), as well as titanium implant surfaces, could be treated with lasers. Currently, a variety of lasers are being employed for the management of periodontal and peri-implant disease (22, 114, 116) (Table 1). With increasing evidence for benefits, phototherapy plays an important role in wound healing/tissue regeneration in the treatment of oral diseases (21, 22, 51, 55, 66, 116, 122, 264, 265, 284, 317).

Table 1. U.S. Food and Drug Administration marketing clearances by wavelength in the field of periodontal therapy. Note that these clearances are for specific models of lasers—not every laser in the wavelength has every clearance listed. This information is abstracted and reprinted with permission from the Academy of Laser Dentistry (Sulewski JG. Making the most of the 21st Annual Conference and Exhibition: a practical orientation for attendees, February 26, 2014, pp. 7-26. Academy of Laser Dentistry, 21st Annual Conference, February 27 – March 1, 2014, Scottsdale, Arizona, USA) and the Institute for Advanced Dental Technologies.

Laser type	Procedures
Carbon dioxide	Intraoral soft tissue surgery (ablating, incising, excising, coagulating)
	Aphthous ulcer treatment
	Sulcular debridement
	Coagulation of extraction sites
	Laser-assisted new attachment procedure (LANAP; cementum-mediated peridoontal ligament, new attachment to the root surface in the absence of long junctional epithelium)
Nd:YAG	Intraoral soft tissue surgery (ablating, incising, excising, coagulating)
	Aphthous ulcer treatment
	Sulcular debridement
	Laser-assisted new attachment procedure (LANAP; cementum-mediated periodontal ligament, new attachment to the root surface in the absence of long junctional epithelium)
Er:YAG	Intraoral soft tissue surgery (ablating, incising, excising, coagulating)
	Aphthous ulcer treatment
	Sulcular debridement
	Cutting, shaving, contouring and resection of oral osseous tissue (bone)
	Osteotomy, osseous crown lengthening, osteoplasty
	Removal of subgingival calculus in periodontal pockets
Er,Cr:YSGG	Intraoral soft tissue surgery (ablating, incising, excising, coagulating)
	Aphthous ulcer treatment
	Sulcular debridement
	Cutting, shaving, contouring and resection of oral osseous tissue (Bone)
	Osteotomy, osseous crown lengthening, osteoplasty
	Removal of highly inflamed edematous tissue affected by bacterial penetration of the pocket lining and junctional epithelium
	Removal of subgingival calculus in periodontal pockets
Diode	Intraoral soft tissue surgery (ablating, incising, excising, coagulating)
	Aphthous ulcer treatment
	Sulcular debridement
	Coagulation of extraction sites
	Reduction of bacterial level (decontamination) and inflammation
	Aid in detection and localization of subgingival dental calculus
	Removal of highly inflamed edematous tissue affected by bacterial penetration of the pocket lining and junctional epithelium

Characteristics of laser therapy

In this section, several factors of laser irradiation related to wound healing are discussed.

Penetration depth of lasers

When laser energy reaches the tissue surface, it can be reflected, scattered, absorbed or transmitted to the surrounding tissues. Among the four different interactions in biological tissue, the performance of a laser is determined by the degree of absorption. In biological tissue, the main influences on absorption are the presence of free water molecules, proteins, pigments, inorganic components (such as apatite) and other macromolecules (Fig. 1). Generally, the degree of absorption (i.e. the depth of penetration of a laser in biological tissue) of a laser is dependent on its wavelength. In particular, absorption is strongly influenced by the absorption coefficient in water (110, 201). As shown in Fig. 1, a lower absorption coefficient into water indicates deeper penetration into biological soft tissues, whereas a higher absorption coefficient exhibits superficial absorption.

Thus, lasers are generally classified into two types, depending on their wavelength: (i) a deeply penetrating type, such as neodymium-doped yttrium-aluminium-garnet (Nd:YAG) and diode lasers, in which the laser light penetrates and scatters deeply into tissue, and

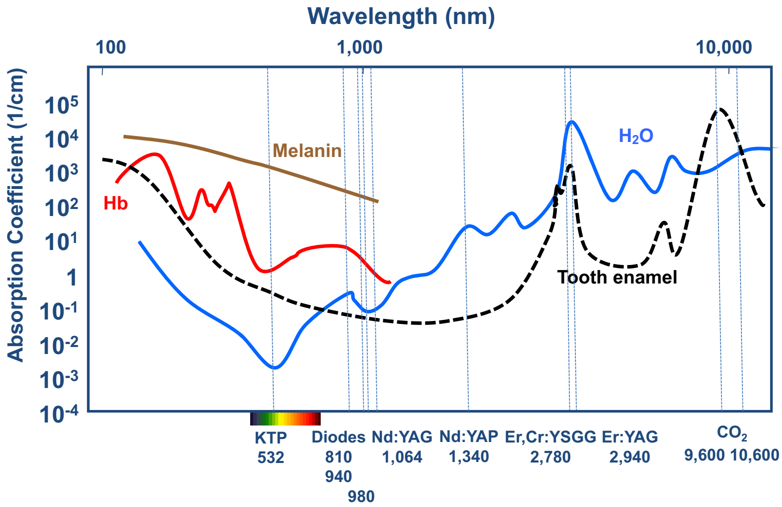


Fig. 1. **Approximate absorption curves of various components in biological tissues: water (H_2O), tooth enamel, melanin and hemoglobin (Hb). CO_2, carbon dioxide; Er,Cr:YSGG, erbium, chromium-doped yttrium-scandium-gallium-garnet; Er:YAG, erbium-doped yttrium-aluminium-garnet; KTP, potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium-aluminium-garnet; Nd:YAP, neodymium-doped yttrium-aluminum-perovskite. [Picture from Coluzzi. Fundamentals of lasers in dentistry: basic science, tissue interaction, and instrumentation. *J Laser Dent* 16 (Spec. Issue): 4–10, 2008; with permission. Journal of Laser Dentistry© copyright (2008) Academy of Laser Dentistry (54)].**

(ii) a superficially absorbed type (shallowly penetrating type), such as carbon dioxide (CO_2), Er:YAG and Er,Cr:YSGG lasers, in which the laser light is absorbed in the superficial layer and does not penetrate or scatter deeply (116, 129, 211) (Fig. 2).

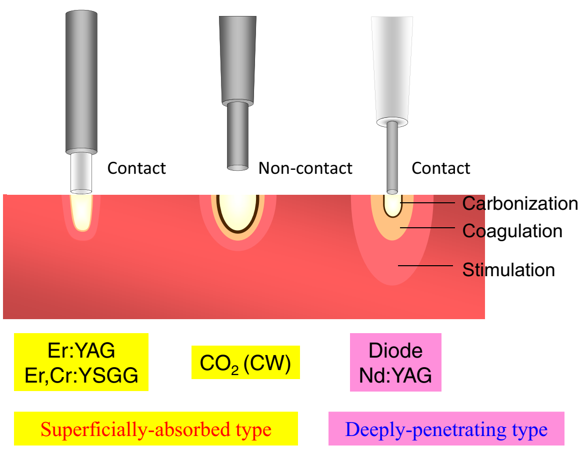


Fig. 2. **Classification of lasers according to penetration depth in tissue. One is a deeply penetrating type, in which the laser light penetrates and scatters deeply into the tissue, and the other is a superficially absorbed type (shallowly penetrating type), in which the laser light does not penetrate or scatter deeply (129). CO_2, carbon dioxide; CW, continuous wave; Er,Cr:YSGG, erbium, chromium-doped yttrium-scandium-gallium-garnet; Er:YAG, erbium-doped yttrium-aluminium-garnet; Nd:YAG, neodymium-doped yttrium-aluminium-garnet.**

Tissue ablation

Basically, most surgical (high-power) lasers produce a photo-thermal effect on tissue and thereby evaporate soft tissues by thermal effects. In particular, CO_2 and erbium lasers directly and easily evaporate soft tissues by photo-thermal effects. Regarding the two types of erbium lasers, the effect of soft-tissue ablation seems to be greater following treatment with an Er:YAG laser than with an Er,Cr:YSGG laser (333). On the other hand, for Nd:YAG and diode lasers, part of the emitting light is converted into heat by refraction or diffused reflection at the tip end, creating a condition called “hot tip”. Thus, the secondary thermal effects of the heated tip can cut or incise soft tissues. The tissue is coagulated and vaporized as a result of contact with the overheated tip rather than by the laser energy itself (21).

Regarding hard tissues, hard-tissue ablation with the Er:YAG laser (2,940 nm) has been speculated to occur as a result of “thermo-mechanical” effects based on photo-thermal interactions (287, 288). The Er,Cr:YSGG laser, closely related in wavelength (2,780 nm) to the Er:YAG laser (2,940 nm), shows physical and biological performances clinically comparable with those of the Er:YAG laser. However, the Er,Cr:YSGG laser is more highly absorbed by hydroxide (OH) ions than by water molecules (81). The mechanism of tissue ablation by the Er:YAG laser begins with thermal evaporation because the laser is readily absorbed in water and organic molecules within the biological tissues. In this process, water molecules within the hard tissues are vaporized as they absorb the laser energy, thus increasing intratissue pressure, producing vapor within the tissue and provoking "micro-explosions" that cause mechanical break down of tissues and physically contribute to the ablation process (21, 22, 198, 204). The ablated surface exhibits a microstructured appearance with minimal thermal alteration (21, 22) (Fig. 3).

Thermal side effects and hemostasis

Following ablation caused by photo-thermal effects of lasers, various degrees of thermal denaturation can be observed at the irradiated site (Figs 2 and 4). As the Nd:YAG laser is a deeply penetrating type of laser, it produces a relatively thick coagulation layer on the lased soft-tissue surface (Fig. 2) and thereby exhibits strong hemostasis. Hence, the Nd:YAG laser is basically effective for ablation of potentially hemorrhagic soft tissue. Perry et al. (216) and White et al. (337, 339) reported that the width of the coagulation layer was 0.3–0.8 mm in an incision of bovine oral soft tissue *in vitro* at 3–10 W.

Diode lasers also belong to the deeply penetrating types of laser, and White et al. (337) reported that the width of the coagulation layer following irradiation in continuous mode was more than 1.0 mm in an incision of bovine oral soft tissue *in vitro*. However, depending on the experimental conditions and method of evaluation, the width of the changed layer is considerably different. Goharkhay et al. (101) demonstrated that the width of soft-tissue damage on pig oral mucosa was 20–100 μm in the continuous wave and pulsed modes at 0.5–4.5 W. Beer et al. (36) reported that the average depth of necrosis and the depth of reversible damage in the incision on bovine liver specimens were approximately 80–190 μm and 300 μm to 2 mm, respectively, for the pulsed mode, and were 70–150 μm and 150–600 μm, respectively, for the micro-pulsed mode, depending on the speed of probe movement at 1.2–2.2 W.

The CO_2 laser is a shallow-penetrating type of laser that is absorbed at the tissue surface with very little scatter or penetration (Fig. 2). As the ablation is mainly caused by heat generation, carbonization occurs easily on the irradiated surface but the heat produced does not scatter. Therefore, the CO_2 laser produces a relatively thin layer of coagulation around the ablated site. Arashiro et al. (26) reported that the width of the coagulation layer was 100–300 μm in an incision of porcine skin with the continuous-mode CO_2 laser at 6 W, and Vaderhobli et al. (329) reported

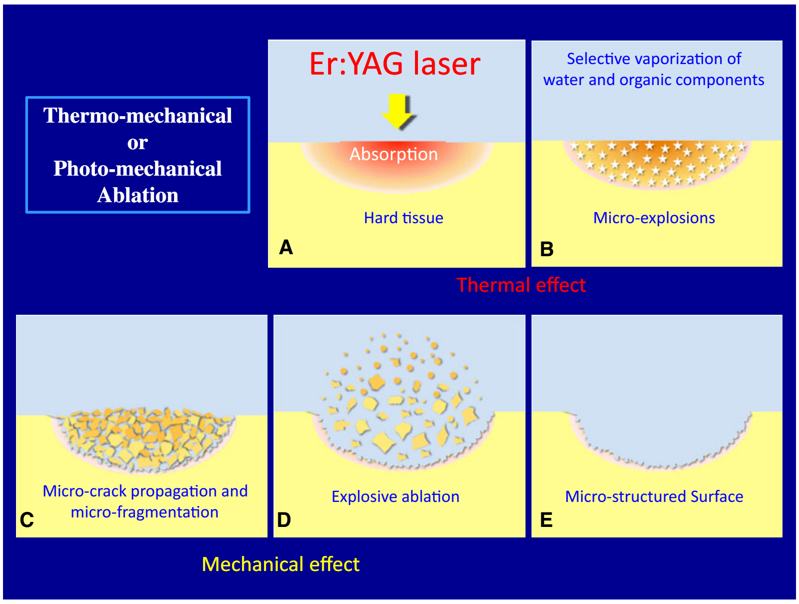


Fig. 3. Mechanism of hard-tissue ablation with an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser. The Er:YAG laser penetrates the hard tissues superficially (A) and water molecules and organic molecules within the hard tissues are selectively vaporized by thermal effects as they readily absorb the laser energy, thus increasing the intra-tissue pressure, producing vapor within the tissue and provoking "micro-explosions" (B) that cause mechanical tissue to break down by inducing micro-crack propagation and micro-fragmentation (C) and physically contribute to the water-mediated explosive ablation process (D), leaving a minimally affected layer with microstructures on the lased surface (E). Thus, the mechanism of hard-tissue ablation with the Er:YAG laser has been speculated as a "photo-mechanical" or a "thermo-mechanical" effect.

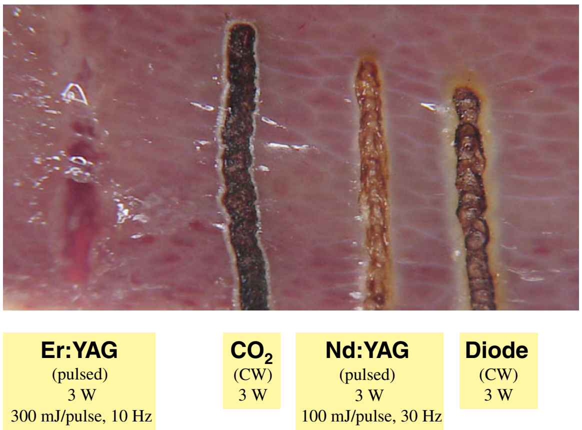


Fig. 4. Effects of lasers on soft tissue. Following photo-thermal ablation caused by lasers, various degrees of thermal denaturation were observed on the irradiated site (chicken liver). The pulsed erbium-doped yttrium-aluminium-garnet (Er:YAG) laser effectively ablates soft tissue, with minimal coagulation and no carbonization. The continuous wave (CW) carbon dioxide (CO_2) laser also easily ablated soft tissue but severe carbonization was evident with relatively thin coagulation. The pulsed neodymium-doped yttrium-aluminium-garnet (Nd:YAG) laser produced relatively thick coagulation with moderate carbonization. The CW diode laser produced the greatest coagulation as well as moderate carbonization (Courtesy of Dr. Junji Kato).

a width of less than 200 μm in an incision of porcine tongue with the microsecond pulsed-mode CO_2 laser at 0.2–3.5 W. Cercadillo-Ibarguren et al. (47) found that in the case of incisions of porcine oral mucosa, the width of the thermal effect was 20–35 μm at 1–10 W.

Among dental lasers, the Er:YAG laser has the highest absorption into water, which minimizes the thermal effects on the surrounding tissues during irradiation (Fig. 2). Walsh et al. (334) reported that the width of the thermally changed layer was only 10–50 μm following Er:YAG laser incision of porcine skin in noncontact mode. Sawabe et al. (259) reported that the width of the thermally changed layer was approximately 20 μm following Er:YAG laser (10.4 J/cm^2/pulse, 30 Hz) contact ablation of gingival tissue without water spray in rats. Cercadillo-Ibarguren et al. (47) demonstrated, with Er,Cr:YSGG laser incisions of porcine oral mucosa, that the width of the thermal effect was 9–15 μm at 1–4 W with water spray, in contrast to 10–60 μm at 1–2 W without water spray.

Merigo et al. (180) compared the thermal influence on bovine tongue tissue for different lasers and reported that the greatest changes evident within the stroma were collagen fusion and homogenization, which were observed in widths of 500–600 μm for the 5-W continuous-wave diode laser and the 4-W Nd:YAG laser. The corresponding widths of other wavelengths were approximately 200 μm for the 3-W continouous-wave diode laser, more than 100 μm for the 3–5 W continuous-wave or superpulsed CO_2 laser and the smallest, less than 100 μm, was observed for the 5-W (250 mJ/pulse, 20 Hz) Er:YAG laser. The thermal increase induced by the Er:YAG laser was lower than that induced by CO_2 and diode lasers, whereas CO_2 and diode lasers revealed a good histological quality to the cut surface (incision morphology).

Regarding hard tissues, the Er:YAG laser, when used with water cooling, is capable of effectively ablating hard tissues, producing a thermally affected layer of approximately 5–30 μm thickness on cementum, dentin and bone tissues (10, 18, 19, 87, 257). Other high-power lasers, such as Nd:YAG and CO_2 (10,600 nm), generally produce major thermal changes, such as carbonization, melting and resolidification on hard tissues (86, 120, 147, 178, 223, 257, 258). The diode laser generally does not interact with root cementum; however, in the presence of blood, this laser also results in carbonization of cementum (150).

Disinfection and detoxification effects

Most surgical lasers are capable of killing bacteria by photo-thermal effects. Bacteria are evaporated, destroyed or denatured by laser irradiation, resulting in their devitalization or inactivation (6, 13, 53, 67, 143, 244, 262, 263). Therefore, the bactericidal effect of laser therapy is considered advantageous for postoperative wound healing because lasers are capable of creating a disinfected field during surgery and reducing the risk of infection (191). In addition, because the Nd:YAG laser exhibits selective absorption in pigments, it is conceivable that this laser would be effective for devitalizing some of the pigmented bacteria, such as *Porphyromonas gingivalis*, that are associated with periodontal disease. Moreover, lasers ablate or inactivate toxic substances, such as bacterial endotoxins (lipopolysaccharide) (84, 89, 143, 313, 343). These additional decontamination and detoxification effects may positively influence wound healing of the treated site and offer several advantages over conventional mechanical treatment. Furthermore, it is possible that laser irradiation of the root surface might provide an antimicrobial effect and inhibit bacterial attachment/colonization following irradiation (119). The effect would also be beneficial for healing and maintenance of periodontal pockets.

Another advantageous aspect of laser therapy is its potential systemic effect when bacteremia following periodontal treatment is prevented (107). Bacteremia occurs as a consequence of various dental procedures (160, 234). Assaf et al. (28) reported that pre-irradiation of periodontal pockets with a diode laser before ultrasonic scaling significantly reduced the incidence of odontogenic bacteremia in the treatment of gingivitis. When comparing diode laser plus ultrasonic scaling with ultrasonic scaling alone in a split-mouth design, the incidence of bacteremia was 68% (15 of 22 patients) after ultrasonic scaling alone and 36% (eight of 22 patients) following ultrasonic scaling plus laser therapy. Komatsu et al. (144) compared the Er:YAG laser with conventional hand instruments for scaling and root planing and reported that the incidence of bacteremia during scaling and root planing was 0% (0 of 10 patients) in the Er:YAG laser group and 80% (eight of 10 patients) in the hand instrument group, with a significant difference found between the groups. They concluded that scaling and root planing with the Er:YAG laser could be a novel prophylactic treatment to prevent or minimize transient bacteremia. Thus, if the use of lasers can reduce the incidence of bacteremia during pocket therapy, it may offer advantages for elderly patients and patients with systemic diseases in whom periodontitis is a recognized comorbidity.

Biostimulation (photobiomodulation)

A further interesting and characteristic property of laser therapy is the biostimulation (photobiomodulation) of tissues and cells following irradiation, which is a completely unique aspect and different from that of mechanical therapy (182, 183). The effects may be related to photochemical reactions within cells, rather than to thermal events; however, the mechanism is still unclear. Nevertheless, the various biological effects of laser irradiation may have interesting applications, such as promotion of wound healing (78, 183, 341) and reduction of inflammation (7), as well as pain relief (40, 78). In the process of periodontal soft- and hard-tissue repair/regeneration, the biostimulatory effects may allow faster or more favorable wound healing, relative to conventional mechanical therapy.

Depending on the energy level applied, the use of lasers can be divided into two categories: high-level laser therapy/treatment; and low-level laser therapy/treatment (205) (Fig. 5). High-level laser therapy usually aims to ablate diseased tissues and leave the treated sites aseptic and nontoxic, thereby leading to improved healing and regeneration. Conversely, low-level laser therapy stimulates tissues and cells without producing irreversible changes (photobiomodulation), thus promoting periodontal wound healing (205). High-level laser therapy and low-level laser therapy can be employed simultaneously because a reduced or markedly reduced amount of energy penetrates or scatters into the surrounding tissues during high-level laser irradiation. Also, the photo-thermal effect generated by high-level laser irradiation may have a positive influence on wound healing as one of the biostimulation effects (205). Currently, high-level laser therapy is performed for ablation of diseased tissues, with concurrent photobiomodulation in the adjacent tissues, as a desired effect (23, 122).

Soft-tissue surgery

Advantages of laser surgery over conventional treatment modalities

Dental laser instruments have been widely employed in soft-tissue procedures, such as gingivectomy, gingivoplasty and frenectomy, and for the removal of benign tumors in oral surgery and periodontics (2, 21, 55, 116, 211, 220). The major beneficial properties of lasers are their relatively easier ablation of soft tissues than that of mechanical instruments and their hemostatic and bactericidal effects. Intra-oral tissues, particularly gingiva, display a complex topography and often cannot be reached with a conventional scalpel blade. Compared with a scalpel, a laser can more easily cut, ablate and reshape the oral soft tissues in the oral cavity, with no or reduced bleeding and less pain, as well as with no or less suturing.

Most lasers can be used in soft-tissue surgery where they exert a photo-thermal effect. In this, soft tissues are evaporated or incised, leaving different degrees of thermal denaturation, such as carbonization and coagulation, of the treated surface (Figs 2 and 4). Few studies have precisely compared wound healing among conventional instruments and lasers because it is basically difficult to prepare wounds with the same dimensions for both scalpel and laser incisions. As comparative studies available are limited and the results differ depending upon the type of laser employed, a consensus regarding the speed of wound healing following the use of lasers has not been reached.

Alternatively, electrosurgery has frequently been employed and is capable of easily incising soft tissues with good hemostasis (318). However, delayed wound healing is a potential risk of unwanted thermal damage (259), and necrosis of the underlying periosteum and alveolar bone during gingival tissue management can be a complication (32, 296, 297). Lasers offer greater patient comfort and safety than electrosurgery, with less postoperative pain and fewer complications (259). In particular, lasers do not induce severe pulpal pain, which is frequently associated with the contact of the probe on the root surface during electrosurgery.

Wound healing following soft-tissue surgery

The healing of soft tissues following laser therapy is largely influenced by the degree of thermal side-effects on the lased tissue surfaces caused by each laser system. Each laser wavelength performs differently on soft tissues, depending upon the degree of absorption and the penetration depth of the laser (Figs 2 and 4). Generally, wound healing (primary closure) following a soft-tissue incision with surgical lasers is delayed compared with that of a scalpel incision, as a result of the collateral thermal side effects (26, 83, 297). In particular, diode and Nd:YAG lasers penetrate more deeply, and can cause more thermal effects and produce a relatively thicker coagulation layer on the treated surface, than superficially absorbed lasers (22, 109). Thus, thermal denaturation of the lased surface would affect the adhesion of the incised surfaces for primary closure, resulting in delayed wound healing. However, lasers are not usually employed for incisions in oral soft-tissue surgery, their target uses generally being excision and ablation of soft tissues. The thermal side effects on the ablated surface do not necessarily affect the process of secondary epithelialization following excision or ablation. On the other hand, because of the production of a thicker coagulum, deeply penetrating lasers can be applied even for the treatment of lip and tongue tissues, which bleed easily. However, when applying deeply penetrating types of lasers for periodontal procedures, there is concern regarding the impact of the thermal effects on the underlying and surrounding tissues such as tooth pulp, periosteum and bone tissue, which may jeopardize wound healing following treatment.

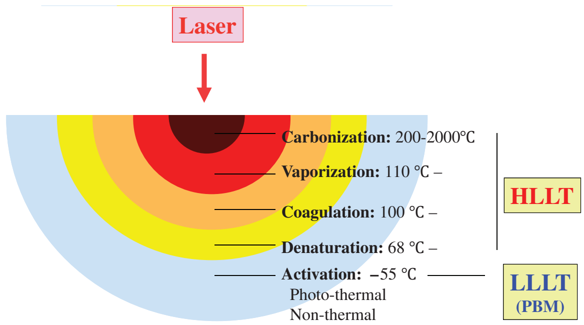


Fig. 5. High-level laser therapy (HLLT) and low-level laser therapy (LLLT) (205). High-level laser treatment/therapy can cause various degrees of thermal effects on tissues, including coagulation and ablation of soft tissue, and removal of hard tissue. Simultaneously, a low level of energy penetrates or scatters into the surrounding tissues during high-level laser treatment. Low-level laser treatment stimulates tissues/cells without producing irreversible thermal changes in the tissues, resulting in activation or stimulation (photobiomodulation) of wound healing in the surrounding tissues. When using a high-level laser at a low-energy level, the thermal effect may also induce wound healing, as in the purely low-level laser effect photobiomodulation (PBM).

CO_2 laser

In periodontology, there were several reports on laser application for gingivectomy and gingivoplasty in the late 1980s (34, 221, 246). The CO_2 laser can be used for rapid soft-tissue removal, with excellent hemostasis, producing a clear operating field that sometimes requires no suturing (220, 246) (Fig. 6). Compared with use of a scalpel, laser surgery offers the advantages of minimal scarring and wound contraction (83, 171, 172). Regarding the histology of wound healing, Fisher et al. (83) reported that the CO_2 laser wound on buccal gingival mucosa differed from the conventional wound: there was minimal damage to the adjacent tissue; initially a coagulum of denatured protein formed on the surface; the inflammatory reaction was reduced; fewer myofibroblasts were present and there was little wound contraction; and less collagen was formed and epithelial regeneration was delayed and more irregular. Luomanen et al. (170) reported that in the incision of rat tongue mucosa the regenerative process with concomitant re-epithelialization took place more slowly in laser-treated than in scalpel-incised wounds. The relative resistance of matrix proteins to laser irradiation and the slow removal and replacement of the residual matrix is suggested to account, at least partially, for the lack of scarring and contraction frequently observed in laser-treated areas. Also, Arashiro et al. (26) reported that wound healing following CO_2 laser and electrosurgery incisions in porcine skin was delayed relative to that of scalpel incisions. Ryu et al. (251) reported that although a CO_2 laser had better hemostatic ability, its use caused greater tissue damage than a scalpel and the Er,Cr:YSGG laser. Goultschin et al. (105) demonstrated that there was no difference between CO_2 laser and scalpel treatment in clinical wound healing following gingivectomy; however, the healing of laser wounds was histologically delayed with epithelial ulcerations and a dense inflammatory infiltrate accompanied by the formation of crater-like defects

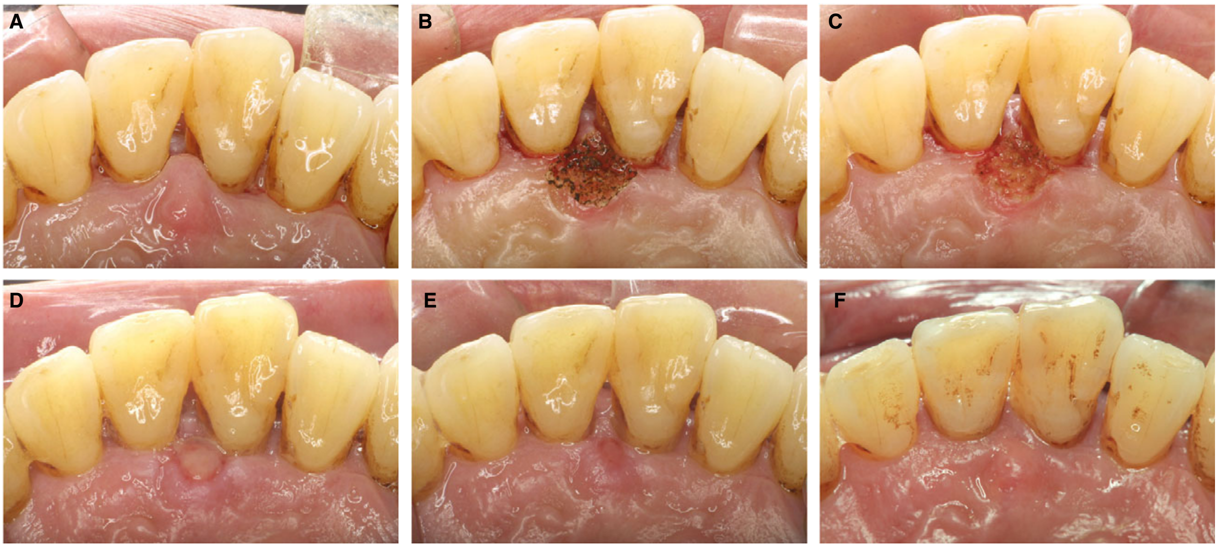


Fig. 6. Clinical application of carbon dioxide laser in gingivectomy/gingivoplasty. Before surgery (A), a large incisal papilla is observed at the mesio-palatal site of the maxillary incisors in a 55-year-old male patient, resulting in 6-mm-deep pockets with bleeding on probing (March 2007). First of all, the diseased root surfaces were treated by scaling and root planing using mechanical scalers. During the same session, the incisal papilla was removed to help reduce the depth of the periodontal pockets. Under local anesthesia, a carbon dioxide laser was used at 3–4 W in noncontact, continuous-wave mode. The fibrous, relatively hard, gingival papilla was very easily vaporized without any bleeding. The papilla was removed and leveled out, leaving a moderate layer of carbonized and coagulated tissue on the surface (B). The carbonized tissue was easily removed with a cotton swab (C). Afterwards, a moderately coagulated surface is observed. One week after surgery (D), a white pseudomembrane is observed over the surface of the wound during epithelialization. Approximately 6 weeks after surgery (E), the tissue was stabilized, and the periodontal pocket was reduced to 2–3 mm with no bleeding on probing. Five years after surgery (F), the tissue was still stable with 2–3 mm probing depth and no bleeding on probing. (Case details provided by A. A.) [Photographs a-d from Aoki et al. Current status of clinical laser applications in periodontal therapy. *Gen Dent* 56: 674–87, 2008. Erratum in: Gen Dent 57(1): 94, 2009; with permission. General Dentistry © copyright (2008) The Academy of General Dentistry (21)].

in the enamel and cementum. It should be noted that CO_2 laser radiation perpendicular to the tooth and root surface produces substantial and undesirable changes that must be clinically avoided.

Nd:YAG laser

Oral soft-tissue surgery using the Nd:YAG laser has been widely accepted (220, 238, 338). White et al. (338) successfully used the Nd:YAG laser for intra-oral soft-tissue application, without anesthesia and with minimal bleeding compared with scalpel surgery. Romanos et al. (242, 243) reported that in rat skin incisions, Nd:YAG laser wounds produced with this laser at a low energy level could not be significantly differentiated from conventional incisions. However, although less damage and a lower inflammatory reaction occurred, increased matrix production and a small amount of wound contraction could be demonstrated with laser usage at a low energy level, and tissue exposed to high energy presented extensive damage, such as necrosis and an increased inflammatory reaction, and demonstrated a slower rate of wound healing.

Diode laser

The diode laser shows an excellent cutting and coagulation ability with soft tissues and its clinical application is considered to be beneficial for daily practice in oral soft-tissue surgery owing to sufficient hemostasis and precise incision margins (101, 123, 237), although more tissue damage occurs compared with that observed following use of a scalpel or an Er, Cr:YSGG laser (123). Jin et al. (123) demonstrated that in comparison with scalpels and Er,Cr:YSGG laser wounds, the highest level of tumor necrosis factor-alpha expression was found at day 1 postsurgery in the diode laser wounds of pig oral mucosa. Mavrogiannis et al. (177) compared gingivectomy by diode laser (810 nm) for drug-induced gingival overgrowth with that performed by scalpel and reported that, at 6 months, there was significantly less overgrowth recurrence in patients treated with laser excision compared with those treated by conventional gingivectomy. To et al. (323) performed diode laser gingivectomy as an adjunct to nonsurgical periodontal treatment in the management of periodontal health among patients receiving fixed orthodontic appliance therapy. Significant improvements in periodontal health were evident earlier among the test-group subjects for gingival overgrowth index, gingival index and probing pocket depth. They reported that the adjunctive use of lasers can produce an earlier and greater improvement in gingival health. Also, quite recently, using a diode laser, Romanos et al. (240) reported favorable wound healing without scarring following laser patterned microcoagulation as a minimally invasive microsurgical approach, which aims to initiate gingival and oral mucosal tissue regeneration. This novel technique might offer promise for treating degenerative diseases of the oral soft tissues in the future.

Erbium lasers

Watanabe et al. (336) first reported that an Er:YAG laser was useful for oral soft-tissue surgery. In the case of an Er:YAG laser, owing to the minimal thermal degeneration of the laser-treated surface (180, 334), wound healing following gingivectomy in dogs was relatively fast and clinically and histologically comparable with that of scalpel surgery (20) (Fig. 7). Repair of Er,Cr:YSGG laser wounds is also histologically similar to that of the scalpel wounds (219, 251). Ryu et al. (251) reported that an Er,Cr:YSGG laser has many advantages in oral surgery because of the low inflammatory response and minimal damage to tissue. Sawabe et al. (259) compared gingival tissue healing after Er:YAG laser ablation with that following electrosurgery in rats. They reported that in the electrosurgery sites, the postoperative tissue destruction caused by thermal damage continued, whereas in the Er:YAG laser-ablated sites, tissue degradation was limited and the defects were re-epithelialized early. High levels of heat shock protein-72/73 expression, which is induced by cellular stress, were expressed remote from the wound in the electrosurgery sites, whereas only low levels were observed in close proximity to the wound in the Er:YAG laser sites. Expression of heat shock protein-47, which is associated with collagen synthesis, was observed throughout the connective tissues early in wound healing and was found to be limited to the wound area later. This phenomenon proceeded faster in the Er:YAG laser-treated sites than in the electrosurgery sites. Sawabe et al. (259) concluded that the results demonstrated faster and more favorable gingival wound healing in Er:YAG laser-treated sites compared with electrosurgery sites, which suggests that the Er:YAG laser is a safe and suitable tool for periodontal soft-tissue management.

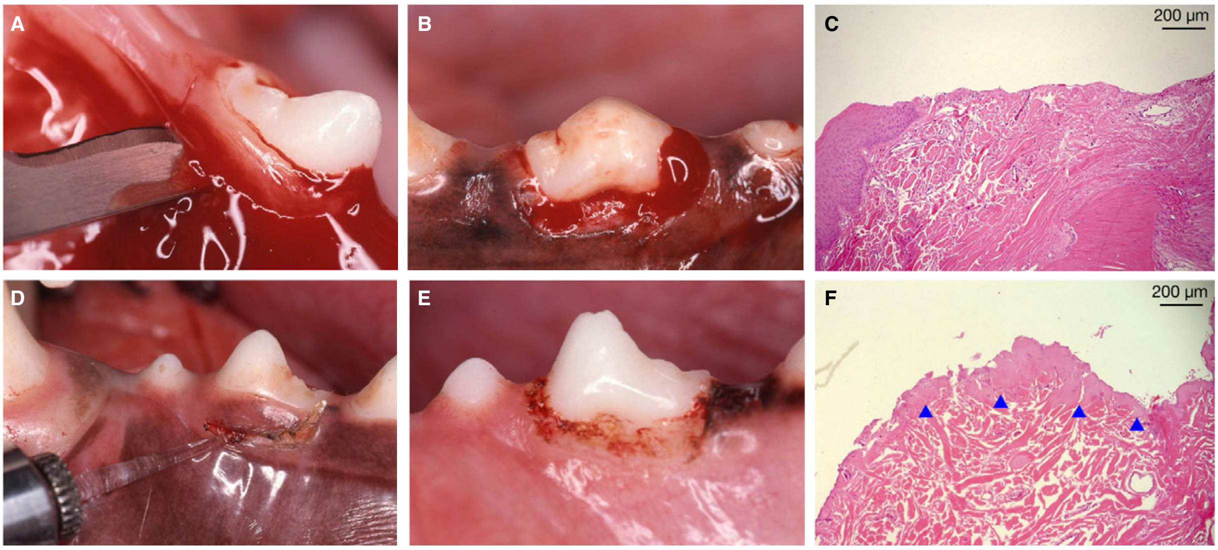


Fig. 7. Conventional scalpel gingivectomy vs. erbium-doped yttrium-aluminium-garnet (Er:YAG) laser gingivectomy at premolars in Beagle dogs. During scalpel surgery (A), a large amount of bleeding is noted. Immediately after surgery (B), the treated surface shows marked bleeding (a different case from that shown in panel A). A photomicrograph of a histological section immediately after scalpel surgery demonstrates a smooth surface (C). During Er:YAG laser surgery (energy output of 30 mJ/pulse and 30 Hz without water spray in contact irradiation using a tapered tip) (D), gingival tissue is effectively excised without bleeding. Immediately after laser therapy (E), the laser-treated surface exhibits no visible thermal damage, such as carbonization or coagulation. Hemostasis is achieved [A different case from (D)]. A photomicrograph of a histological section immediately after laser surgery shows irregularity of the treated surface with a layer of thin thermal coagulation (arrowheads) approximately 60–220 µm thick and without major carbonization (F). (Azan stain, original magnification ×33).

Hemostasis is less effective with the erbium family of lasers because of the minimal tissue denaturation induced, compared with other wavelengths. A low hemostatic effect is generally considered a shortcoming of the Er:YAG laser because the hemostatic effect is clinically useful in soft-tissue surgery as it stops bleeding, providing a clear operation field and reducing the necessity of suturing after surgery. However, with respect to the wound healing of periodontal soft tissues, the low hemostatic effect of erbium lasers is clinically advantageous because the hemostasis is histologically achieved by formation of a thick coagulation layer. When a substantial defect is created after laser ablation, the thick coagulation layer affects wound healing by inhibiting sufficient blood supply as well as blood-clot formation and by interfering with the subsequent replacement/filling in the new tissues following treatment, occasionally resulting in a gingival defect, deformity and recession. Thus, the minimal hemostasis in erbium laser surgery guarantees subsequent sufficient bleeding and blood clot formation in the ablated defects and thereby induces favorable wound healing (259).

Wound healing following esthetic surgery

Esthetic gingival procedures, such as recontouring or reshaping of gingiva, crown lengthening and depigmentation, have been performed by lasers (56). Various wavelengths can be used for depigmentation of melanin-containing tissues (29, 31, 131, 195, 245, 319, 349). However, there is a risk of gingival recession and ulceration in the areas of thin and delicate gingiva when CO_2, diode and Nd:YAG lasers are employed because of their extensive ablation or excessive thermal-effect potential (29). In contrast, one recent study reported the efficacy of diode lasers for photoablative de-epithelialization of hyperpigmented gingival tissue with some advantages compared with the Er:YAG laser in terms of less injury and postoperative discomfort and pain (98).

For esthetic gingival procedures, an erbium laser can be more safely utilized because of its minimal thermal side effects than CO_2, diode and Nd: YAG lasers (180). In particular, use of water cooling further minimizes thermal effects. If small and delicate contact tips are used, the amount of soft tissue ablated with an Er:YAG laser can be controlled with more precision than with the other lasers; in addition, with less thermal alteration of the treated surface, wound healing can be more rapid (22, 114, 116, 336). In a study on dogs, melanin depigmentation using an Er:YAG laser resulted in a thermally affected layer, approximately 5–25 μm wide, in the connective tissue (17). Recent case reports revealed that this laser can safely and effectively remove both gingival melanin pigmentation (31, 131, 245, 319) and even metal tattoos (114), followed by esthetically significant improvements of gingival discoloration, without any complications or side effects.

Furthermore, when used in combination with a surgical microscope, an Er:YAG laser can almost completely eliminate even small areas of remaining pigmentation or metal fragments, by carefully irradiating the delicate and fragile gingival margin and papilla without causing postsurgical gingival recession (17, 114). These technical advantages of Er:YAG laser microsurgery also lead to improved wound healing and facilitate delicate and complicated procedures, compared with conventional therapy.

Effect of biostimulation (photobiomodulation) in wound healing

It is speculated that photobiomodulation effects, such as promotion of cell proliferation and differentiation, as well as anti-inflammatory effects, are simultaneously produced following high-level laser therapy, and that this should positively modulate wound healing.

However, the amount of wound healing is clinically determined by the balance between the degree of tissue denaturation and the degree of tissue/cell stimulation induced by each laser wavelength. The rate of wound healing is strongly influenced by the degree of remaining collateral thermal injuries. In the case of deep-penetrating lasers, such as Nd:YAG and diode lasers, where tissue denaturation is relatively strong, the photobiomodulation effect may not be exerted effectively. On the other hand, in the case of superficially absorbed lasers, the coagulation layer is thinner and thus the photobiomodulation effect should potentially work well, although the effect would be much weaker compared with the deeply penetrating lasers owing to the lower amount of energy penetration and scattering. Therefore, the actual photobiomodulation effect on wound healing during soft-tissue surgery is complicated and varies among lasers.

Tajima et al. (315) reported that CO_2 laser radiation for a hole preparation in rat ear induced more rapid and greater activation of extracellular signal regulated protein kinase 1/2 in skeletal muscle cells surrounding the injury after surgery, compared with that of mechanical injury. Yamazaki et al. (345, 346) reported that low-level CO_2 laser-induced coagulation resulted in the expression of heat shock proteins with a different intensity and pattern to those expressed following scalpel surgery. The number of bromodeoxyuridine-labeled connective tissue cells on day 1 was significantly greater in the laser wound than in the scalpel wound, and the repair process progressed more rapidly in the laser-induced wound than in the scalpel wound. It seems that the coagulation necrosis produced by the low-level pulsed CO_2 laser does not disturb the repair process but promotes its steady progress and subsequent tissue remodeling (346). Thus, CO_2 laser-induced coagulation may positively influence wound healing. As studies investigating the photobiomodulation effect of lasers during soft-tissue surgery are still limited, further research is required to clarify the advantageous effects of lasers on wound healing.

Summary

Ablation, disinfection and hemostasis are easier to achieve during soft-tissue surgery when a laser is used compared with conventional instrumentation. However, wound healing following laser surgery varies depending on the wavelength of the laser as well as on the irradiation conditions. In consideration of wound healing, differences in the effects of deeply and shallowly penetrating lasers should be precisely understood. Among the dental lasers available, erbium lasers result in the most rapid, favorable and uneventful wound healing because of their precise ablation with minimal thermal effects.

Nonsurgical pocket therapy

Within periodontal pockets, pathogenic bacterial plaque, calculus, as well as bacterial endotoxins contaminate the exposed root surfaces and infiltrate cementum (4). It is essential to remove these harmful substances completely to restore biocompatibility and to allow new attachment or reattachment of the periodontium. The significant density of the periodontal biofilm can also impede the infiltration of antibiotics. Thus, the biofilm must be disrupted mechanically in order to decontaminate the diseased root surfaces (63). However, owing to anatomical complexity, complete disinfection and debridement of periodontal pockets may not always be achieved with conventional mechanical therapy.

Following recent developments in laser technology, several types of surgical laser have been identified as promising new technical modalities for decontamination of periodontal pockets and root surfaces in nonsurgical treatment owing to their effective ablation and strong bactericidal and detoxification effects (13, 22, 52, 343). Currently, lasers are employed as an adjunct or alternative to conventional mechanical instruments, such as hand instruments or power scalers, in the clinic.

Nd:YAG laser

Characteristics and basic studies

Conventionally, the Nd:YAG laser, with its thin flexible fiber delivery, has been mainly employed for pocket treatment. This procedure is sometimes an adjunctive one that is performed after conventional debridement with curettes or ultrasonic scaling. Debridement of the soft-tissue wall (gingival curettage) can be performed by a dental laser more effectively than with conventional instruments. The Nd:YAG laser can decontaminate periodontal pockets (52) and vaporize the pocket-lining epithelium without causing necrosis or carbonization of the underlying connective tissue (103, 351).

Several manufacturers have gained US Food and Drug Administration 510(k) clearance for a nonsurgical procedure (actually more a definitive surgical procedure) described as “cementum-mediated periodontal ligament new attachment to the root surface in the absence of long junctional epithelium”. However, only one company and one technique has human histologic evidence (200, 351). That company has trademarked the technique as a Laser-Assisted New Attachment Procedure (LANAP®), which involves specific steps (Fig. 8) (106, 111). The Nd:YAG laser exhibits good absorption by pigment; therefore, another important aspect could be its bactericidal effect on some pigmented bacteria, such as *P. gingivalis* (146). Giannelli et al. (97) reported that periodontopathogens can persist within cells outside the pocket epithelium, despite conventional mechanical periodontal treatment, and that the Nd:YAG and diode lasers are capable of eradicating periodontopathogenic bacteria trapped within gingival epithelial cells.

Regarding the root surface, the Nd:YAG laser cannot remove calculus sufficiently (326) and may cause thermal damage, such as carbonization, melting and resolidification of root cementum and dentin, if used incorrectly (188), in particular, when a high-energy output is applied to the root surface. However, clinically, it appears that the Nd:YAG wavelength is usually safe and effective for pocket irradiation when used with appropriate parameters (119). However, as a result of the wavelength penetrability, care must be taken to avoid excessive heat accumulation and

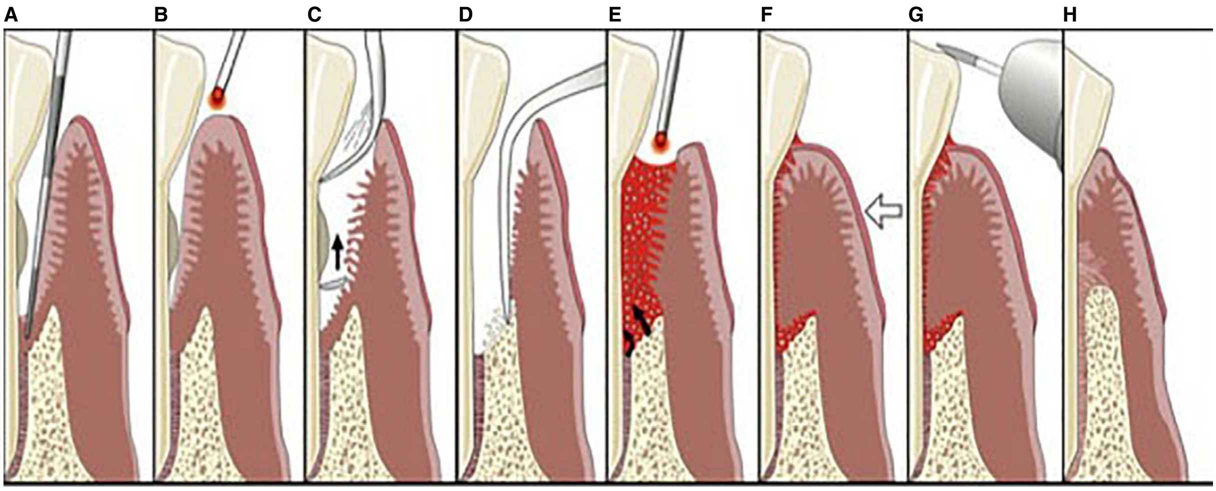


Fig. 8. Schematic illustration of the steps of the Laser-Assisted New Attachment Procedure® (LANAP®). This is a single laser treatment using a 1064-nm free-running pulsed neodymium-doped yttrium-aluminium-garnet (Nd:YAG) laser with typical periodontal-treatment follow up. This therapy is not a nonsurgical procedure but rather a surgical one in nature. (A) Bone sounding under anesthesia to identify bony defect depths. (B) Laser removal of pocket epithelium from the coronal to the apical direction to initiate gingival flap reflection at 3.6–4.0 W (180–200 mJ/pulse, 20 Hz, 100 μs). (C) Root-surface instrumentation (debridement), typically with ultrasonic scalers. Note intact connective-tissue rete ridges. (D) Bone modification/intramarrow penetration to release stem cells and growth factors. No granulation tissue removal. (E) Laser initiation of fibrin clot from the bottom of pocket coronally at 3.6–4.0 W (180–200 mJ/pulse, 20 Hz, 650 μs). Generally, 200–300 J per tooth are delivered in total for the two laser applications combined. (F) Flaps secured to tooth and bone with fibrin clot. No sutures needed. (G) Occlusal adjustment to relieve trauma and remove damaging forces. (H) Anticipated healing. (LANAP® is patented and a registered trademark of Millennium Dental Technologies, Cerritos, CA, USA).

thermal damage to the underlying periodontal tissues during Nd:YAG laser irradiation, which would affect postoperative wound healing. This requires proper understanding and training.

Clinical studies

According to evidence from basic studies, the wavelength characteristics of the Nd:YAG laser would favor its usage as an adjunctive tool. This has been verified by various practitioners, who have obtained satisfactory results when combining laser with mechanical instruments. However, clinical studies were limited until recently (165, 184, 196, 203), despite widespread usage of the wavelength. In particular, studies indicating positive clinical effects of this laser beyond conventional treatment are few in number.

The American Academy of Periodontology-commissioned review in 2006 by Cobb (50) reported that at that time there was insufficient evidence to suggest that any specific wavelength of laser is superior to the traditional modalities of therapy. Current evidence suggests that use of Nd:YAG or Er:YAG lasers for treatment of chronic periodontitis may be equivalent to scaling and root planing in terms of reduction in probing depth and subgingival bacterial populations. Also, a recent systematic review conducted in 2009 by Slot et al. (299) analyzed the effect of pulsed Nd:YAG laser as monotherapy or adjunctive to scaling and root planing in nonsurgical periodontal therapy, and suggested that there is no evidence to support the superiority of the Nd:YAG laser mono/combination therapy over traditional nonsurgical modalities of periodontal therapy.

However, quite recently, Qadri et al. (227, 229) clearly demonstrated that scaling and root planing in combination with a single application of a water-cooled Nd:YAG laser at 4 W (80 mJ/pulse, 50 Hz, a pulse duration of 350 μs), using a fiber diameter of 600 μm, significantly improved clinical signs associated with periodontal inflammation, such as probing pocket depth and gingival crevice fluid volume at 3 and 20 months, compared with treatment with scaling and root planing alone. Also, interleukin-1beta and matrix metalloproteinase-8 levels in gingival crevice fluid were significantly reduced after 1 week, and radiographic examination revealed significantly less marginal bone loss 20 months after treatment with laser plus scaling and root planing compared with treatment with scaling and root planing alone. Thus, a single application of water-cooled Nd:YAG laser in combination with scaling and root planing had a positive long-term effect on periodontal health compared with treatment with scaling and root planing alone. Gomez et al. (104) compared scaling and root planing with scaling and root planing plus Nd:YAG laser (the laser therapy was performed 1 day after scaling and root planing) and reported that although there were no statistically significant differences in clinical or microbiological variables between scaling and root planing and scaling and root planing plus Nd:YAG laser treatment, the levels of interleukin-1beta and tumor necrosis factor-alpha in gingival crevice fluid were significantly lower after scaling and root planing plus Nd:YAG laser treatment than after scaling and root planing alone, 4 and/or 8 weeks after treatment. Furthermore, Eltas et al. (77) investigated the difference of the effects between scaling and root planing plus Nd:YAG laser and scaling and root planing alone. At 9 months, reduction of gingival index, probing pocket depth and clinical attachment level were significantly higher after scaling and root planing plus Nd:YAG laser treatment than after scaling and root planing alone. The levels of interleukin-1beta and matrix metalloproteinase-8 in gingival crevice fluid after treatment were lower with scaling and root planing plus Nd:YAG laser treatment. They concluded that in the long term, scaling and root planing plus Nd:YAG laser treatment was more effective than scaling and root planing alone. Nevins et al. (199) reported, in a prospective 9-month clinical case series of eight patients using the LANAP® protocol, substantial probing-depth reduction in 88% of sites (from 6.5 mm to 2.1 mm on average) and clinical attachment level gain in 74% of sites (from 7.4 mm to 5.8 mm on average) when probing depths were ≥5 mm. Their conclusion was that the majority of sites demonstrated clinical improvement. On the other hand, Slot et al. (300) reported that in residual pockets ≥5 mm, treated in a periodontal maintenance care program, the adjunctive use of an Nd:YAG laser (4W) did not provide a clinically significant additional advantage. Thus, some recent studies indicate a beneficial effect on wound healing after adjunct usage of the Nd:YAG laser in nonsurgical pocket therapy; however, a consensus has not yet been reached.

Diode laser

As a result of their potential to perform curettage as well as to reduce periodontal pathogenic bacteria, diode lasers have been used in a protocol similar to the adjunctive protocol of Nd:YAG. Borrajo et al. (42) examined the effect of scaling and root planing combined with diode laser (indium-gallium-arsenide-phosphide [InGaAsP] 980 nm) in comparison with scaling and root planing alone. At 6 weeks, scaling and root planing plus laser showed significantly greater improvements in papilla bleeding index and bleeding on probing than did scaling and root planing alone, but clinical attachment level change was similar for both treatments. Kreisler et al. (148) compared scaling and root planing plus diode laser (gallium-aluminum-arsenide [GaAlAs] 809 nm) with scaling and root planing plus saline irrigation, and reported that at 12 weeks, scaling and root planing plus laser revealed a significantly higher reduction in tooth mobility, pocket depth and clinical attachment level than did scaling and root planing plus saline irrigation. They speculated that the higher reduction in tooth mobility and probing depth is probably not predominantly related to bacterial reduction in periodontal pockets but rather to the de-epithelialization of the periodontal pockets, leading to enhanced connective tissue attachment. They concluded that diode laser application is a safe clinical procedure that can be recommended as an adjunct to conventional scaling and root planing. Kamma et al. (124) compared the effect of scaling and root planing combined with diode laser (980 nm) treatment, scaling and root planing alone and diode laser treatment alone in patients with aggressive periodontitis. The scaling and root planing plus laser group showed a statistically significantly lower total bacterial load and lower levels of *P. gingivalis* and *Treponema denticola* 6 months post-treatment compared with scaling and root planing or laser treatment alone. Significant differences were also observed for probing pocket depth and clinical attachment gain between the scaling and root planing plus laser group and both the scaling and root planing-alone and laser-alone groups. They suggested that diode laser-assisted treatment with scaling and root planing was superior to scaling and root planing or laser alone in terms of certain microbial and clinical parameters in patients with aggressive periodontitis over the 6-month monitoring period. Dukic et al. (72) reported that compared with scaling and root planing alone, multiple adjunctive applications of a diode laser (980 nm) with scaling and root planing showed probing pocket depth improvements only in moderate periodontal pockets (4–6 mm) at 18 weeks. Saglam et al. (253) reported that the use of a diode laser (940 nm) as an adjunct to scaling and root planing produced significant improvements in whole-mouth clinical parameters, including probing pocket depth and clinical attachment gain, after 6 months compared with conventional treatment and also that scaling and root planing plus laser treatment was more effective than scaling and root planing alone in reducing the gingival crevice fluid matrix metalloproteinase-8 levels at the first month, suggesting epithelial involvement in healing in response to laser treatment. On the other hand, De Micheli et al. (65) compared scaling and root planing plus diode laser (808 nm) treatment with scaling and root planing alone and reported that the clinical probing depth and the clinical attachment level showed significantly more improvement in the scaling and root planing group after 6 weeks when compared with the scaling and root planing plus laser group. They concluded that the high-power diode laser adjunct to the nonsurgical periodontal treatment did not promote effects additional to those produced by the conventional periodontal treatment. Euzebio Alves et al. (80) also reported that after 6 months of evaluation, the diode laser (808 nm) did not demonstrate any additional benefits over conventional periodontal treatment.

With respect to the combination with antimicrobial photodynamic therapy, Giannelli et al. (99) reported that diode laser treatment with photoablation, followed by multiple photodynamic cycles (once weekly, 4–10 applications), adjunctive to conventional scaling and root planing, significantly improved healing compared with scaling and root planing alone, after 1 year, in patients with chronic periodontitis.

According to a recent systematic review of the meta-analysis of nine eligible publications, undertaken in 2014 by Slot et al. (298), the collective evidence regarding adjunctive use of a diode laser with scaling and root planing indicates that the combined treatment provides an effect comparable with that of scaling and root planing alone. With respect to bleeding scores, the results showed a small, but significant, effect favoring the diode laser; however, the clinical relevance of this difference remains unknown. The systematic review questions the adjunctive use of diode laser with traditional mechanical modalities of periodontal therapy in patients with periodontitis and the strength of the recommendation for the adjunctive use of the diode laser is considered to be 'moderate' for changes in probing pocket depth and clinical attachment level. Thus, the effect of adjunctive use of diode lasers remains controversial.

CO_2 laser

The CO_2 laser is not appropriate for root debridement, as both calculus and the root surface are instantly carbonized by this laser when used with high-energy output in a continuous-wave mode (328). However, when used with relatively low energy output in a pulsed and/or defocused mode, the CO_2 laser may potentially exhibit root conditioning, detoxification and bactericidal effects on contaminated root surfaces (35, 53, 59). As this laser does not have a suitable system for delivery into periodontal pockets, its nonsurgical usage is limited and clinical application into periodontal pockets has not been reported so far. Only one report, by Miyazaki et al. (184), indicated that CO_2 laser irradiation on the external surface of the marginal gingiva for pocket treatment resulted in decreased inflammation and probing depth after treatment.

Er:YAG and Er,Cr:YSGG lasers

Unlike other hard lasers, erbium lasers are capable of ablating subgingival calculus effectively without causing significant thermal damage on the root surface by reacting with the water contained within the structural micropores as well as in intrinsic components of the calculus (16, 19, 22, 322). Numerous *in vitro* and *in vivo* studies reporting the effect of an Er:YAG laser for calculus removal and root-surface debridement have been summarized in detail in previous reviews (22, 116, 265). At present, it is generally accepted that the Er:YAG laser can be used for nonsurgical periodontal treatment without producing any major side effects and complications, if the proper irradiation conditions are observed (22, 50, 51, 116, 264, 265). Currently, the Er:YAG laser is used both as an alternative and an adjunct to mechanical therapy for pocket treatment in clinical practice (22, 116, 265). However, the superiority of erbium lasers has not yet been clearly demonstrated. In addition, there are still some concerns regarding the clinical application of these lasers. As visualization is very limited, calculus detection and judgement of completion of removal during subgingival scaling is still dependent on the tactile sensation with the contact tip and periodontal probe and the accuracy has not been established completely in Er:YAG laser monotherapy (74). Use of a novel detection system for subgingival calculus using the fluorescence induced by diode lasers has been proposed (279); however, the clinical efficacy of the system has not yet been clearly demonstrated. With respect to the biocompatibility of intact root cementum or dentin, which incurred slight thermal and morphological changes following irradiation with an Er:YAG laser, the effect of the resulting microstructure on cell attachment was not consistent, favorable (41) or not favorable (175) between studies, and the positive effect of additional root-surface treatment to improve the biocompatibility of the Er:YAG laser-irradiated cementum has been demonstrated *in vitro* (175). However, *in vitro*, Er:YAG laser irradiation of diseased root surfaces seems to offer improved fibroblast adherence compared with mechanical scaling alone (37, 82, 266). As detailed histological evidence of periodontal tissue attachment to Er:YAG-lased root surfaces is limited (270), further *in vivo* studies are necessary to clarify questions and solve these problems.

Clinical studies

In 1996, Watanabe et al. (336) first reported the safety and utility of Er:YAG laser therapy for subgingival calculus removal in nonsurgical pocket therapy. Later, in 2001, Schwarz et al. (281) performed the first randomized controlled trial on Er:YAG laser application in periodontal pocket treatment and reported similar or better results in terms of reduction of bleeding on probing and pocket depth, and improvements in clinical attachment level, when comparing conventional scaling and root planing therapy with Er:YAG laser therapy. These results were maintained for 2 years (278). Schwarz et al. (277) also reported that additional scaling and root planing on the laser-treated root surface seemed to be unnecessary following laser therapy alone because no additional improvement of clinical outcomes were detected. Sculean et al. (285) reported equal clinical improvements following therapy with an Er:YAG laser and ultrasonic scaling. Crespi et al. (60) demonstrated significantly higher probing depth reduction and clinical attachment level gain with Er:YAG laser treatment compared with ultrasonic scaler treatment, 2 years after therapy. Tomasi et al. (324) evaluated the effect of an Er:YAG laser in supportive periodontal therapy and reported less patient discomfort during the procedure and faster probing depth reduction and clinical attachment level gain after 1 month of Er:YAG laser treatment compared with ultrasonic scaling, although 4 months later, there were identical treatment outcomes.

According to a systematic review in 2008 undertaken by Schwarz et al. (264), the Er:YAG laser seems to possess characteristics most suitable for nonsurgical treatment of chronic periodontitis; however, the research conducted so far has indicated that its safety and effects might be expected to be within the range reported for conventional mechanical debridement. In a recent review paper incorporating a meta-analysis published in 2012, Sgolastra et al. (289) investigated the efficacy of Er:YAG laser monotherapy in the treatment of chronic periodontitis. The paper reported that no statistically significant differences between Er:YAG laser and scaling and root planing treatments were found in any of the clinical parameters investigated in the five randomized controlled trials (166, 250, 278, 281, 285) entered into the study, indicating no evidence of superior effectiveness of Er:YAG laser therapy compared with scaling and root planing. They concluded that future long-term, well-designed randomized controlled trials are needed to assess the scientific evidence for Er:YAG laser efficacy as an alternative treatment strategy to scaling and root planing. Badran et al. (33) compared scaling and root planing with Er:YAG laser therapy and demonstrated a statistically significant superiority of the Er:YAG laser only for clinical attachment level scores after 2 months. They suggested that Er:YAG laser therapy may serve as an alternative to mechanical treatment in the management of chronic periodontitis and that Er:YAG laser irradiation may be performed on patients who are sensitive to the use of injectable anesthetics. Krohn-Dale et al. (157) compared pocket debridement using an Er:YAG laser with ultrasonic scaler/curettes at 3-month intervals in maintenance patients who were smokers with recurring chronic inflammation. After 12 months, no significant between-treatment differences were shown in clinical parameters or microbiological analysis. The results failed to support the superiority of Er:YAG laser therapy over conventional debridement in the treatment of smokers with recurring chronic inflammation.

With regard to combined therapy, Rotundo et al. (250) recently compared supragingival debridement, scaling and root planing plus Er:YAG laser, Er:YAG laser, and scaling and root planing, and reported that 6 months after therapy, the adjunctive use of an Er:YAG laser with conventional scaling and root planing was not more effective than scaling and root planing alone. Lopes et al. (166) also reported that Er:YAG laser monotherapy and laser therapy combined with scaling and root planing were effective in nonsurgical treatment, but they did not present clinical benefits compared with scaling and root planing alone. The microbiological evaluation at 12 months showed that compared with scaling and root planing alone, scaling and root planing plus laser treatment reduced the prevalence of sites with *Aggregatibacter actinomycetemcomitans*, *P. gingivalis* and *Prevotella nigrescens*, and laser treatment alone reduced the prevalence of *A. actinomycetemcomitans* and *P. gingivalis*. They suggested that nonsurgical periodontal treatment with an Er:YAG laser may serve as an alternative treatment for reduction and control of the proliferation of microorganisms in persistent periodontitis. On the other hand, Kelbauskiene et al. (133) compared scaling and root planing alone with scaling and root planing plus Er,Cr:YSGG laser therapy. They reported that, after 12 months, the mean probing depth reduction and clinical attachment level gain were significantly greater and bleeding on probing was significantly less after scaling and root planing plus laser therapy than after scaling and root planing alone. They suggested that the adjunct application of an Er,Cr:YSGG laser appeared to be more advantageous in nonsurgical periodontal therapy. Thus, the evidence obtained to date on the usage of an Er:YAG laser indicates that Er:YAG laser monotherapy and traditional scaling and root planing exhibit comparable results for wound healing. Regarding the adjunct usage, a consensus has not been reached yet because of the limited number of studies and wide variation in irradiation methods and/or experimental conditions.

Wound healing and regeneration in nonsurgical therapy

The effectiveness of high-level laser application for nonsurgical pocket therapy in comparison with conventional mechanical tools has been reported in several clinical studies (116, 265). However, positive histological results have been very limited to date in terms of wound healing/tissue regeneration and have only been demonstrated in humans for the Nd:YAG laser. Yukna et al. (351) reported a case series of six patients in which LANAP® using the Nd:YAG laser (3.6 W) was associated with cementum-mediated new connective tissue attachment and periodontal regeneration on all six previously diseased root surfaces after 3 months. Nevins et al. (200) also performed full-mouth LANAP® therapy using an Nd:YAG laser (4W) in eight patients presenting with 12 teeth predetermined to be surgically extracted. After 9 months of healing, 10 teeth were analyzed histologically to assess the periodontal wound healing. Five teeth demonstrated a degree of periodontal regeneration with new cementum, periodontal ligament and alveolar bone, one tooth had new attachment with new cementum and inserting collagen fibers and four teeth healed via a long junctional epithelium, providing further evidence that LANAP® therapy can induce periodontal regeneration. Clinical applications of LANAP® provide promising results (Fig. 9). Also, Schwarz et al. (270) observed that Er:YAG laser therapy used with water irrigation seemed to stimulate new cementum formation after pocket irradiation in dogs. The histological evidence is still limited, but adjunctive or alternative use of lasers in periodontal pocket therapy may have the potential to promote wound healing with more periodontal tissue regeneration than that stimulated by conventional mechanical treatment alone.

Nonsurgical high-level laser therapy may provide a more comprehensive method of treatment by achieving more extensive decontamination and detoxification of both root and soft-tissue walls of periodontal pockets including bone defects (22, 23). In addition, the simultaneously exerted low-level laser effect might modulate cell metabolism, stimulate and promote gingival- and bone-cell proliferation and differentiation, alleviate the inflammatory process and improve wound healing/regeneration of periodontal tissues (23).

Based on this hypothesis, Aoki (15) introduced an effective approach of the Er:YAG laser-assisted comprehensive periodontal pocket therapy (Er-LCPT) (Fig. 10). One of the patients treated with this method is presented in Fig. 11. The main concept of this comprehensive procedure has already been published (23). In this treatment, comprehensive debridement and photobiomodulation of the inside of the pocket (22, 23) are performed using mechanical instruments in combination with the Er:YAG laser. This therapy includes removal of lining epithelium (106, 111) and diseased connective tissue in the pocket inner wall and vertical bone defect (22, 23), and removal of epithelial and/or connective tissue on the external surface of the gingiva.

Laser treatment inside the pocket aims to improve healing by thorough decontamination and debridement, as well as to increase bleeding from the debrided bone surface into the pockets and bone defects, which would be advantageous for tissue regeneration. Epithelial tissue is removed from the external gingival surface to prevent downgrowth of the epithelial tissue caused by immediate collapse of the epithelial end at the pocket entrance into the hollow space of the debrided pocket as well as to delay epithelial tissue migration into the pocket during healing (46, 248). At the same time, external gingival ablation produces an ablated rough surface, which may enhance retention of the blood clot formed at the pocket entrance. Final defocused irradiation coagulates blood (91, 168) at the pocket entrance, which may stabilize blood clot formation, assure its sealing of the pocket entrance and also may activate the blood clot (25, 91) and surrounding gingival tissue. The applicability of the Er:YAG laser to treat bone tissue facilitates this comprehensive pocket treatment. This therapy is not a nonsurgical procedure but rather a surgical one in nature and could be considered as flapless surgery (50). This

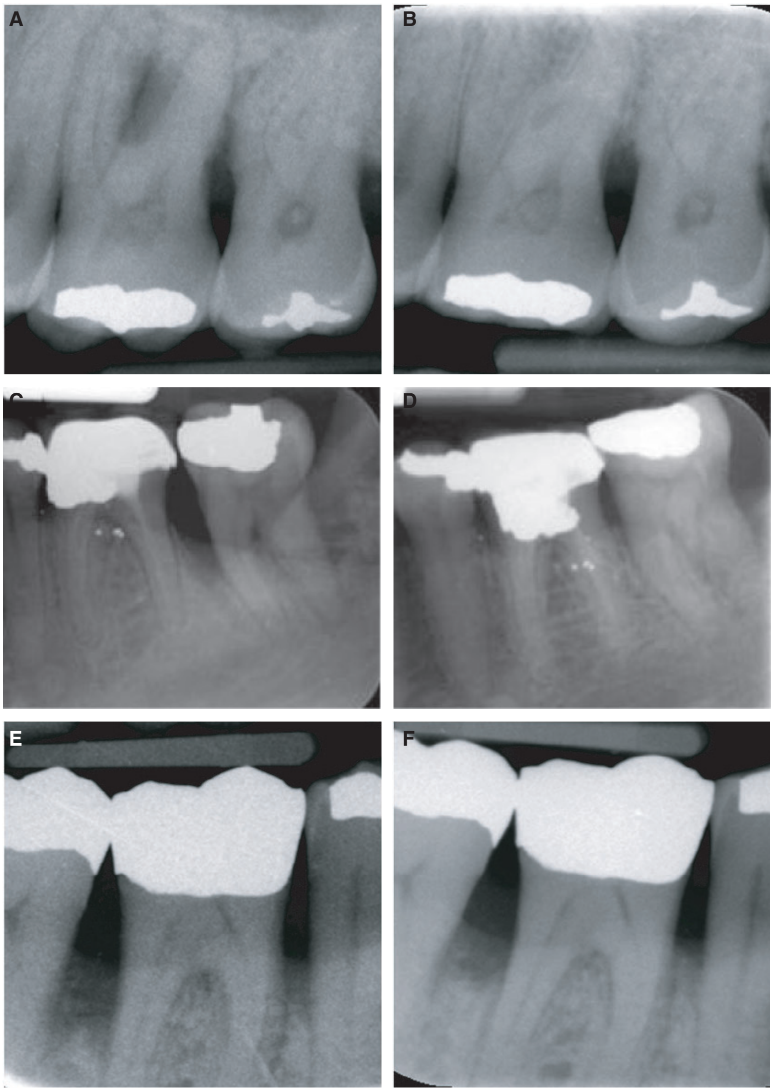


Fig. 9. **Clinical application of the Laser-Assisted New Attachment Procedure® (LANAP®) using a neodymium-doped yttrium-aluminium-garnet (Nd:YAG) laser. (A, B) A 59-year-old systemically healthy man with generalized moderate/severe chronic periodontitis. (A) Severe chronic periodontitis was observed at the maxillary left first molar showing a probing depth of 9 mm distally, bleeding on probing, and Grade I and II furcation involvement. The pretreatment dental radiograph demonstrates distally and in the furcation bone loss. (B) The 3-year post-treatment radiograph shows favorable bone repair on distal and furcation. The probing depths were successfully reduced to <3 mm with no bleeding on probing, only Grade I clinical furcation involvement and no mobility. (C, D) A 46-year-old woman with osteoporosis treated with oral bisphosphonate for 2 years. (C) Localized severe chronic periodontitis was detected at the mandibular left second molar showing 10-mm probing depths circumferentially around the tooth, bleeding on probing, facial and lingual Grade II furcation involvements and Class 3 (depressible) mobility. The pretreatment dental radiograph demonstrates deep angular bony defects and furcation bone loss. (D) The 1-year post-treatment radiograph shows favorable bone repair with a small residual defect distally. The probing depths were successfully reduced to 3–4 mm with no bleeding on probing, no clinical furcation involvement and no mobility. (E, F) A 52-year-old man with slight hypertension and cholesterolemia diagnosed with generalized moderate/severe chronic periodontitis. (E) Severe chronic periodontitis was detected at the mandibular right second premolar and the first molar, showing a probing depth of 9 mm distal to the second premolar and of 10 mm distal to the first molar, bleeding on probing and Class 1 mobility in both teeth. The pretreatment dental radiograph demonstrates deep intrabony defects for both teeth. (F) An 18-month post-treatment radiograph shows favorable bone repair on both teeth with a small residual bone defect distal to the first molar. The probing depths were reduced to 4 mm distal to the second premolar and 5 mm distal to the first molar with no bleeding on probing and no mobility (Case details provided by Raymond A. Yukna).**

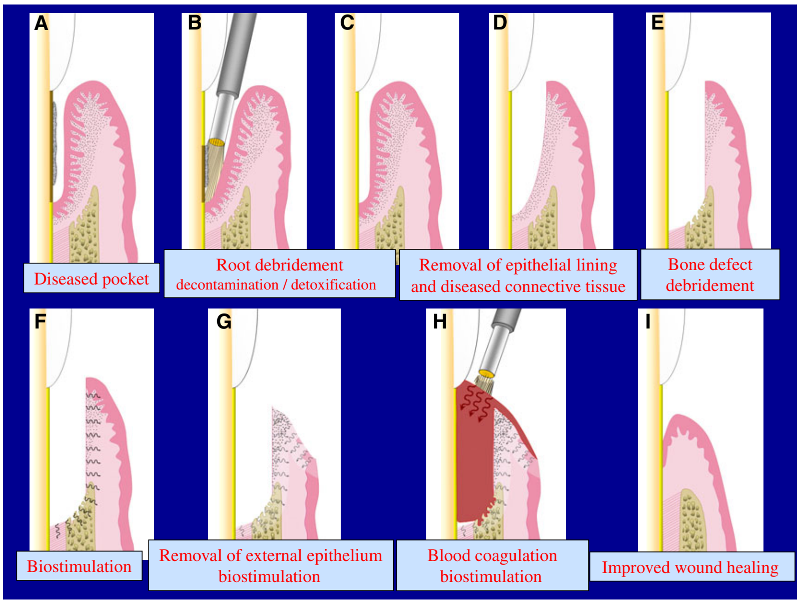


Fig. 10. Schematic illustration of the procedures of erbium-doped yttrium-aluminium-garnet (Er:YAG) laser-assisted comprehensive periodontal pocket therapy (Er-LCPT). (A) Advanced periodontal pocket showing gingival tissue detachment, subgingival calculus deposition and contamination of the tooth-root surface, epithelial down-growth and lining of the inner surface of diseased gingival connective tissue with inflammation, vertical bone resorption and diseased connective tissue formation in the bone defect. (B, C) Laser-assisted debridement (or laser-only debridement) following mechanical instrumentation (curettes and ultrasonic scalers) of the diseased root surface for removal of the deposited subgingival calculus and decontamination and detoxification of the root surface. (D, E) Ablation of lining epithelium and diseased connective tissue on the inner surface of the gingival tissue as well as diseased connective tissue in the vertical bone defect during pocket irradiation for comprehensive treatment, which aims for thorough decontamination of the whole pocket and increased bleeding in the bone defect from the bone surface, which may be advantageous for tissue regeneration. Adjunctive use of a mini-curette and/or a mini bone curette is helpful for completion of this procedure. (F) Expected simultaneous photobiomodulation effects activating the surrounding gingival and bone tissues from the inside by penetration of a low-level laser during pocket irradiation. (G) Laser ablation of epithelial tissue from the external gingival surface. Depending on the case, the underlying connective tissue is also ablated to some extent, helping in pocket-depth reduction. Removal of epithelial tissue intends to prevent the down-growth of the epithelial tissue as a result of the immediate collapse of the epithelial end at the pocket entrance into the hollow space of the debrided pocket. Removal of the inflamed epithelial and connective tissues on the external surface may result in rapid reduction of the inflamed condition. Exposure of connective tissue delays epithelial tissue migration from the external surface into the pocket, and production of the ablated rough surface enhances retention of the blood clot formed at the pocket entrance, thereby assuring sealing of the pocket entrance. At the same time, stimulation of the surrounding gingival tissue from the external surface is expected by simultaneous low-level laser penetration during high-level laser irradiation. (It is acceptable to remove external epithelial tissue as well as connective tissue before debriding the inside of the pocket.) (H) Blood clot coagulation at the pocket entrance by defocused irradiation without water spray, which may stabilize blood-clot formation and sealing of the pocket entrance and may also activate the blood clot and surrounding gingival tissue. Use of diode lasers may be more advantageous for blood coagulation at deeper sites in the pocket than use of the Er:YAG laser. (I) Favorable pocket healing with gingival connective tissue attachment and bone tissue regeneration. The above procedure should be used for moderate/advanced periodontal pockets as a flapless surgery. This treatment concept can also be applied to peri-implant mucositis or the initial stage of peri-implantitis. [Modified pictures from Aoki et al. Photobiomodulation laser strategies in periodontal therapy. Proceedings of Light-Activated Tissue Regeneration and Therapy II, Springer pp.181–190, 2008; with permission. © copyright (2008) Springer Science and Business Media, LLC (23)].

procedure can be also applied for the treatment of peri-implant mucositis and initial peri-implantitis.

Recently, a similar treatment procedure using the Er,Cr:YSGG laser was described by Kelbauskiene et al. (133) and also an excellent treatment outcome for the case series using minimal invasive surgery to treat the remaining periodontal pockets following scaling and root planing was reported by Dyer & Sung (73). They observed that in the 7–9 mm probing depth group, the mean probing depth and the mean clinical attachment level successfully improved from 7.5 ± 0.6 mm and 7.6 ± 0.6 mm at baseline to 3.7 ± 1.2 mm and 3.6 ± 1.2 mm at 2 years, respectively. They concluded that the Er,Cr:YSGG laser is an effective, minimally invasive surgical modality for the treatment of moderate to advanced periodontal diseases, resulting in significant clinical improvement that was maintained for at least 2 years post-treatment. Also, a procedure similar to the above report has been advocated as Deep Pocket Therapy™ by Biolase Inc. (39). Furthermore, considering the relatively strong penetration/scattering effect of the deeply penetrating lasers, the photobiomodulation effect of those lasers would be stronger than that of the shallow-penetrating laser types and thereby the deeply penetrating lasers may offer advantages for enhancement of wound healing/tissue regeneration in periodontal pocket therapy if the major thermal side effects are minimized. Therefore, if properly used, the combination of the debridement effect of erbium lasers (Er:YAG or Er, Cr:YSGG) and the photobiomodulation effect of deeply penetrating lasers (Nd:YAG or diode) might offer a new strategy for more effective promotion of wound healing in nonsurgical therapy.

Summary

As discussed above, there is still controversy regarding the use of lasers as either an adjunctive or a stand-alone nonsurgical periodontal therapy, and several questions remain unanswered about their effects (51). In 2011, the American Academy of Periodontology (1) published a statement on the efficacy of lasers in the nonsurgical treatment of inflammatory periodontal disease. It was stated that there is minimal evidence to support the use of a laser for the purpose of subgingival debridement, either as a monotherapy or adjunctive to scaling and root planing. Therefore, further well-designed clinical studies based on the most suitable wavelength for each treatment procedure are necessary to identify effective and reliable laser therapies with clear clinical benefits in periodontal pocket treatment. Based on the current evidence, lasers should not be used universally in all cases of periodontal pockets but specifically for moderate to advanced or difficult cases of periodontitis, as well as recurring, remaining or persistent periodontal pockets in supportive periodontal therapy (22). Also, with the recent emergence of antimicrobial photodynamic therapy, use of antimicrobial photodynamic therapy and combination therapy of laser and antimicrobial photodynamic therapy may be required for evaluation.

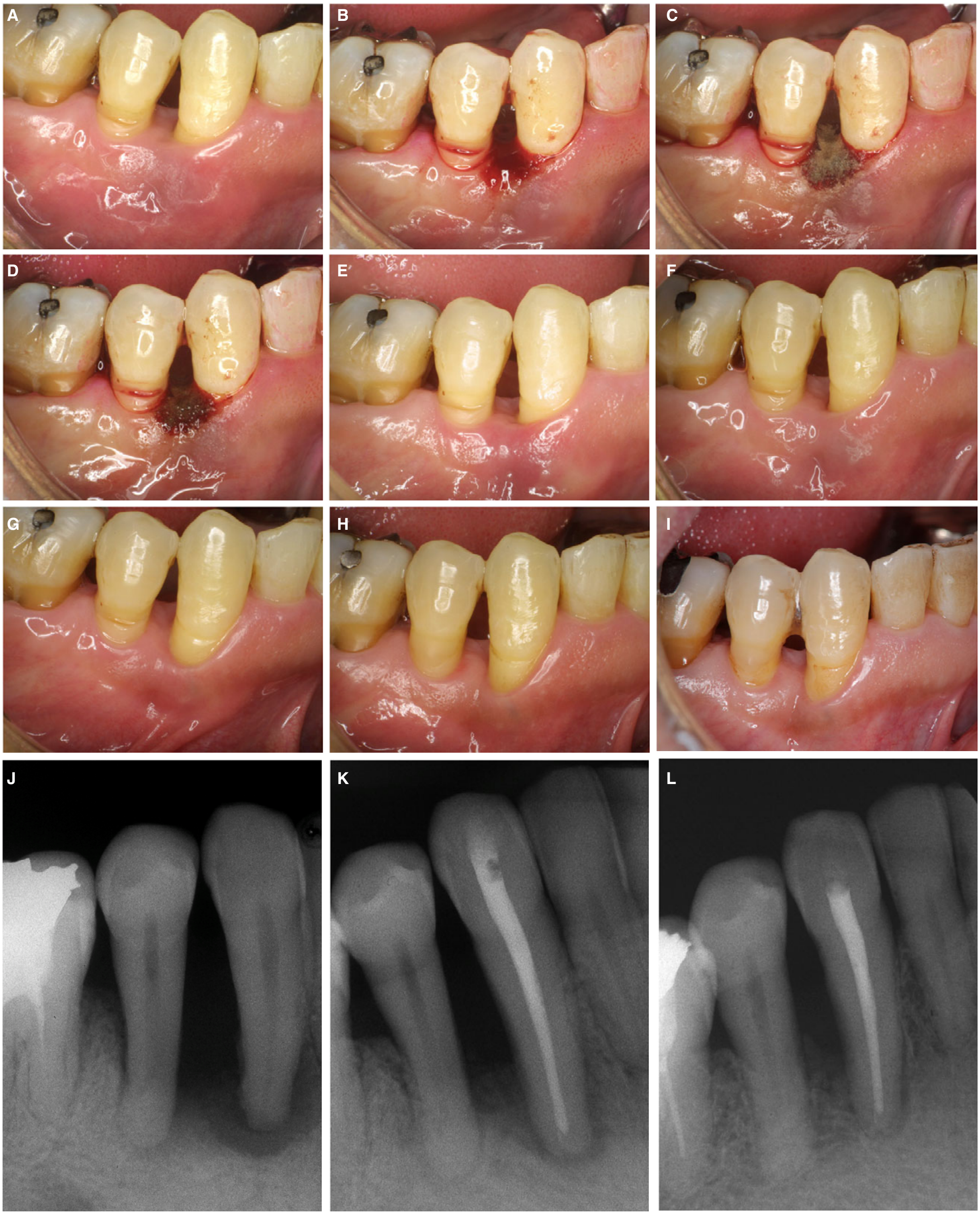
Surgical pocket therapy

Recently, the use of lasers has been gradually introduced as an adjunct or alternative tool in surgical therapy. Basically, lasers are expected to facilitate root-surface and bone-defect debridement using various small and delicate shaped contact tips, which can access narrow and/or deep intrabony and furcation defects more easily than conventional instruments. In addition to the practical advantages, biological effects are expected with laser therapy, which may accelerate wound healing/tissue regeneration following surgical procedures because of their specific characteristics such as bactericidal and detoxification effects as well as photobiomodulation effects. Hard-tissue lasers – Er:YAG and Er,Cr:YSGG – are the most promising and widely employed for root-surface and bone-defect debridement during surgery (22, 116, 264). However, *in vivo* and clinical studies regarding wound healing/tissue regeneration are still limited.

In vivo studies

Williams et al. (340) histologically examined the healing response of alveolar bone in dogs with chronic periodontitis following removal of granulation and/or connective tissue from interproximal craters by manual curettage or ablation with a CO_2 laser. CO_2 laser-treated specimens exhibited areas of heat-induced tissue necrosis, accumulation of carbonized debris that was initially surrounded by macrophages and eventually phagocytized by multinucleated giant cells, spicules of nonvital bone that exhibited a surface layer of osteoid and little or no inflammatory cell infiltrate. The superficial zone of thermal necrosis was 50–180 μm in width in connective tissue and 40–120 μm in bone tissue underlying the 30- to 100-μm-wide zone of devitalized bone with thermal damage lacking osteocytes in lacunae. New-bone formation in the laser-treated specimens was limited to bone surface areas that did not exhibit a charred surface. On days 21 and 28, the heat-damaged and necrotic bone layers persisted and showed no signs of osteoclastic or osteoblastic activity, or reattachment of new connective tissue. Thus, the use of CO_2 lasers for bone-defect debridement seems unsuitable because of the lack of connective tissue attachment as well as new-bone formation to a persistently charred bone surface.

Crespi et al. (61) applied the CO_2 laser in a defocused pulsed mode for the treatment of experimentally induced Class III furcation defects in dogs



following flap surgery. Based on the potential conditioning, detoxification and bactericidal effects of low-level CO_2 laser therapy, the laser was applied at a low energy output in a defocused mode to the contaminated root surfaces and periodontal soft tissues followed by ultrasonic instrumentation to clean the charred surfaces. The results indicated that laser treatment promoted the formation of greater amounts of new periodontal ligament, cementum and bone tissue, compared with both guided tissue

Fig. 11. Clinical application of erbium-doped yttrium-aluminium-garnet (Er:YAG) laser-assisted comprehensive periodontal pocket therapy (Er-LCPT) in a 58-year-old man. Before treatment (A), a 13-mm-deep periodontal pocket (attachment level: 15 mm) with bleeding on probing was detected at the distal site of the mandibular right canine (March 2008). First of all, endodontic treatment was performed because of the presence of a perio-endo lesion. Initial periodontal therapy using an Er:YAG laser was performed before the planned regenerative surgery. The root surface was debrided by curette, ultrasonic scaler and Er:YAG laser, and the inner surface of the gingival wall and the bone defect were debrided by curette, micro-bone curette and Er:YAG laser. Granulation tissue removal, root-surface and bone-defect debridement, and epithelial tissue removal were effectively and safely performed using an Er:YAG laser at 30–40 mJ/pulse (panel setting 60–80 mJ/pulse) and 30 Hz in contact mode under water spray with 80° curved contact tips of diameter 400 and 600 μm (energy density 14.2–23.9 J/cm^2/pulse). The buccal view immediately after pocket treatment, as well as removal of external epithelial tissue, shows bleeding without major thermal changes (B). Then, the pocket entrance, as well as the surrounding gingival tissue, were repeatedly irradiated in noncontact, defocused mode without water spray and the blood was superficially coagulated and slightly carbonized (C). The coagulated blood was stable after mouth rinsing and the pocket entrance was effectively sealed (D). After 1 and 2 weeks (E and F, respectively), wound healing was favorable and epithelialization was complete. Then, wound healing progressed uneventfully without any clinical complications. At 5 months, the gingival recession progressed slightly and a pocket depth of 6 mm (attachment level: 8 mm) with bleeding on probing was observed (G); however, at around 9 months, the pocket was reduced to 3 mm (attachment level: 6 mm) without bleeding on probing and regenerative surgical therapy was postponed. Supportive therapy was initiated. After 1.5 (H) and 5 (I) years, the condition was maintained and finally the pocket was reduced to 2 mm (attachment level: 6 mm) without bleeding on probing. Pocket reduction of 11 mm and clinical attachment gain of 9 mm were obtained (resin splinting was performed after 2 years). Dental radiographs show that the original bone resorption at the first visit was severe and horizontal (J). After 8 months (K) and 5 years (February 2013) (L), bone regeneration gradually progressed and the bone defect was successfully repaired to some extent but the vertical increase was limited; however, no adverse side effects are observed in the irradiated bone tissue (case details provided by Akira Aoki).

regeneration procedures and scaling and root planing. Rossmann et al. (247–249) proposed a novel surgical technique using the CO_2 laser. The technique aims to retard the apical migration of the epithelium of gingival tissue and thereby to increase the amount of connective tissue attachment after flap surgery by de-epithelializing gingival flaps with the CO_2 laser. First, they (247) used the CO_2 laser for gingival de-epithelialization in a monkey and confirmed complete epithelial destruction with little or no disturbance of the underlying connective tissue layer and viable connective tissue below the impact site. Then, they (249) tried this technique during flap surgery in monkeys and the histological evaluation of the lased sites showed a delay in epithelial migration down the root surface compared with the control sites. They concluded that the CO_2 laser may be a useful tool to retard epithelium and thereby enhance new connective tissue attachment.

Mizutani et al. (185) investigated the effect of the Er:YAG laser for granulation tissue removal and root-surface debridement in flap surgery in dogs. In this study, bilateral premolars with experimentally induced periodontitis in the furcation were treated using an Er:YAG laser or Gracey curettes. With the Er:YAG laser, degranulation and root-surface debridement could be effectively performed in the furcation without visible thermal damage to the root or bone surfaces. In the histological examination 3 months postsurgery, no anomalous structures, such as bone or pulp necrosis, or carbonization (as would be caused by laser irradiation) were observed in any specimen. At both laser and curette sites, periodontal soft-tissue attachment with some degree of bone regeneration was noted in the furcation area. Interestingly, new-bone formation was significantly more pronounced in the laser-treated group than in the curette group (Fig. 12), although equal amounts of connective tissue attachment and cementum formation were observed for both laser and curette sites.

Regarding the lased bone tissue, immediately after laser surgery, a thin affected layer of approximately 5–10 μm in thickness was detected on the irradiated bone surface and was uniformly found on the whole root surface. At 3 months postsurgery, the layer in the bone tissue was scarcely detectable at the bottom of the original bone defect. In only one specimen was the remaining affected layer observed at the interface between the original and the newly formed bone. However, it seemed that this layer is eventually absorbed during the bone-remodeling process (Fig. 13). It is speculated that most of the affected bone tissue was resorbed by bone remodeling during the wound-healing process. Regarding the lased root surface, at 3 months postsurgery, the affected layer still remained on the root dentin surface in the area of epithelial attachment. By contrast, in the area of connective tissue attachment, most of the layer was resorbed and newly formed

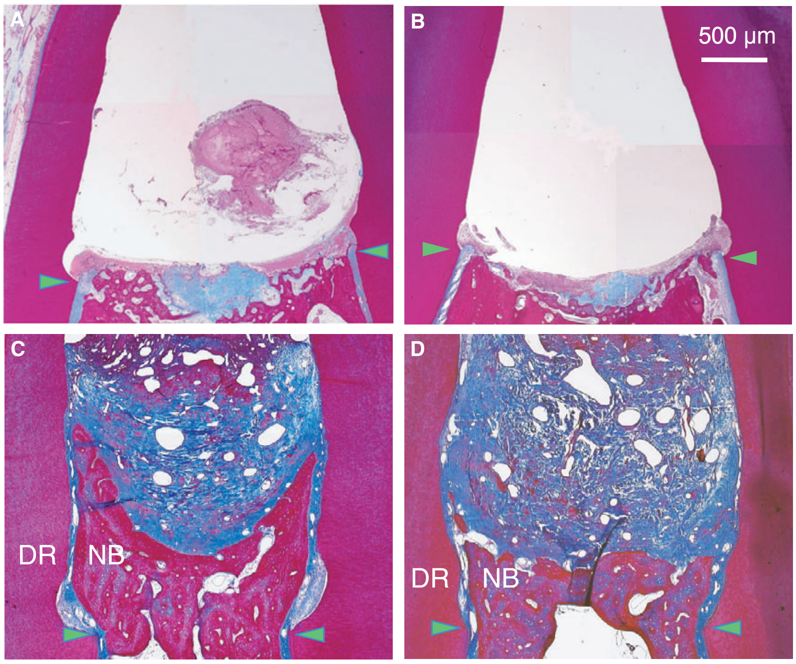


Fig. 12. Application of an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser in periodontal flap surgery in dog. Photomicrographs of mesio-distal sections of the furcation, immediately (A, B) and 12 weeks (C, D) after surgery. The debridement was performed above the notch (arrowheads) using an Er:YAG laser (A) or a hand curette (B). After 12 weeks, in both laser (C) and curette (D) sites, periodontal tissue attachment with bone formation was observed. The newly formed bone (NB) extended along the dental root surface (DR) in the defect. Note the greater amount of new-bone formation in the laser-treated site than in the curette-treated site. (Azan stain, original magnification ×27). [Photomicrographs c and d from Mizutani et al. Periodontal tissue healing following flap surgery using an Er:YAG laser in dogs. *Lasers Surg Med* 38:314–324, 2006; with permission. Lasers in Surgery and Medicine © copyright (2006) John Wiley & Sons, Inc (185)].

cementum with numerous resorption lacunae was observed (Fig. 14). In the site where the affected layer partially remained, the new cementum had directly formed on the remaining affected layer. The ratio of the length of the remaining affected layer vs. the length of connective tissue attachment was 16.9% (an average value calculated from six dogs). In such sites, detachment of new cementum from the remaining affected layer was observed in the decalcified histological specimens (Fig. 14). The cementum detachment was partially observed in both laser- and curette-treated sites, although the length of detachment was generally shorter in the curette-treated site. Thus, this study demonstrated effective and safe granulation tissue removal and root debridement using an Er:YAG laser as well as the potential to promote new-bone formation in flap surgery.

There are several explanations for the increased bone formation (316): thorough granulation tissue removal (185, 316) with high decontamination (6, 13, 155) and detoxification efficiency (343); more pronounced bleeding originating from the bone defect following debridement (185, 316); and the microstructural topography of bone and root surfaces following laser irradiation (19), which enhances blood clot retention (45, 223, 258). In addition, the suggested biostimulatory effect of the low-level Er:YAG laser (8, 224) may have promoted new-bone formation, as reported for other lasers (136, 181, 194, 202).

Clinical studies

Regarding the de-epithelialization technique using a CO_2 laser during and after flap surgery, Israel et al. (121) reported (in a pilot histological human study) that in all control teeth of two patients, the junctional epithelium extended the entire length of the root to the base of the reference notch; however, in the laser-treated teeth of one patient, the notch was filled with connective tissue and limited repair cementum, which was not seen in any control tooth. Centty et al. (46) demonstrated that a CO_2 laser effectively eliminated sulcular and gingival

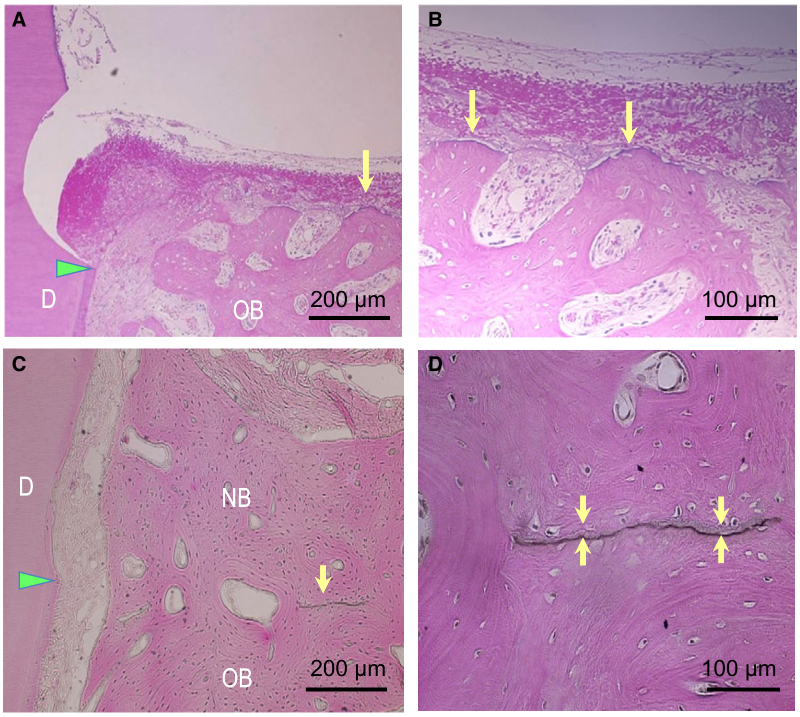


Fig. 13. Photomicrographs of a histological section showing the healing process of an erbium-doped yttrium-aluminium-garnet (Er:YAG)-lased bone tissue. Immediately after laser surgery, a thin affected layer (arrow heads) was locally detected on the bone surface (A,B). After 3 months, the layer was scarcely detectable in the bone tissue. In only one specimen (C) was the remaining affected layer detected between original and newly formed bone. However, it seems that this layer is eventually absorbed during the bone-remodeling process (D). D, dental root; NB, new bone; OB, old bone. arrows: original bottom level of bone defect. (Hematoxylin-eosin stain; A and C: original magnification ×100; B and D: original magnification ×200). [Photomicrograph c from Mizutani et al. Periodontal tissue healing following flap surgery using an Er:YAG laser in dogs. Lasers Surg Med 38:314–324, 2006; with permission. Lasers in Surgery and Medicine © copyright (2006) John Wiley & Sons, Inc (185)].

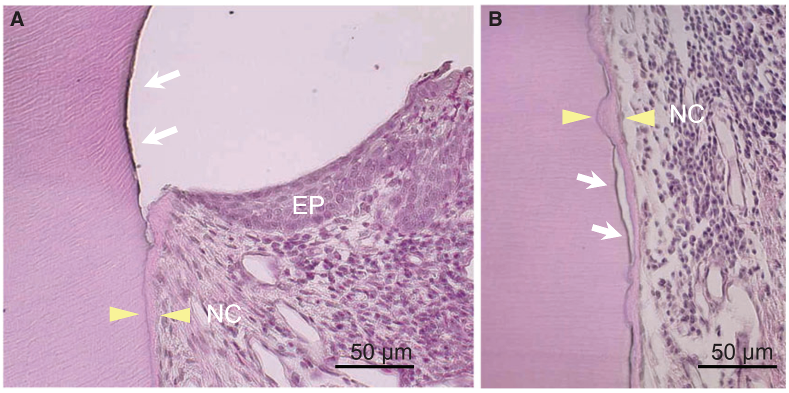


Fig. 14. Photomicrographs of histological sections showing attachment of the newly formed cementum to the erbium-doped yttrium-aluminium-garnet (Er:YAG)-lased root surface. In the area of the epithelial attachment, the affected layer (arrows) mostly remained. On the lased root surface, most of the layer had disappeared and newly formed cementum with numerous resorption lacunae (arrowheads) were observed (A). Occasionally, a thin affected layer partially remained and the new cementum had directly formed on the remaining changed layer. In such sites, detachment of new cementum from the remaining affected layer (arrows) was detected in the decalcified sections (B). EP, epithelium; NC, new cementum. (Hematoxylin-eosin stain; bar = 50 μm, original magnification ×200.) [Photomicrographs from Mizutani et al. Periodontal tissue healing following flap surgery using an Er:YAG laser in dogs. *Lasers Surg Med* 38:314–324, 2006; with permission. Lasers in Surgery and Medicine © copyright (2006) John Wiley & Sons, Inc (185)].

external epithelium without disturbing underlying connective tissue at the time of flap surgery. Rossmann & Israel (248) reported, in case studies, that the greatest gain in attachment level occurred in intrabony defects treated with an osseous graft in conjunction with the de-epithelialization technique. The de-epithelialization technique using a CO_2 laser seems promising; however, the real benefit of this technique has not yet been demonstrated by randomized controlled trials.

In the application of laser to periodontal flap surgery, Choi et al. (48) examined the effect of the additional use of CO_2 laser irradiation on the root surface during flap surgery and reported that the clinical attachment level and crevicular interleukin-1beta level were significantly lower in the 0.8 W laser-applied group than in the nonirradiated control group, although the differences in clinical parameters between the groups were not significant. Dilsiz et al. (70) reported that in a clinical study using enamel matrix proteins, Nd:YAG laser root conditioning did not improve the outcome of application of enamel matrix proteins compared with ethylenediaminetetraacetic acid root conditioning.

Gokhale et al. (102) used a diode laser to remove the pocket lining on the undersurface of the flap as an adjunct to open flap debridement compared with conventional flap surgery in a split-mouth study design. Although the difference between the clinical parameters in the test and control groups did not reach statistical significance, there was a statistically significant reduction in the number of colony-forming units of obligate anaerobes in the test group compared with the control group. Sanz-Moliner et al. (256) investigated the effect of the additional use of a diode laser (810 nm) for de-epithelializing the inner part of the periodontal flap and photobiostimulating the surgical area during flap surgery. They reported that the use of a diode laser provided additional benefits to flap surgery in terms of less edema and postoperative pain.

Regarding the Er:YAG laser, Sculean et al. (286) reported that application of the Er:YAG laser in the treatment of periodontal intrabony defects with access flap surgery is effective and safe, with significant clinical improvements apparent at 6 months following surgery; however, laser treatment was as effective as mechanical debridement alone. Gaspirc & Skaleric (95) reported the long-term clinical outcome of Er:YAG laser-assisted periodontal flap surgery. The results indicated that the laser surgery resulted in greater probing depth reduction and clinical attachment gains for up to 3 years compared with conventional flap surgery. Schwarz et al. (280) confirmed that regeneration therapy using an enamel matrix protein derivative was equally effective on a root surface irradiated with the Er:YAG laser when compared with the conventional procedure using enamel matrix protein derivative with ethylenediaminetetraacetic acid root conditioning. Yung (352) reported, in a case series, that periodontal surgery can be performed safely by Er:YAG laser therapy with no collateral damage and that weaker coagulation produced by Er:YAG laser than that by other lasers may be preferable for better wound healing. Accordingly, although evidence is still limited in the application of an Er:YAG laser for surgical debridement, the Er:YAG laser not only facilitates the debridement procedure in flap surgery but also might be advantageous for tissue repair and regeneration (Fig. 15).

Summary

Currently, based on review of the literature, erbium lasers are the most promising laser device for periodontal flap surgery as an alternative or adjunctive therapy to conventional mechanical modalities. During periodontal surgery, erbium laser application for granulation tissue removal as well as root-surface debridement seems to be safe and effective, yielding results equal, or even superior, to those of conventional mechanical methods. The technical equality or superiority of lasers in surgical pocket therapy, and the possibility to enhance the outcomes of conventional flap surgery as well as regenerative surgery with lasers, requires further study.

Osseous surgery

Conventionally, mechanical rotary instruments and hand instruments are employed for osseous surgery. Hand instrumentation minimizes tissue damage (113); however, access is limited and efficiency is low. Rotary instruments have better accessibility and cutting efficiency, but there is a risk of excessive heating of bone tissue and caution must be exercised to avoid the bur becoming entangled with surrounding soft tissues and the reflected flap. In addition to conventional tools, ultrasonic instruments have recently been effectively used for incision and resection in osseous surgery (159, 261). For many years, lasers have been studied as a potentially viable tool for osseous management because of advantages such as better access, precise and easy ablation, improved healing induced by photobiostimulation as well as the lack of noise and vibration that is usually associated with mechanical cutting and grinding during bone ablation. However, the collateral thermal side effects produced by lasers have been a major concern.

Wound healing following bone surgery with CO_2 and Nd:YAG lasers

Previous histological studies have shown that irradiation with continuous-wave CO_2 and pulsed Nd:YAG lasers produce severe heat-related collateral tissue damage, such as coagulation necrosis, loss of collagen fiber, carbonization (charring) and/or microfractures (86, 147, 178, 223, 257, 258). The laser-altered bone tissue seems to be a result of the extremely high temperature rise during bone tissue ablation. CO_2 and Nd:YAG laser-induced osteotomy defects, when compared with those obtained by rotary bur, exhibit a delayed healing response, which is probably related to the presence of residual charred tissues in the osseous defect (86, 178, 301). The carbonized tissue remaining on the lased bone has inherent toxic substances, such as cyanamide or cyanate (258). The presence of those toxins, as well as the lack of proteins in the carbonized tissue, could interfere with the healing process by affecting osteogenic cell attachment (86). Also, the carbonized layer may be resistant to resorption by phagocytosis and thereby acts as a physical barrier that interferes with the exposure of the biocompatible, intact bone surface. With the Nd:YAG laser, even the use of water/air coolant still produces laser-altered tissue and delays wound healing in bone (86, 178). The results reported to date on bone surgery have shown that the wound-healing process could be markedly delayed by continuous-wave CO_2 and pulsed Nd:YAG lasers. Therefore, at present, these lasers are not employed for bone surgery in periodontal and peri-implant therapy.

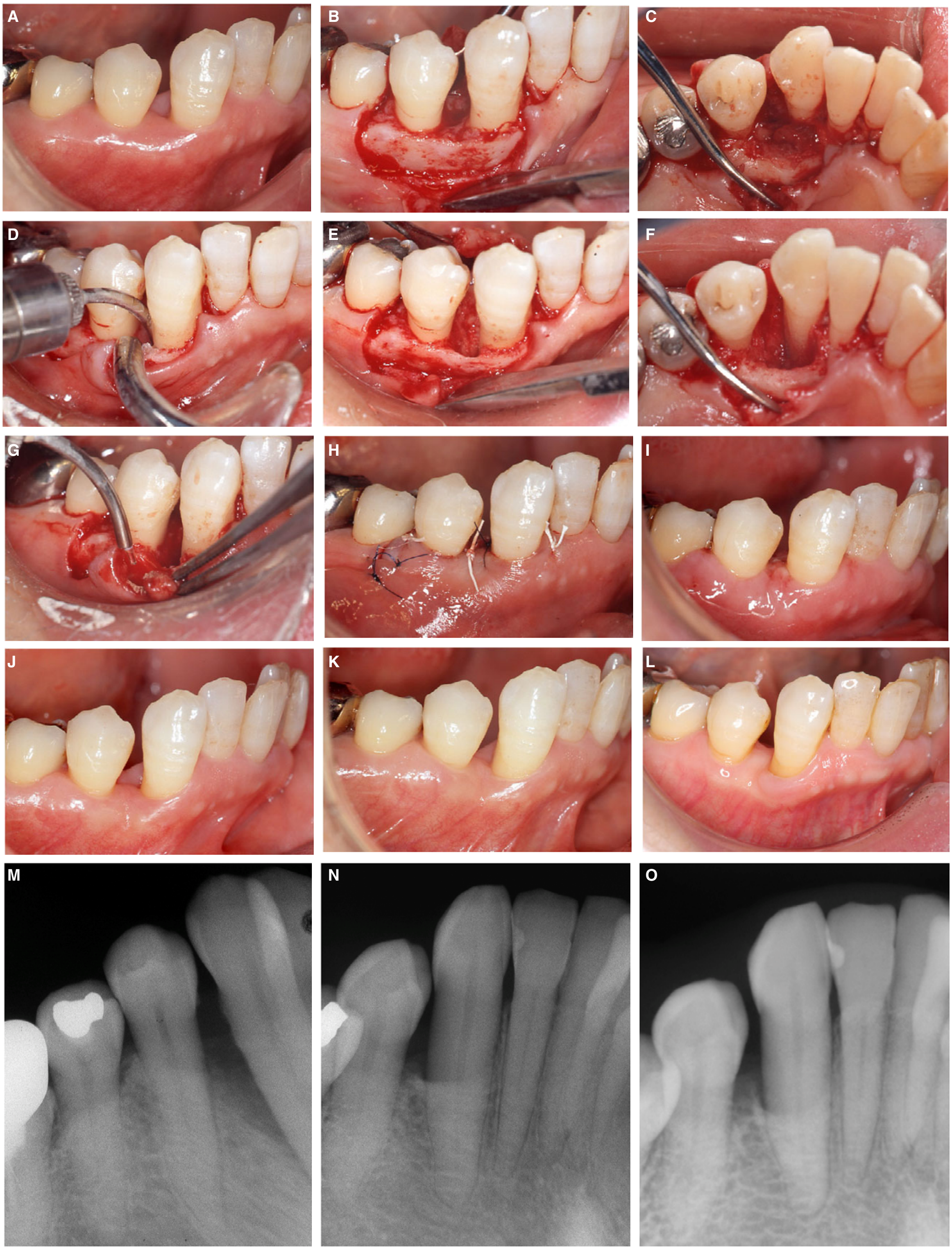
Erbium laser bone ablation and properties of the laser-irradiated bone tissue

The Er:YAG laser (2,940 nm) and the Er,Cr:YSGG laser (2,780 nm), when used with saline water cooling, can effectively ablate bone tissue with minimal thermal changes (125, 141, 257, 258, 335) (Fig. 16). Even without water cooling, Er:YAG laser irradiation produces no visible major thermal damage of bone tissue (348). Histologic and scanning/transmission electron microscopy analysis revealed an affected layer of about 5–30 μm in thickness, with a microstructured surface and irregular borders, permeated with microfractures on the bone surface following Er:YAG laser irradiation with or without water cooling (198, 204, 257, 334, 348). Regarding the presence of osteocytes, Lewandrowski et al. (163) reported that the extent of thermal damage at the osteotomy sites was similar to that of bur drilling and that the extent of thermally damaged nonvital bone (i.e. the distance from the osteotomy site to the presence of vital osteocytes) ranged from 25 to 100 μm in both laser and mechanically cut bone specimens. Sasaki et al. (257) demonstrated that the laser-affected layer consisted of two distinct sublayers: a superficial, greatly altered layer; and a deep, less-affected layer. They (258) also reported that the bone tissue surface ablated with the Er:YAG laser under water coolant was free of toxic substances and that the laser-modified layer had a decreased concentration of organic components. This layer has been also described as an amorphous, mineral-rich carbon layer (75). Therefore, the affected layer produced by Er:YAG laser irradiation without major thermal side effects is considered to be harmless with regard to bone healing. However, it is not clear whether such loss of organic components, in itself, could have any influence on bone healing.

Wound healing following erbium laser bone ablation

To date, a relatively large number of studies have examined the healing process after osteotomy using the Er:YAG laser. Nelson et al. (197) reported an initial study of bone ablation with the Er:YAG laser without water cooling, which indicated delayed healing after laser-assisted bone surgery compared with saw osteotomy. Buchelt et al. (43) reported that Er:YAG laser osteotomy showed less callus formation than saw osteotomy 4 weeks after surgery. Also, el Montaser et al. (75) reported that bone infilling of the lased defect was delayed because the amorphous, mineral-rich carbon layer was resistant to resorption.

On the other hand, most of the recent *in vivo* studies indicate that the healing outcomes following Er:YAG or Er,Cr:YSGG laser osteotomy with water cooling are comparable with (49, 134, 163, 304, 311, 335), or even better than (64, 219, 223), those obtained by conventional mechanical osteotomy. Lewandrowski et al. (163) demonstrated no difference between irradiation with an Er:YAG laser and drilling in the amount of newly formed bone at the osteotomy site in rat mandible, and that the extent of thermal dam-



age at the osteotomy sites was comparable in laser and mechanically cut bone fragments. Pourzarandian et al. (223) and de Mello et al. (64) reported that the laser-treated site revealed faster new-bone formation than the bur-treated site in rat calvaria (Fig. 17). Stübinger et al. (311) demonstrated that Er:YAG laser

Fig. 15. Clinical application of an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser in periodontal flap surgery (open flap debridement) in a 63-year-old woman. Before surgery (A), a 9-mm-deep periodontal pocket with bleeding on probing remained at the distal site of the mandibular right canine after initial treatment (January 2006). Buccal (B) and lingual (C) aspects following flap elevation. Granulation tissue removal and root-surface debridement were effectively and safely achieved by an Er:YAG laser alone at 40 mJ/pulse (panel setting 80 mJ/pulse, energy density: 14.2 J/cm^2/pulse) and 30 Hz (80° curved tip) in contact mode under saline water spray (D). After complete degranulation, a three-wall, large and deep vertical bone defect with a depth of 7 mm was observed and no visible major thermal damage, such as carbonization on the laser-treated root and bone surfaces, was detected (E, F). The inner surface of flaps was also ablated with the Er:YAG laser at 40 mJ/pulse and 30 Hz to decontaminate the surface with diseased granulation tissue and stimulate the gingival flap tissue (G). After suturing (H). Wound healing was uneventful without any clinical complications at 1 week (I), 3 months (J) and 1 year (K) postsurgery. Although gingival recession was observed, finally the probing pocket depth decreased to 2 mm without bleeding on probing; 7 mm of pocket reduction and 5 mm of clinical attachment gain was obtained at 8 years following surgery (February 2014) (L). The vertical bone defect on the distal site observed at the first visit (M) was successfully repaired by bone regeneration at 1 (N) and 8 (O) years. No adverse side effects were observed in the irradiated bone tissue (case details provided by Akira Aoki).

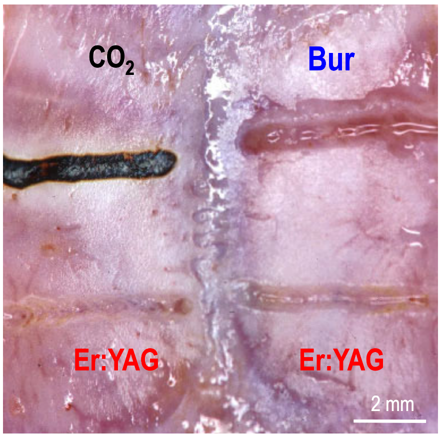


Fig. 16. Macroscopic view of the bone surface following treatment with a bur, an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser and a carbon dioxide (CO_2) laser. Irradiation with the Er:YAG laser was performed at an energy output of 100 mJ/pulse (35.4 J/cm^2/pulse) and 10 Hz (1 W) under saline-solution irrigation in contact mode. Irradiation with the CO_2 laser was performed at 1-W continuous wave without irrigation, in focused noncontact mode. Bur drilling produced a groove accompanied by the soft-tissue remnant on one edge. Irradiation with the Er:YAG laser also produced a groove with precise edges and without major thermal changes. In the CO_2-lased specimen, the tissue removal was minimal. However, the surface showed major carbonization. [Photographs from Sasaki et al. Scanning electron microscopy and Fourier transformed infrared spectroscopy analysis of bone removal using Er:YAG and CO_2 lasers. *J Periodontol* 73: 643–652, 2002; with permission. Journal of Periodontology © copyright (2002) American Academy of Periodontology (258)].

osteotomy could be successfully used in long bones in sheep and that subsequent wound healing was uneventful. Cloutier et al. (49) reported, in a study using rat calvaria, that the femtosecond and Er:YAG lasers were suitable for bone ablation and that they were comparable with mechanical instrumentation in terms of bone healing. Perussi et al. (219) reported that skull defects created with an Er,Cr:YSGG laser showed greater bone formation than defects created with a bur. However, quite recently, Martins et al. (174) reported that bone healing in rat mandibles was faster in bur ostectomy than in Er:YAG laser ostectomy.

Therefore, a consensus has not been reached regarding bone tissue healing after Er:YAG laser irradiation because of differences in the experimental design and irradiation conditions employed in the investigations. However, it appears that Er:YAG laser bone ablation does not affect the ensuing bone-healing process. The adhesion potential of laser-ablated surfaces is of special importance for regenerative and reconstructive treatments. Unlike the carbonized surfaces produced by irradiation with CO_2 and Nd:YAG lasers, the Er:YAG-lased, minimally affected microstructured surface without toxic substances undergoes favorable cell attachment and does not inhibit cell migration and proliferation on the lased surface, or granulation tissue formation in the bone defect (223) (Fig. 18). Also, the affected layer in the cancellous bone is resorbed during the bone-healing process and is replaced with newly formed bone (185) (Fig. 13). The micro-irregularities of the ablated surface are considered to be beneficial for bone healing, as they may promote entrapment of the initial components of blood, fibrin and red blood cells in the early healing process (223, 258) (Fig. 17). New bone was observed to be directly deposited on the lased surface, resulting in favorable repair of the defect (185, 219, 223, 348). Therefore, Er:YAG laser irradiation may be advantageous for faster and improved bone healing compared with conventional mechanical procedures (223). Some *in vivo* reports have indicated that the healing outcomes following Er:YAG laser osteotomy are better than those with mechani-

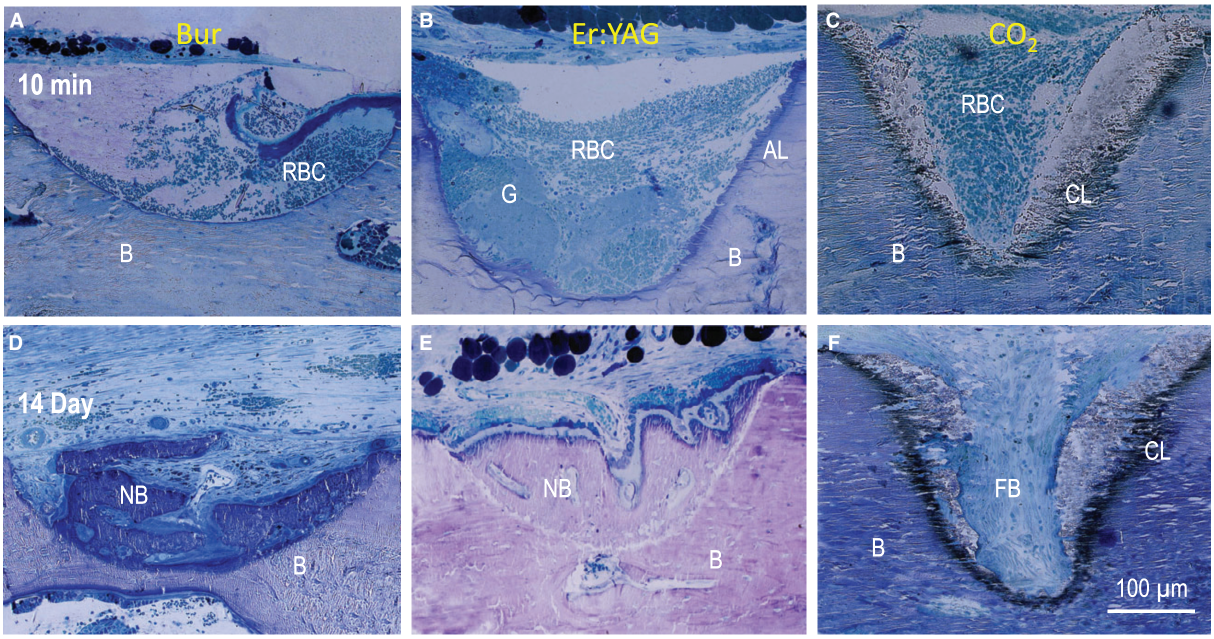


Fig. 17. Photomicrographs of a nondecalcified histological section following osteotomy with a bur, an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser and a carbon dioxide (CO_2) laser. Immediately afterwards (10 min after surgery), the mechanical bur-treated specimen exhibits a smooth and regular border on the treated bone surface and loosely aggregated red blood cells (A). The 10-min Er:YAG laser-treated specimen shows an irregular border and an affected layer (AL) on the treated bone surface and granular precipitate (G) and aggregation of red blood cells (RBC) in the defect (B). The 10-min CO_2 laser specimen demonstrates severe thermal changes of bone tissue with an irregular border and a carbonized layer (CL) on the surface and red blood cells (RBC) in the center of the groove (C). At 2 weeks postsurgery, the mechanical bur specimen demonstrates new-bone formation (NB) accompanied with osteoblasts (D). The 2-week Er:YAG laser specimen shows more favorable new-bone formation (NB) surrounded by osteoblasts and the remaining affected layer on the original bone surface (E). The 2-week CO_2 laser specimen reveals no new-bone formation and connective tissue repair with fibroblasts (FB) in the bone defect and the remaining carbonized layer (CL) (F). B, bone tissue. (Toluidine blue stain, original magnification ×200) [Photomicrographs from Pourzarandian et al. Histological and transmission electron microscopy examination of early stages of bone healing after Er:YAG laser irradiation. *Photomed Laser Surg* 22: 355–363, 2004; with permission. Photomedicine and Laser Surgery © copyright (2004) Mary Ann Liebert (223)].

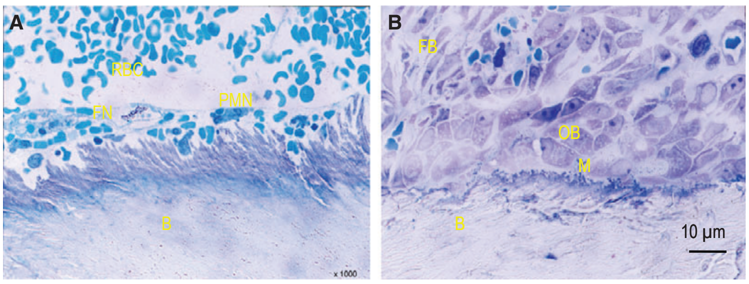


Fig. 18. Photomicrographs of a nondecalcified histological section, 6 h and 7 days following osteotomy with an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser. (A) The 6-h specimen shows red blood cell (RBC) aggregates interspersed in an organized fibrin network (FN) that is trapped by the irregular, serrated microstructure of the ablated bone surface. The irradiated surface shows an affected layer of about 15–20 µm in thickness, which consists of two distinct sublayers: a superficial, greatly altered layer; and a deep, less-affected layer. PMN, polymorphonuclear leukocytes. (B) The 7-day specimen shows cell-rich granulation tissue with clusters of osteoblasts (OB) and spots of mineralization (M) attached directly to the lased bone surface. B, bone tissue; FB, fibroblasts. (Toluidine blue stain, original magnification, ×1,000) [Photomicrographs from Pourzarandian et al. Histological and transmission electron microscopy examination of early stages of bone healing after Er:YAG laser irradiation. *Photomed Laser Surg* 22: 355–363, 2004; with permission. Photomedicine and Laser Surgery © copyright (2004) Mary Ann Liebert (223)].

cal tools (64, 219, 223). Interestingly, Kesler et al. (135) observed that Er:YAG laser irradiation appeared to stimulate the secretion of platelet-derived growth factor in osteotomy sites, and high levels of platelet-derived growth factor may partly contribute to the enhanced bone healing.

However, the affected layer formed in Er:YAG laser osteotomy may have some negative effects on healing. The new bone tissue appeared to detach from the affected layer in the decalcified histological sections, as a result of the fragile structure of the affected layer (348). Furthermore, the affected layer was retained for a long period in the cortical bone when this layer was embedded in the cortical bone tissue, which did not show active bone remodeling (348). These findings suggest that weak integration exists between the lased bone and new bone, which may compromise the longevity of the integration.

Clinical application of erbium lasers for osseous surgery

Er:YAG lasers have been successfully used for osseous surgery (3, 24, 161, 212, 309, 310, 312). Abu-Serriah et al. (3) used an Er:YAG laser to cut bone and tooth for removal of partially erupted lower third molars. They found that although laser surgery was more difficult and more time consuming, there was less postoperative pain and swelling, the cutting was less stressful and less unpleasant, and less prolonged pain was observed after laser treatment, compared with bur drilling. Aoki et al. (24) reported that an Er:YAG laser can be used safely and effectively for osseous recontouring in periodontal surgery (Fig. 19). Lee (161) reported that despite the increased surgical time, use of an Er,Cr:YSGG laser for harvesting ramus/buccal cortical plate grafts holds promise as

Fig. 19. Clinical application of the erbium-doped yttrium-aluminium-garnet (Er:YAG) laser in osseous surgery in a 68-year-old woman. Before surgery (A), a 4-mm-deep periodontal pocket with bleeding on probing remained at the mesial site of the maxillary right first premolar after initial treatment (the original probing depth was 8–9 mm) and open-flap debridement was performed to treat the remaining pocket (February 1998). After flap reflection, a sharp edge of the marginal bone of the one-wall bone defect was observed (B) and osteoplasty was performed with the Er:YAG laser. Bone ablation was effectively and safely achieved with the Er:YAG laser at 40–50 mJ/pulse (panel setting 80–100 mJ/pulse, energy density: 14.2–17.7 J/cm^2/pulse) and 10 Hz (80° curved tip) in contact mode under saline water irrigation (C). No visible major thermal damage, such as carbonization, was observed on the laser-treated bone surface (D). Wound healing was uneventful without any clinical complications and the probing pocket depth decreased to 3 mm without bleeding on probing at 4 months (E). Twelve years postsurgery (October 2010) (F), the periodontal pocket is stable without inflammation, although gingival recession has occurred (case details provided by Akira Aoki).

an alternative method to the high-speed surgical handpiece in osseous surgery. According to Stübinger et al. (309, 310), successful Er:YAG laser osteotomy can be performed for intra-oral bone-grafting procedures without any complications and with an uneventful wound-healing process. In addition, erbium lasers have been applied for flapless crown-lengthening procedures (57, 179). Recent reports also suggest that Er:YAG laser bone surgery may be a new therapeutic approach for the treatment of bisphosphonate-related osteonecrosis of the jaws (14, 305, 330). Various clinical applications of erbium lasers have been reported, but their low efficiency in cutting cortical bone remains a problem. If the ablation process could be accelerated, the Er:YAG laser would be a promising alternative to conventional instruments for osteotomy, even with cortical bone.

Summary

At present, continuous-wave CO_2 and pulsed Nd:YAG lasers are not used for bone surgery as these lasers result in inefficient bone ablation and major thermal damage, as well as delayed wound healing. Erbium lasers can effectively ablate bone tissue with minimal thermal damage and, to date, the clinical procedures have been successful. Based on evidence currently available, erbium-modified bone tissue seems not to interfere significantly with the healing process and treatment outcome. Therefore, treating bone surface during bone-defect debridement in flap surgery using erbium lasers is also accepted. However, the question of whether the affected layer of bone tissue after erbium laser ablation is beneficial, detrimental or innocuous to healing/remodeling/regeneration processes remains unanswered. Clinical studies showing improved bone healing/regeneration have not yet been reported; however, irradiation with an erbium laser may potentially enhance the process of bone regeneration and the molecular basis of the mechanism should be demonstrated more scientifically. Further studies may provide more detailed information on the biological response of bone tissue following laser surgery, particularly its effect on new-bone formation and integration with new bone and implant surfaces.

Implant therapy

Currently, the use of laser technology with implants offers a fascinating range of applications, starting from soft- and hard-tissue management during implant placement, reducing pain and inflammation, and promoting osseointegration and tissue regeneration (low-level laser therapy), to the treatment of peri-implant diseases during maintenance (265, 320).

Implant placement

Gingival tissue management and osseous surgery with lasers during implant placement have been studied. One of the major applications is uncovering the submerged implant for placement of the healing abutment in the second stage of a two-stage procedure. Laser soft-tissue management, such as gingivectomy and gingivoplasty, in this procedure, provides several advantages, such as better hemostasis, a fine cutting surface with less patient discomfort during the postoperative period, and favorable and rapid healing following abutment placement (27, 347). Lasers are also considered for various applications in osseous surgery, such as osteoplasty, fixture hole preparation, alveolar split osteotomy and lateral window opening during sinus lifting procedures.

Regarding implant site preparation, laser application has been considered in order to facilitate implant placement and achieve faster osseointegration and less bone tissue damage in comparison with conventional bur drilling (76, 134, 274). el-Montaser et al. (76) confirmed osseointegration of implants in channels prepared using an Er:YAG laser, in rat calvaria. Kesler et al. (134) reported that preparation of implant sites in the tibia of rats using an Er:YAG laser resulted in a significantly greater length of bone-to-implant contact in comparison with bur drilling. Salina et al. (255) reported that in comparison with the traditional drilling procedures in the tibia of rabbits, the Er:YAG laser can be considered efficient in bone surgery, without inducing irreversible damage, and that although the presence of some carbonized amorphous tissue was observed in the early part of the healing process, the tissue was progressively resorbed and did not impede the bone-formation and osseointegration processes. Schwarz et al. (274) reported, in dogs, that although the Er:YAG laser produced a significantly wider peri-implant gap compared with drilling, it caused no identifiable thermal side effects on the alveolar bone and did not compromise bone healing and osseointegration of titanium implants (Fig. 20). More recently, Stübinger et al. (304) prepared implant sites in sheep using an Er:YAG laser, or piezoelectric or drill osteotomy, and reported that although the initial response was less favorable in the laser group, at 8 weeks the osseointegration of titanium implants was comparable regardless of the sur-

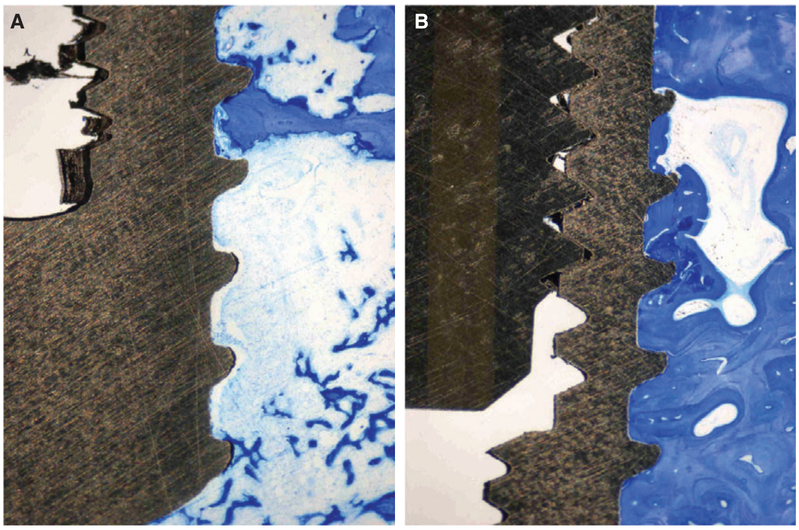


Fig. 20. Photomicrographs of a histological section showing wound healing following implant site preparation using an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser and the osseointegration of titanium implants in dogs. Irradiation with the Er:YAG laser was performed at focused mode at 300 mJ / pulse and15 Hz (spot size 0.2 mm, calculated energy density 35 J/cm^2 per pulse) with saline irrigation. After irradiation, clinically, no signs of any carbonization or melting were noted on the irradiated bone surface. Histological observation of the adjacent alveolar bone revealed no identifiable signs of any thermal side effects, such as carbonization, melting or cracking. While the laser-treated site was associated with wide peri-implant gaps at 2 weeks (A), postoperative wound healing progressed uneventfully, and ongoing and undisturbed trabecular woven bone formation was commonly observed at 12 weeks (B). Implants appeared to be surrounded by a firmly attached mature lamellar bone (Toluidine blue stain, original magnification ×40).

gical tool employed. Lee et al. (162) reported that the effects of bone bed preparation with an Er,Cr:YSGG laser on the relationship between implant stability quotient values and implant insertion variables were comparable with those of drilling in an *in vitro* study using pig rib bones. These studies demonstrated that the laser-prepared fixture holes exhibited safe wound healing and that, clinically, the laser-modified bone interface did not negatively affect the attachment between bone and the implant fixture. However, the results are still controversial, and a consensus could not be reached regarding the superiority of laser application in terms of the rate of osseointegration. Another drawback is that the preparation time for the Er:YAG laser is much longer than that required for conventional drilling (274). The risk of damage to the underlying nerves and blood vessels and perforation of the maxillary sinus during fixture hole preparation are also of concern. On the other hand, Luk & Seto (169) found, in their clinical case series, that Er:YAG laser conditioning of an osteotomy site prepared by conventional drilling could improve the early stability of implants. Also, application of low-level laser therapy has been expected to enhance the osseointegration of implants (see the section entitled 'Low-level laser therapy'). These findings suggest that lasers may be a promising tool for use in both the first and second stages of implant surgery. However, soft-tissue procedures in the second stage of two-stage therapies are still the main application of lasers during implant placement.

Peri-implantitis therapy

In vitro studies

In recent years, the increasing occurrence of peri-implantitis has become of great concern in implant therapy (353). "Cumulative Interceptive Supportive Therapy" was recently proposed by Mombelli & Lang (186) for the treatment of peri-implant diseases. Similarly to the treatment of periodontitis, decontamination of the infected sites around implant fixtures as well as the diseased fixture surfaces is the basic procedure; however, no instruments completely suitable for decontaminating fixture surfaces are available. In particular, as a result of the development of implant fixtures with various microstructured surfaces, their debridement with mechanical tools alone is problematic. Thus, an optimal treatment protocol with suitable instruments has not yet been established (79).

Recently, several researchers have focused on the application of lasers, and lasers are expected to play an important role in peri-implant therapy on the whole, because of their effective ablation and bactericidal and photobiomodulation effects. Tosun et al. (325) reported that the complete, or near complete, elimination of surface bacteria on titanium surfaces can be accomplished *in vitro* using a CO_2, diode or Er:YAG laser under appropriate circumstances. However, irradiation of titanium with an Nd:YAG laser at the standard energy settings is basically contraindicated because [in contrast to irradiation at a very low energy level (100)] at these settings this laser readily causes thermal reactions, such as melting, cracks and crater formation, on the titanium surface (153, 239) because of the moderate reflection rate (moderate absorption) on titanium (265) as well as the high pulse rate and high peak power in the standard irradiation protocols.

As a result of the high reflection rate of titanium to wavelengths of around 10 μm (265), irradiation with a CO_2 laser generally does not result in any morphological changes on the titanium surface and the CO_2-lased titanium surface does not affect osteoblast attachment (130, 235). However, generally there is a risk of temperature elevation on the titanium implant surface and carbonization of the adjacent bone tissue during CO_2 laser irradiation (151, 189, 207) and, depending on the irradiation parameters employed, melting and other surface alterations can arise, especially in the superpulse mode of CO_2 laser irradiation (68). When used at clinically applicable power densities of 2 and 4 W in a continuous mode for up to 4 s, the CO_2 laser did not cause a temperature change in excess of 7° F (3.9 °C) (93).

The diode laser does not damage the titanium surface either and this laser is capable of decontaminating rough implant surfaces (153, 239). However, this laser has the risk of heat generation on peri-implant bone tissue when used with improper irradiation parameters and techniques (156).

The Er:YAG and Er,Cr:YSGG lasers cause no visible changes to the titanium surface under appropriate irradiation conditions (176, 214, 275, 321), although irradiation at high energy levels produces distinct surface changes on titanium (176, 214, 306, 321) as a result of the moderate reflection rate on titanium (265). Matsuyama et al. (176) demonstrated that the use of water spray minimizes temperature elevations of titanium during Er:YAG laser irradiation, and Kreisler et al. (149) showed that there was no temperature elevation at the implant–bone interface during surface decontamination with the Er:YAG laser. The Er, Cr:YSGG laser can also be applied safely and effectively on the titanium surface (239, 273). Regarding the optimal irradiation conditions, Taniguchi et al. (321) reported that Er:YAG irradiation at pulse energies below 10.6 J/cm^2 per pulse and 30 Hz (pulse width 200 μs) with water spray in near-contact mode seems to cause no damage and appears to be effective for debriding microstructured surfaces. They also reported that irradiation with water spray reduced the carbon and oxygen contents of the microstructured surface. Moreover, recent *in vitro* data have indicated that the Er:YAG laser did not cause any visible surface alterations of zirconia ceramic; however, high penetration of the Er:YAG laser into this particular material was detected (308). The clinical impact of these findings needs to be elucidated further.

The Er:YAG laser is capable of effectively removing calculus and plaque from contaminated abutments (176) and microstructured surfaces (321) and removing biofilms grown on sandblasted and acid-etched titanium surfaces without producing injuries *in vitro* (282). The Er:YAG laser possesses a high bactericidal potential on implants with different surface characteristics, even when it is used at low energy densities (155). In particular, Schwarz et al. (282) reported that irradiation with an Er:YAG laser was most suitable for the removal of plaque biofilm on a sandblasted and acid-etched surface prepared in the oral cavity (mean residual plaque area: 5.8 ± 5.1%) compared with an ultrasonic system (28.3 ± 2.0%) or plastic curette plus chlorhexidine rinsing (61.1 ± 11.4%). However, all treatment methods failed to restore the biocompatibility of previously contaminated sandblasted and acid-etched titanium surfaces to the level of the noncontaminated control. Schwarz et al. (273) also reported that the Er,Cr:YSGG laser exhibited high efficiency in removing plaque biofilm from the contaminated sandblasted and acid-etched surface in an energy-dependent manner.

With regard to the biological compatibility of the Er:YAG-lased surface, Schwarz et al. (275) reported that irradiation with an Er:YAG laser did not affect osteoblast attachment on the titanium surfaces, whereas use of an ultrasonic scaler with a carbon fiber tip significantly decreased it. Kreisler et al. (154) reported that treatment of a *P. gingivalis*-contaminated microstructured titanium surface with an Er: YAG laser resulted in greater proliferation of fibroblasts on the surface compared with that in untreated specimens, which was similar to that in sterile specimens. Friedmann et al. (85) reported that Er:YAG laser treatment of sandblasted and acid-etched titanium implant surfaces contaminated with *P. gingivalis* produced new attachment of osteoblast cells, which was different from the nonlaser-treated control surfaces, on which no further attachment of osteoblast cells was observed. However, recently, Shin et al. (293) reported peeling of an anodic oxidized surface after Er:YAG laser irradiation. The anodized surface seems to have a specific structure and poor mechanical properties or structural weakness. Taniguchi et al. (321) also reported that the anodized microstructure was always removed with the Er:YAG laser, resulting in exposure of a fresh rough titanium surface, which was beneath the original microstructure, without thermal damage. Galli et al. (92) reported that Er:YAG laser irradiation to machined, sandblasted and acid-etched and titanium plasma-sprayed surface surfaces produced no or minimal alterations at the scanning electron microscopy level, but the irradiated surfaces negatively affected the viability and activity of osteoblastic cells attached on the surfaces.

Thus, erbium lasers generally show effective and safe application to microstructured titanium surfaces, except for anodized surfaces. However, the titanium microstructure can be affected by thermal effects induced by erbium laser irradiation. There are various important parameters associated with the concentration or accumulation of heat during irradiation: pulse energy; pulse repetition rate; amount of water spray; tip movement speed; pulse width; and, in particular, the considerably different energy-distribution profiles and intensities of the irradiation spot for different laser-delivery systems (fiberoptic, hollow waveguide and direct delivery) (321). Consequently, further detailed studies are still required to clarify the effects of these parameters on microstructured surfaces, as well as the influence of the irradiated titanium surfaces on biocompatibility, and to establish safe and reliable irradiation conditions of erbium lasers.

In vivo studies

Deppe et al. (68) reported that histologic examination, 4 months after surgical treatment of peri-implantitis in dogs, showed evidence of new direct bone-to-implant contact after CO_2 laser-assisted therapy, especially when the implants had been treated concomitantly with submerged membranes. They concluded that peri-implant defects could be treated successfully by CO_2 laser decontamination without damage to the surrounding tissues. Stübinger et al. (307) demonstrated that CO_2 laser decontamination of diseased implant surfaces in the surgical treatment of experimentally induced peri-implantitis in dogs produced significantly more new-bone formation, especially 5–8 weeks postoperatively, than did air–powder abrasive decontamination, although the beneficial effects could only be demonstrated for a limited period of time. In contrast, Persson et al. (218) reported that the use of CO_2 laser and hydrogen peroxide during surgical therapy had no apparent effect on bone formation and re-osseointegration.

Erbium lasers, in contrast to other hard lasers, are beneficial not only for fixture debridement but also for degranulation in the peri-implant bone defect, similarly to periodontal surgery (116, 232, 265, 284). In animal studies on surgical therapy of peri-implantitis, Schwarz et al. (271) reported that irradiation with an Er:YAG laser during flap surgery resulted in improvements in all parameters investigated, and that the Er:YAG laser seemed to promote re-osseointegration on contaminated implant surfaces to a greater degree than did plastic curettes plus metronidazole gel and ultrasonic devices in a circumferential crater-like bone defect. Histomorphometric analysis revealed comparably low amounts of new bone-to-implant contact (1.0–1.2%) at sites receiving nonsurgical treatment, and these values were significantly higher in the groups undergoing open flap surgery. In particular, mean bone-to-implant contact values ranged from 44.8% (Er:YAG laser) to 14.8% (mechanical debridement + local application of metronidazole) and 8.7% (ultrasonic device). Despite the lack of statistical significance, these data indicate that surgical treatment of peri-implantitis using an Er:YAG laser may be more suitable for promoting re-osseointegration at contaminated implant surfaces (Fig. 21). Takasaki et al. (316) also demonstrated that an Er:YAG laser tended to produce greater bone-to-implant contact than did curette treatment in flap surgery for experimentally induced peri-implant infection in dehiscence-type defects in dogs. In the histological analysis, at 6 months postsurgery, the newly formed bone was more coronally positioned on the laser-treated implant surface in comparison with mechanical treatment. The Er:YAG-lased implant surface seemed biocompatible and did not inhibit the formation of new bone and osseointegration (Fig. 22).

Clinical studies

The CO_2 laser is commonly applied for decontamination of implant surfaces (69, 236, 241). Deppe et al. (69) reported that the treatment outcome of peri-implantitis could be accelerated by using a CO_2 laser concomitant with soft-tissue resection during surgery. Romanos et al. (241) reported that decontamination of implant surfaces with a CO_2 laser, in combination with augmentative techniques, can be

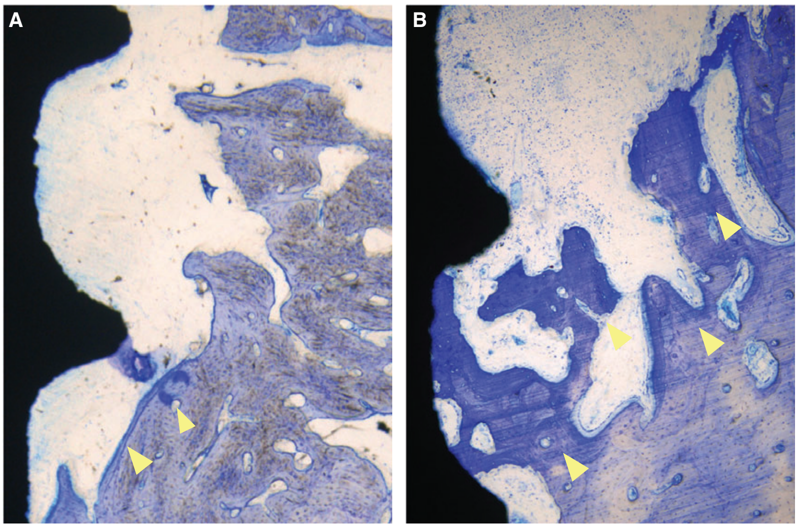


Fig. 21. Photomicrographs of a histological section showing peri-implant wound healing at 3 months following nonsurgical and surgical treatment of peri-implantitis lesions using an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser in dogs. Nonsurgically treated sites were not associated with new-bone formation or re-osseointegration (A). A certain amount of new-bone formation (arrowheads) and re-osseointegration was observed at surgically treated sites that were left to heal in a submerged position (B). No identifiable signs of any thermal side effects, such as carbonization, were detected. Arrows indicate the former defect borders (Toluidine blue stain, original magnification ×100).

an effective treatment method for peri-implantitis. Romanos et al. (236) also reported that a surgical protocol for implant surface decontamination using a CO_2 laser, grafting of the defect and coverage with a membrane appears to be promising and may improve the long-term clinical outcome of failing dental implants.

The nonsurgical application of an Er:YAG laser has been evaluated (267, 268, 283). Schwarz et al. (283) demonstrated that treatment with an Er:YAG laser led to significant clinical improvements 6 months after therapy, which were similar to conventional mechanical debridement using plastic curettes. The reduction of bleeding on probing was significantly higher in the Er:YAG laser treatment group. However, between 6 and 12 months after treatment, increased mean bleeding on probing scores and loss of mean clinical attachment level were observed at both laser and mechanically treated sites (267). In another clinical long-term study, Schwarz et al. (268) reported that although clinical improvements were achieved following 24 months of healing, the histopathological examination revealed the presence of a mixed chronic inflammatory cell infiltrate in the connective tissue stroma. Renvert et al. (230) compared the nonsurgical treatment effects of an air-abrasive device and Er:YAG laser monotherapy in patients with severe peri-implantitis. Six months after therapy, bleeding on probing and suppuration significantly decreased in both groups, but the clinical treatment results were limited and similar between the two methods. Persson et al. (217) reported the microbiologic effects of the nonsurgical treatment of peri-implantitis lesions using either an Er:YAG laser or an air-abrasive subgingival polishing method. At 1 month, the counts of *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus anaerobius* were reduced in the air-abrasive group and those of *Fusobacterium* spp. were reduced in the laser group. Six-month data demonstrated that both methods failed to reduce bacterial counts and that the clinical improvements were limited.

A systematic review of Muthukuru et al. (192), in 2012, reported that the available evidence suggested that Er:YAG laser treatment may reduce clinical signs of peri-implant mucosal inflammation to a greater extent relative to submucosal debridement using curettes with adjunctive irrigation with chlorhexidine. However, nonsurgical therapy does not always seem to be sufficient for complete healing of peri-implantitis sites (268), which indicates that, depending on the patient, a surgical approach may be necessary for the treatment of peri-implant lesions to achieve favorable clinical healing. Also, a systematic review by Kotsakis et al. (145) reported that based on the limited information currently available, any superiority of laser treatment over conventional treatment of peri-implantitis could not be identified. Considering the wide heterogeneity and the small number of included studies, nonsurgical laser therapy may be investigated as a Phase I

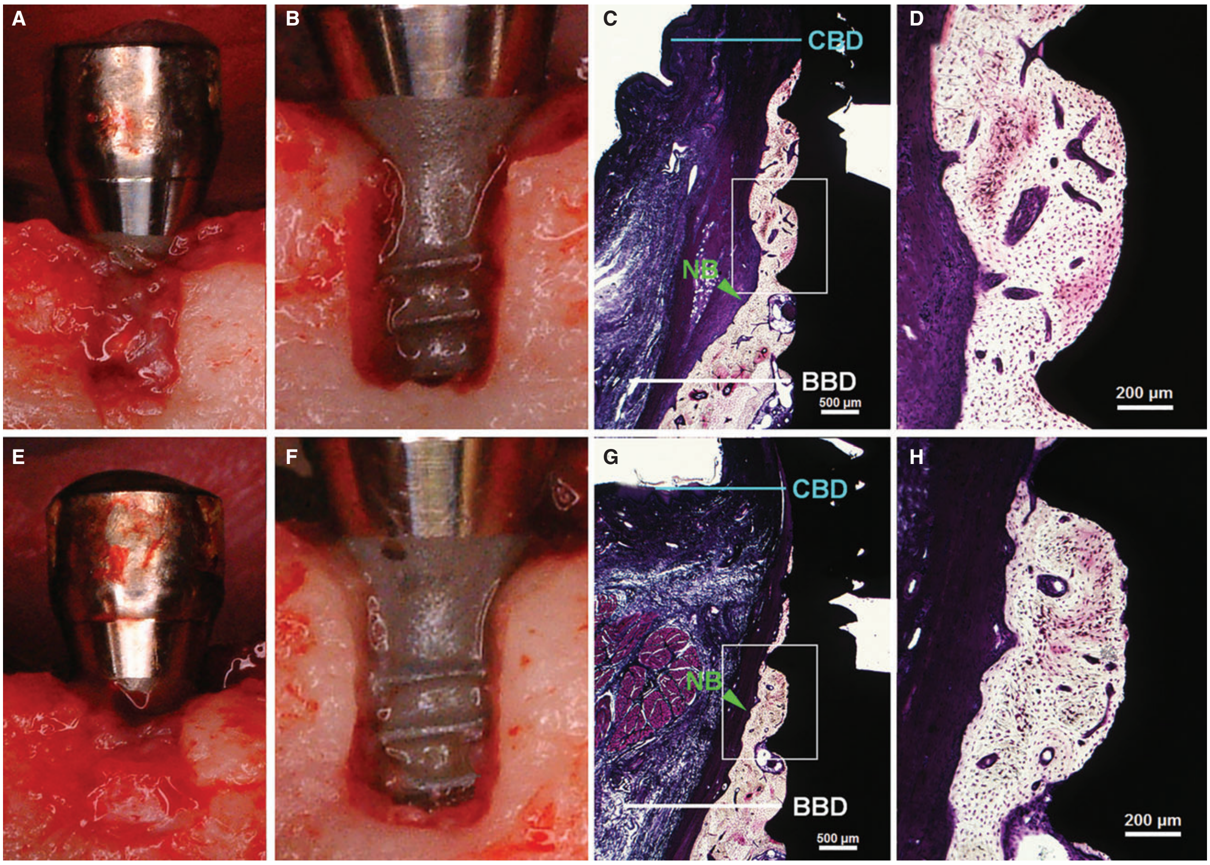


Fig. 22. Operative view of the surgical treatment of experimentally induced peri-implant infection in dog using an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser (A, B) and a plastic curette (E, F), and representative photomicrographs of the buccolingual nondecalcified histological sections parallel to the long axis of the implant in the center of the dehiscence defect at 24 weeks after surgical therapy using an Er:YAG laser (C, D) and a plastic curette (G, H). On elevation of the mucoperiosteal flap, it was observed that the bone tissue adjacent to the defect had resorbed to some extent and the defects were filled with diseased connective tissue (A, E). Buccal view of the defects immediately after degranulation and implant surface debridement. Degranulation and implant surface debridement were performed by irradiation using an Er:YAG laser under sterile water spray in contact mode at 62 mJ/pulse (panel setting: 95–105 mJ/pulse, energy density 10.0 J/cm^2/pulse) and 20 Hz using a chisel tip (B). In the mechanically treated site, granulation tissue removal and implant surface debridement were performed using a plastic curette and then the titanium surface was meticulously cleaned by irrigation with copious volumes of physiological saline solution (F). Histological images showing some degree of new-bone formation with no structural differences noted in the defect area treated with laser and plastic curettes (C, G). In the laser-treated sites (C), the newly formed bone (NB) was generally more coronally extended along and in direct contact with the implant surface from the bottom of the bone defect (BBD) than the curette-treated sites [coronal level of bone defect (CBD)]. In the curette-treated sites (G), a smaller amount of new-bone formation was in direct contact with the treated implant surface. Higher magnifications of the area within the squares in C (D) and G (H) show that direct contact was established between the newly formed bone and the treated implant surface in both the laser- and curette-treated sites. The Er:YAG laser-treated implant surface did not inhibit the attachment and formation of new bone to its surface. (Villanueva Golder stain, original magnification ×30 for C and G, and ×100 for D and H.) [Photographs from Takasaki et al. Er:YAG laser therapy for peri-implant infection: a histological study. *Lasers Med Sci* 22: 143–157, 2007; with permission. Lasers in Medical Science © copyright (2007) Springer-Verlag London Limited (316)].

therapy for the treatment of peri-implantitis. Future research should emphasize the detailed description of the specific laser characteristics and power settings in clinical studies.

Regarding the surgical approach with erbium lasers, the advantageous effect in peri-implant surgery is their potential to produce improved or favorable bone healing (116, 265, 284). In particular, erbium lasers allow more effective debridement of the narrow and deep bone defects in the early stage of peri-implantitis than do conventional mechanical instruments (Fig. 23). However, to date, few clinical

studies have been performed to demonstrate these advantages. Azzeh et al. (30) reported that the Er,Cr:YSGG laser enabled regenerative osseous surgery around an implant with no complications and with high patient and operator satisfaction. Recently, Yamamoto et al. (344) proposed complete removal of the oxidation layer by Er:YAG laser irradiation for debridement of the contaminated anodized surfaces and they reported successful clinical application of this method for the surgical treatment of peri-implantitis. A review paper by Renvert et al., in 2012 (231), reported that surgical therapy is a predictable method for treating peri-implant disease but laser treatment of the exposed implant surface during surgery of peri-implantitis was not shown to be beneficial.

Fig. 23. Clinical application of an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser in the surgical treatment for peri-implantitis in a 64-year-old man. Before surgery (A), the probing depth around implants, at the site of implants 14–16, was maximally 7 mm with bleeding on probing. The mesial site of the 14 implant showed a probing depth of 7 mm with bleeding on probing (B). Palatal view before surgery (C). After flap reflection, debridement of the bone defect and fixture surface was effective with the Er:YAG laser at 30–40 mJ/pulse (panel 60–80 mJ/pulse, 10.7–14.2 J/cm^2/pulse) and 20–25 Hz under saline water spray. In particular, the bone defect around the 14 implant (14i) was very narrow and deep, and only the thin, 400-μm-diameter contact tip was available for inserting and debriding the defect (D). In such a case, entire fixture debridement using the laser was incomplete, but a decontamination effect by the explosive ablation of water was expected during irradiation. After debridement, moderate/severe vertical bone defects were observed around the 14 and 16 implants (14i and 16i) and also fenestration (arrow) was observed on the buccal bone tissue around the apex of the 15 implant fixture (15i) (E). The palatal site of the 14 implant (14i) also demonstrated vertical bone resorption with reduced marginal bone height (F). Before flap replacement, osseous recontouring was performed around implants to correct the irregular bone shape using the Er:YAG laser. Autogenous bone collected from the distal site of the 16 implant was grafted in the vertical bone defects around all the implants and guided bone regeneration using absorbable membrane was performed at the buccal fenestration site of the 15 implant (15i) and the palatal vertical bone defect of the 14 implant (14i) (G). One week after surgery, wound healing was uneventful (H), except for membrane exposure (arrow), which was noted at the palatal inter-implant area of the 14 and 15 implants (I), but later it was gradually minimized and diminished. Eight months postsurgery, peri-implant tissue became stable without inflammation, although gingival recession occurred (J, K, L). The probing depth of all the sites, including the mesial site of the 14 implant, decreased to 2–3 mm without bleeding on probing (K). The original bone resorption at the first visit was vertical and narrow, in particular, around the 14 implant (M). At 8 months postsurgery (N), the horizontal bone height had decreased to some extent but the vertical defect around the 14 implant was improved by bone regeneration. The vertical bone defects were almost diminished and no adverse side effects were observed in the irradiated bone tissue. (Case details provided by Akira Aoki and Yoichi Taniguchi).

With regard to decontamination of the fixture surface, Schwarz et al. (269, 272, 276) indicated that the method of surface debridement and decontamination had no significant impact on clinical outcomes following surgical therapy of advanced peri-implantitis lesions. The intrabony aspect of the defect was treated using either an Er:YAG laser or plastic curettes in combination with cotton pellets soaked in sterile saline. In both treatments, the intrabony component was augmented with a natural bone mineral and covered with a collagen membrane. At 48 months, sites treated with the cotton pellets soaked in sterile saline tended to reveal higher reductions in mean bleeding on probing (cotton pellets: 85.2 ± 16.4% vs. Er:YAG laser: 71.6 ± 24.9%) and clinical attachment level values (cotton pellets: 1.5 ± 2.0 mm vs. Er:YAG laser: 1.2 ± 2.0 mm). In both groups, comparable radiographic bone fill in the intrabony defect component was observed. The 4-year clinical outcomes obtained following combined surgical resective/regenerative therapy of advanced peri-implantitis were not influenced by the method of surface decontamination. It is not clear whether the above results were caused by the difficulty in applying sufficient and precise irradiation to the entire fixture surface with complicated threads and within the narrow intrabony defect or the potential alteration of the biocompatibility of the Er:YAG-lased titanium surface. For clinical application of erbium lasers, the contact tip should be modified to provide adequate irradiation to the fixture surface. In a systematic review and meta-analysis of seven human prospective clinical trials and two animal studies in 2014, Mailoa et al. (173) reported that in a short-term follow-up, lasers resulted in similar probing-depth reduction when compared with conventional implant surface decontamination methods.

Summary

Lasers are being applied generally in soft-tissue management during implant placement and gradually in the treatment of peri-implantitis. Although laser peri-implant therapy shows favorable results in animal studies, there are few clinical studies, and significant differences between laser and conventional therapies have not yet been demonstrated. According to the current evidence, erbium lasers are the most promising laser system as they can be used to debride both contaminated fixture surfaces and bone defects. However, the influence of erbium lasers on titanium still needs to be clarified in detail. Further clinical and animal studies are necessary to prove the superiority of application of lasers in the treatment of peri-implantitis. Nevertheless, based on previous reports and clinical experience, it can be concluded that the application of lasers has some technical and therapeutic advantages as an alternative or adjunctive tool in the management of peri-implant diseases.

Low-level laser therapy

In vitro studies

Low-level lasers have various biostimulatory effects on wound healing (126, 127, 182, 183). These photobiomodulation effects include promotion/activation of cell proliferation (9, 38, 94, 215), collagen synthesis (58), mitochondrial respiration (350) and ATP synthesis (128, 187). It has been suggested that it is the change in the cellular redox state that leads to the photobiostimulative process (167). In periodontal therapy, promotion of proliferation and differentiation of periodontal cells is advantageous for early wound healing. The activation and proliferation of human gingival fibroblasts, periodontal ligament cells, osteoblasts and mesenchymal stem cells, and the release of growth factors *in vitro*, were enhanced by low-level laser irradiation, according to several studies (8, 11, 137, 152, 208, 224, 225, 260, 303, 327, 342). Reduction of inflammation with low-level laser irradiation is also effective for promoting wound healing. Several *in vitro* studies indicated the reduction of proinflammatory molecules, such as prostaglandin E_2, interleukins and tumor necrosis factor-alpha, or their gene expression (96, 254, 291).

Low-level laser therapy has been reported to promote osteogenesis. Ozawa et al. (208) and Stein et al. (303) reported that low-level laser irradiation could promote bone nodule formation by inducing the proliferation and differentiation of osteoblasts. In addition, low-level laser irradiation increased alkaline phosphatase activity (208) and expression of the mRNA for osteoblastic differentiation markers, such as osteopontin (303), osteocalcin (208) and bone sialoproteins (303), in osteoblasts. Low-level laser irradiation also stimulated *in vitro* mineralized nodule formation through increased insulin-like growth factor-1 and bone morphogenetic protein production via Runx2 expression and extracellular signal-regulated kinase phosphorylation in osteoblasts (88, 142, 290) and accelerated the differentiation of bone morphogenetic protein-induced osteoblasts by stimulating the bone morphogenetic protein/Smad signaling pathway (112). The expression of osteoprotegerin, RANKL and RANK, and increased activity of bone tissue cells, following low-level laser irradiation have also been reported (140). Fukuhara et al. (90) demonstrated that low-level laser therapy induces not only acceleration of bone formation but also initial G2/M arrest, which may cause wound healing, such as tissue repair. Kushibiki et al. (158) reported that induction of the extracellular calcification of mouse mesenchymal stem cells as a result of irradiation with a low-level blue laser (405 nm) is associated with alteration of intracellular localization of the circadian rhythm protein cryptochrome 1. Recently, photobiomodulation effects of light-emitting diodes on cells were also exhibited (138, 164, 332). Kim et al. (138) and Li et al. (164) reported that exposure to red light-emitting diode light enhances the osteogenic differentiation of mesenchymal stem cells.

In vivo studies

Regarding inflammation, Albertini et al. (7) reported reduction of inflammation by low-level laser therapy. Aimbire et al. (5) reported that low-level laser therapy induces dose-dependent reduction of tumor necrosis factor-alpha levels in acute inflammation in rats. Safavi et al. (252) demonstrated that low-level laser irradiation accelerates wound healing by changing the expression of genes responsible for the production of inflammatory cytokines. Shimotoyodome et al. (292) reported that irradiation with a low-level CO_2 laser improves macromolecular clearance via the lymph flow in hamster gingiva.

With regard to osteogenesis, several *in vivo* studies have demonstrated the promotion of healing of bone defects by low-level laser therapy using diode lasers (108, 136, 181, 222, 295). These histological studies indicated increased angiogenesis and connective tissue formation (136), and increased new-bone formation (108, 132, 136, 181, 222, 295) in the laser-treated site, compared with the untreated control. Friesen et al. (86) and Tajima (314) observed that following irradiation with a high-level CO_2 laser, unlike normal bone healing in the tibia, remodeling of the tibial wall adjacent to the bone marrow was observed opposite the site of irradiation, in contrast to little or no bone formation noted on the periosteal side (irradiated side). Also, Shiozaki et al. (294) reported that irradiation with a low-level CO_2 laser from the skin surface induced marked osteoid formation on the surface of laser-irradiated tibiae of rat. Ninomiya et al. (202) reported that Q-switched Nd:YAG laser irradiation with a high-intensity pulse from the skin surface accelerated bone formation in metaphyseal trabecular bone in rat femur and speculated that this might be caused by laser-induced pressure waves. These phenomena require further investigation, and it needs to be clarified whether it is the biostimulation (photobiomodulation) induced by penetration and scattering of the low-level laser and/or the thermal effect that is responsible for the enhanced bone formation. Kim et al. (139) also investigated the capacity of bone repair using a high-intensity, Q-switched Nd: YAG laser in postoperative treatment targeting local bone healing. Laser irradiation significantly increased new-bone formation by approximately 45%, not only in the collagen sponge-filled defects of rats but also when the defects were left empty, compared with the nonirradiated group.

With regard to the treatment of periodontal bone defects, Nagata et al. (193) analyzed the influence of platelet-rich plasma, low-level laser therapy (660-nm diode laser), separately or combined, on the healing of periodontal fenestration defects in rats. Low-level laser therapy and platelet-rich plasma, separately or combined, all promoted new cementum formation with a functional periodontal ligament. However, the combination of platelet-rich plasma and low-level laser therapy did not show additional positive effects when compared with the use of either therapy alone.

In implant therapy, low-level laser therapy applied after conventional techniques shows promise for increased and faster osseointegration of implants following irradiation in animal studies. Khadra et al. (136) reported that bone-to-implant contact and the amounts of calcium and phosphorus increased at the sites treated with additional low-level laser therapy (830 nm diode laser) compared with nonirradiated sites, suggesting that bone maturation progressed faster in irradiated bone. Dortbudak et al. (71) revealed that osteocyte viability was significantly higher at the early stages of healing in bone sites irradiated with a diode laser (690 nm) before implant placement than in nonirradiated implant sites. Naka & Yokose (194) also reported that irradiation of bone with a CO_2 laser before implantation was effective in promoting bone formation and acquiring osseointegration of titanium implants and proposed laser-induced bone therapy. Omasa et al. (206) reported that therapy with a low-level diode laser (830 nm) enhanced the stability of mini-implants placed in rat tibiae and accelerated peri-implant bone formation by increasing expression of the bone morphogenetic protein-2 gene in surrounding cells.

Recently, with an increased demand for implant therapy, much attention has been paid to the preservation of alveolar bone following tooth extraction. The application of lasers on socket preservation has been investigated. Arrany et al. (25) reported that low-power laser irradiation is capable of activating the latent transforming growth factor-beta1 complex *in vitro*, and its expression pattern in an *in vivo* oral tooth-extraction healing model suggested that transforming growth factor-beta plays a central role in mediating the accelerated healing response. Fukuoka et al. (91) reported the effect of CO_2 laser irradiation on the extraction socket healing process in rats. They performed high-level laser irradiation to coagulate blood and prevent the loss of blood clots immediately after tooth extraction and low-level laser irradiation 1 day postextraction to stimulate wound healing. Consequently, the alveolar crest height was significantly higher in the laser group than in the control group. Immunostaining revealed many alpha-smooth muscle actin-positive cells (myofibroblasts) in the control group but very few in the laser group. The appearance of fewer myofibroblasts in the granulation tissue in the laser group indicated subsequent mild cicatrization, which may have been closely associated with favorable new-bone formation. Laser-irradiated extraction wound healing showed characteristics different from those of the normal healing process, suggesting promotion of healing. Park et al. (213, 214) reported that low-level irradiation with a diode laser had positive effects on bone healing of extraction sockets in rats by increasing expression of the genes encoding Runx2, collagen type 1, osteocalcin, platelet-derived growth factor-B and vascular endothelial growth factor. They concluded that low-level irradiation with a diode laser is beneficial in the early stages of alveolar bone healing.

Clinical studies

There are several possible benefits of applying low-level laser therapy as part of surgical and postoperative therapy, such as suppression of the inflammatory processes, pain control and promotion of wound healing/tissue regeneration. In the medical field, a meta-analysis of Woodruff et al. (341) reported that low-level laser therapy is an effective tool for promoting wound repair.

Qadri et al. (228) examined the effect of low-level laser therapy following scaling and root planing. Irradiation with both 635-nm (10 mW, 90 s, 0.9 J) and 820-nm (70 mW, 25 s, 1.75 J) diode lasers to the external surface of gingiva was performed 1 week later and was continued once a week for 6 weeks. The clinical variables (i.e. probing pocket depth, and plaque and gingival indices) were reduced more on the laser side than on the placebo side. The authors concluded that additional treatment with low-level lasers reduced gingival inflammation. In a similar study, Qadri et al. (226) also examined the differences between the effects of low-level helium–neon (HeNe) (632.8 nm, 3 mW) and diode (650 nm, 3 mW) laser therapies. Laser irradiation to the external surface of the gingiva (180 s per point, energy 0.54 J) was started 1 week later and was continued once a week for 6 weeks. The clinical signs of inflammation, such as gingival index and probing pocket depth, were significantly more reduced on the HeNe laser-treated side compared with the diode laser-treated side. They concluded that coherence length appears to be an important factor in laser phototherapy.

Riberio et al. (233) performed low-level diode laser therapy (GaAlAs; 660 nm, 35 mW, 10 s per site) immediately, and 24 and 48 h after subgingival scaling and root planing. They reported that utilization of a low-level diode laser as an auxiliary in scaling and root planing did not provide any apparent clinical benefit for shallow to moderate periodontal pockets. Calderin et al. (44) reported that therapy with a low-level diode laser (670 nm, 200 mW, 60 s/tooth), used in a single or repeated doses, did not produce a significant reduction in clinical parameters; however, the levels of interleukin-1beta in gingival crevice fluid were significantly reduced in scaling and root planing plus single laser therapy and scaling and root planing plus repeated laser therapy groups compared with the scaling and root planing group, and the scaling and root planing plus repeated laser therapy group showed a significant reduction in the proinflammatory cytokine, tumor necrosis factor-alpha, and in the RANKL/osteoprotegerin ratio at 4 weeks post-treatment compared with the scaling and root planing plus single laser therapy and scaling and root planing groups ($P < 0.05$). Multiple sessions of diode laser therapy showed a faster and greater tendency to reduce proinflammatory mediators and the RANKL/osteoprotegerin ratio.

In relation to surgical therapy, Ozcelik et al. (210) demonstrated that the additional application of low-level laser therapy (diode; 588 nm, 120 mW, during and after periodontal regenerative therapy using enamel matrix protein derivative (after enamel matrix protein application, immediately after surgery, and daily for 5 days, 10 min each), resulted in greater improvements in clinical parameters, such as gingival recession, swelling and reduced postoperative pain, in comparison with therapy with enamel matrix protein derivative alone. Amorim et al. (12) reported that low-level laser therapy (diode; 685 nm, 50 mW, 80 s; immediately following, and 1, 3 and 7 days after treatment) appeared to promote healing following gingivectomy. Ozcelik et al. (209) also demonstrated that the additional low-level laser therapy using a diode laser (588 nm, 120 mW, 5 min, daily for 7 days) on gingival tissues following gingivectomy and gingivoplasty enhanced epithelialization and improved wound healing compared with the nonirradiated control. In contrast, Damante et al. (62) reported that low-intensity laser therapy (diode; 670 nm, 15 mW, 4 J/cm^2 per point, four sessions for 1 week, i.e. one session on each of days 0, 2, 4, and 6) did not accelerate oral mucosal healing after gingivoplasty.

For tooth extractions, Mozzaiti et al. (190) reported that unlike the nonirradiated control, superpulsed diode laser (904 nm) irradiation (pulse width 200 ns, peak power 33 W, 30 kHz, 200 mW/cm^2, 15 min, 180 J/cm^2, three applications; immediately after molar extraction and at days 3 and 5) prevented the increase of interleukin-1beta, interleukin-6, interleukin-10 and cyclooxygenase-2 in the extraction socket, and induced an insignificant increase in collagen, 7 days postextraction. Patients reported less pain at the site treated with superpulsed laser irradiation than at the control site. The study suggested that superpulsed diode laser irradiation is able to reduce inflammation and pain following tooth extraction. Ishikawa et al. (118) investigated a novel photocoagulation method of treating tooth extraction sockets using a blue–violet light emitting diode. Irradiation with the blue–violet light-emitting diode (750 mW/cm^2, 10–20 s) yielded immediate hemostasis of the socket. Transmission electron microscopy showed the formation of a thin amorphous layer and an adjacent agglutination of platelets and other cellular elements under the layer at the interface of the irradiated blood. One week later, the light-emitting diode-irradiated sockets demonstrated uneventful healing with epithelial covering. Thus, blue–violet light-emitting diode irradiation of bleeding sockets may facilitate immediate clot formation and hemostasis. In the field of oral surgery, Vescovi et al. (331) reported the effectiveness of low-level laser therapy for the management of bisphosphonate-related osteonecrosis of the jaw. Two-hundred and seventeen patients received 589 tooth extractions under antibiotic treatment and were additionally treated with low-level Nd:YAG laser therapy (1.25 W; 15 Hz, 1 min, five applications) after 3 days and once a week for 2 months. Minimal bone exposure was observed in five cases and this was treated with high-level Er:YAG laser vaporization and then healed. The authors proposed that the combination of antibiotic treatment and low-level laser therapy can be effective in preventing osteonecrosis after tooth extraction in patients under bisphosphonate therapy.

Summary

Currently, a large number of basic studies are reporting biostimulative effects of low-level laser therapy on periodontal tissues. In the medical field, clinical studies are increasing; however, in the dental field, few clinical studies have shown positive effects of adjunctive phototherapy using low-level lasers or light-emitting diodes with respect to promotion of wound healing/tissue regeneration. Although there continues to be improved performance and technical advances of the instrumentation, the superiority of this novel treatment approach to conventional treatment has not yet been clearly demonstrated. Therefore, it is hoped that further extensive clinical studies will be conducted, utilizing present and future devices that will efficiently stimulate the regeneration of diseased periodontal tissues, in order to demonstrate the beneficial effects of low-level laser therapy in periodontal and implant therapy.

Summary and future perspectives

Nowadays, lasers are being increasingly incorporated into conventional mechanical therapy and chemotherapy for various periodontal and peri-implant diseases, and favorable wound healing has been demonstrated following irradiation. In nonsurgical and surgical periodontal therapy, the maximum possible level of wound healing/tissue regeneration that can be achieved with conventional mechanical therapy has been reached. Advances in tissue-engineering techniques are expected to result in additional improvements in healing following flap surgery. These include guided tissue regeneration with membranes, the use of enamel matrix protein derivative and growth factors and, quite recently, the use of cultured stem cells and cell sheet engineering (117, 122). In order to yield further improvements in the treatment outcome of nonsurgical and surgical therapy, including regenerative surgery, preparation of the diseased site by better decontamination methods and activation of the surrounding tissues/cells may be required. The use of high-level and low-level lasers offers promise in this regard. As discussed in this article, lasers are expected to help tissues in an inflamed and/or damaged state enter rapidly the healing and regenerative phases by thorough debridement and decontamination of diseased tissues, and by modulating or activating cell metabolism in the surrounding tissues (23, 122).

As a future strategy for periodontal and peri-implant treatment, a series of periodontal/peri-implant phototherapy procedures will be developed. Those procedures aim for thorough bacterial elimination before and during treatment, thorough debridement and biostimulation during treatment, as well as enhancement of wound healing by repeated biostimulation post-treatment. Adjunct/alternative use of high-level lasers, as well as antimicrobial photodynamic therapy (302, 317), may be considered as a novel therapeutic modality for debridement and preparation of diseased sites, and low-level lasers/light-emitting diodes may also be important tools for activation of the tissues/cells. Extensive study of periodontal phototherapy at the molecular level is needed to understand tissue responses, and elucidation of their effects could lead to direct and/or adjunctive improvements in the current physical, chemical and mechanical treatment procedures of periodontitis and peri-implantitis (21, 122).

At present, clinical evidence for the promotion of periodontal wound healing/tissue regeneration by phototherapy is still limited. However, the laser offers a novel technical approach that is completely different from mechanical instruments and has several beneficial effects, and thus may play an important role. With better understanding of the characteristics of laser/light as well as the development of laser/light-emitting diode devices, the role of light energy in periodontal and peri-implant treatment is expected to expand rapidly in the future. To obtain more detailed information on how wound healing/tissue regeneration can be enhanced, an increasing number of studies on photomediated periodontal tissue engineering, utilizing various sources of light energy, are needed.

Acknowledgments

The authors would like to thank Dr Hisashi Watanabe and Dr Junji Kato (Tokyo Medical and Dental University, Japan), Dr Amir Pourzarandian (private practice, Iran) and Mr John Sulewski (the Institute for Advanced Dental Technologies, USA) for their kind help and contribution in manuscript preparation. This review was supported by the grant from the Global Center of Excellence (GCOE) Program of the International Research Center for Molecular Science in Tooth and Bone Diseases at Tokyo Medical and Dental University.

References

1. AAP. American Academy of Periodontology statement on the efficacy of lasers in the non-surgical treatment of inflammatory periodontal disease. *J Periodontol* 2011: **82**: 513–514.

2. 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.
3. Abu-Serriah M, Critchlow H, Whitters CJ, Ayoub A. Removal of partially erupted third molars using an Erbium (Er):YAG laser: a randomised controlled clinical trial. *Br J Oral Maxillofac Surg* 2004: **42**: 203–208.
4. Adriaens PA, Edwards CA, De Boever JA, Loesche WJ. Ultrastructural observations on bacterial invasion in cementum and radicular dentin of periodontally diseased human teeth. *J Periodontol* 1988: **59**: 493–503.
5. Aimbire F, Lopes-Martins RA, Castro-Faria-Neto HC, Albertini R, Chavantes MC, Pacheco MT, Leonardo PS, Iversen VV, Bjordal JM. Low-level laser therapy can reduce lipopolysaccharide-induced contractile force dysfunction and TNF-alpha levels in rat diaphragm muscle. *Lasers Med Sci* 2006: **21**: 238–244.
6. Akiyama F, Aoki A, Miura-Uchiyama M, Sasaki KM, Ichinose S, Umeda M, Ishikawa I, Izumi Y. In vitro studies of the ablation mechanism of periodontopathic bacteria and decontamination effect on periodontally diseased root surfaces by erbium:yttrium-aluminum-garnet laser. *Lasers Med Sci* 2011: **26**: 193–204. Erratum in: Lasers Med Sci 2011; 2026(2012):2277.
7. Albertini R, Aimbire FS, Correa FI, Ribeiro W, Cogo JC, Antunes E, Teixeira SA, De Nucci G, Castro-Faria-Neto HC, Zangaro RA, Lopes-Martins RA. Effects of different protocol doses of low power gallium-aluminum-arsenate (Ga-Al-As) laser radiation (650 nm) on carrageenan induced rat paw ooedema. *J Photochem Photobiol, B* 2004: **74**: 101–107.
8. Aleksic V, Aoki A, Iwasaki K, Takasaki AA, Wang CY, Abiko Y, Ishikawa I, Izumi Y. Low-level Er:YAG laser irradiation enhances osteoblast proliferation through activation of MAPK/ERK. *Lasers Med Sci* 2010: **25**: 559–569.
9. AlGhamdi KM, Kumar A, Moussa NA. Low-level laser therapy: a useful technique for enhancing the proliferation of various cultured cells. *Lasers Med Sci* 2012: **27**: 237–249.
10. Almehdi A, Aoki A, Ichinose S, Taniguchi Y, Sasaki KM, Ejiri K, Sawabe M, Chui C, Katagiri S, Izumi Y. Histological and SEM analysis of root cementum following irradiation with Er:YAG and CO_2 lasers. *Lasers Med Sci* 2013: **28**: 203–213.
11. Almeida-Lopes L, Rigau J, Zangaro RA, Guidugli-Neto J, Jaeger MM. Comparison of the low level laser therapy effects on cultured human gingival fibroblasts proliferation using different irradiance and same fluence. *Lasers Surg Med* 2001: **29**: 179–184.
12. Amorim JC, de Sousa GR, de Barros Silveira L, Prates RA, Pinotti M, Ribeiro MS. Clinical study of the gingiva healing after gingivectomy and low-level laser therapy. *Photomed Laser Surg* 2006: **24**: 588–594.
13. Ando Y, Aoki A, Watanabe H, Ishikawa I. Bactericidal effect of erbium YAG laser on periodontopathic bacteria. *Lasers Surg Med* 1996: **19**: 190–200.
14. Angiero F, Sannino C, Borloni R, Crippa R, Benedicenti S, Romanos GE. Osteonecrosis of the jaws caused by bisphosphonates: evaluation of a new therapeutic approach using the Er:YAG laser. *Lasers Med Sci* 2009: **24**: 849–856.
15. Aoki A. Current Status of Er:YAG laser in Periodontics. World Federation for Laser Dentistry, 2010 Dubai Congress (Dubai, March 9-11, 2010), Conference Booklet 2010: 23.
16. Aoki A, Ando Y, Watanabe H, Ishikawa I. In vitro studies on laser scaling of subgingival calculus with an erbium: YAG laser. *J Periodontol* 1994: **65**: 1097–1106.
17. Aoki A, Ishikawa I Application of the Er:YAG laser for esthetic management of periodontal soft tissues. In: Brugnera Junioir A, Pinheiro A, Pecora JD editors. *The 9th International Congress on laser in dentistry, Sao Paulo (Brazil)*, July 21–24, 2004. Bologna, Italy: Medimond, 2005, 1–6.
18. Aoki A, Ishikawa I, Yamada T, Otsuki M, Watanabe H, Tagami J, Ando Y, Yamamoto H. Comparison between Er: YAG laser and conventional technique for root caries treatment in vitro. *J Dent Res* 1998: **77**: 1404–1414.
19. Aoki A, Miura M, Akiyama F, Nakagawa N, Tanaka J, Oda S, Watanabe H, Ishikawa I. In vitro evaluation of Er:YAG laser scaling of subgingival calculus in comparison with ultrasonic scaling. *J Periodontal Res* 2000: **35**: 266–277.
20. Aoki A, Miura M, Akiyama F, Sasaki K, Matsuyama T, Eguchi T, Otsuki M, Watanabe H, Tagami J, Ishikawa I. Soft tissue treatment with the Er:YAG laser at a high pulse repetition rate: gingivectomy and melanin removal in beagle dogs. *7th International Congress on Lasers in Dentistry, Brussel, Belgium, abstract handbook p1*, 2000.
21. 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. Erratum in: Gen Dent 2009; 2057(2001):2094.
22. Aoki A, Sasaki K, Watanabe H, Ishikawa I. Lasers in non-surgical periodontal therapy. *Periodontol 2000* 2004: **36**: 59–97.
23. Aoki A, Takasaki A, Pourzarandian A, Mizutani K, Ruwanpura S, Iwasaki K, Noguchi K, Oda S, Watanabe H, Ishikawa I, Izumi Y. Photo-bio-modulation laser strategies in periodontal therapy. *Proceedings of Light-Activated Tissue Regeneration and Therapy II, Springer* 2008: 181–190.
24. Aoki A, Watanabe H, Akiyama F, Shoji S, Horiuchi H, Ishikawa I. Clinical evaluation of periodontal osseous surgery with Er:YAG laser. *J Acad Laser Dent* 2004: **12**: 13.
25. Arany PR, Nayak RS, Hallikerimath S, Limaye AM, Kale AD, Kondaiah P. Activation of latent TGF-beta1 by low-power laser in vitro correlates with increased TGF-beta1 levels in laser-enhanced oral wound healing. *Wound Repair Regen* 2007: **15**: 866–874.
26. Arashiro DS, Rapley JW, Cobb CM, Killoy WJ. Histologic evaluation of porcine skin incisions produced by CO_2 laser, electrosurgery, and scalpel. *Int J Perio Rest Dent* 1996: **16**: 479–491.
27. Arnabat-Dominguez J, Espana-Tost AJ, Berini-Aytes L, Gay-Escoda C. Erbium:YAG laser application in the second phase of implant surgery: a pilot study in 20 patients. *Int J Oral Maxillofac Implants* 2003: **18**: 104–112.
28. Assaf M, Yilmaz S, Kuru B, Ipci SD, Noyun U, Kadir T. Effect of the diode laser on bacteremia associated with dental ultrasonic scaling: a clinical and microbiological study. *Photomed Laser Surg* 2007: **25**: 250–256.
29. Atsawasuwan P, Greethong K, Nimmanon V. Treatment of gingival hyperpigmentation for esthetic purposes by Nd: YAG laser: report of 4 cases. *J Periodontol* 2000: **71**: 315–321.

30. Azzeh MM. Er, Cr:YSGG laser-assisted surgical treatment of peri-implantitis with 1-year reentry and 18-month follow-up. *J Periodontol* 2008: **79**: 2000–2005.
31. Azzeh MM. Treatment of gingival hyperpigmentation by erbium-doped:yttrium, aluminum, and garnet laser for esthetic purposes. *J Periodontol* 2007: **78**: 177–184.
32. Azzi R, Kenney EB, Tsao TF, Carranza FA Jr. The effect of electrosurgery on alveolar bone. *J Periodontol* 1983: **54**: 96–100.
33. Badran Z, Boutigny H, Struillou X, Weiss P, Laboux O, Soueidan A. Clinical outcomes after nonsurgical periodontal therapy with an Er:YAG laser device: a randomized controlled pilot study. *Photomed Laser Surg* 2012: **30**: 347–353.
34. Barak S, Kaplan I. The CO_2 laser in the excision of gingival hyperplasia caused by nifedipine. *J Clin Periodontol* 1988: **15**: 633–635.
35. Barone A, Covani U, Crepsi R, Romanos GE. Root surface morphological changes after focused versus defocused CO_2 laser Irradiation: a scanning electron microscopy analysis. *J Periodontol* 2002: **73**: 370–373.
36. Beer F, Korpert W, Passow H, Steidler A, Meinl A, Buchmair AG, Moritz A. Reduction of collateral thermal impact of diode laser irradiation on soft tissue due to modified application parameters. *Lasers Med Sci* 2012: **27**: 917–921.
37. Belal MH, Watanabe H, Ichinose S, Ishikawa I. Effect of Er: YAG laser combined with rhPDGF-BB on attachment of cultured fibroblasts to periodontally involved root surfaces. *J Periodontol* 2007: **78**: 1329–1341.
38. Ben-Dov N, Shefer G, Irintchev A, Wernig A, Oron U, Halevy O. Low-energy laser irradiation affects satellite cell proliferation and differentiation in vitro. *Biochim Biophys Acta* 1999: **1448**: 372–380.
39. Biolase Technology I. Deep pocket therapy with new attachment. http://www.biolase.com/ProductOwner/Documents/RFPT5-14mm-RFPT-Tips-Waterlase%20MD.pdf (Aug 6, 2014 accessed).
40. Bjordal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RA. Low-level laser therapy in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. *Photomed Laser Surg* 2006: **24**: 158–168.
41. Bolortuya G, Ebihara A, Ichinose S, Watanabe S, Anjo T, Kokuzawa C, Saegusa H, Kawashima N, Suda H. Initial fibroblast attachment to Erbium:YAG laser-irradiated dentine. *Int Endod J* 2011: **44**: 1134–1144.
42. Borrajo JL, Varela LG, Castro GL, Rodriguez-Nunez I, Torreira MG. Diode laser (980 nm) as adjunct to scaling and root planing. *Photomed Laser Surg* 2004: **22**: 509–512.
43. Buchelt M, Kutschera HP, Katterschafka T, Kiss H, Lang S, Beer R, Losert U. Erb:YAG and Hol:YAG laser osteotomy: the effect of laser ablation on bone healing. *Lasers Surg Med* 1994: **15**: 373–381.
44. Calderin S, Garcia-Nunez JA, Gomez C. Short-term clinical and osteoimmunological effects of scaling and root planing complemented by simple or repeated laser phototherapy in chronic periodontitis. *Lasers Med Sci* 2013: **28**: 157–166.
45. Cekici A, Maden I, Yildiz S, San T, Isik G. Evaluation of blood cell attachment on Er: YAG laser applied root surface using scanning electron microscopy. *Int J Med Sci* 2013: **10**: 560–566.
46. Centty IG, Blank LW, Levy BA, Romberg E, Barnes DM. Carbon dioxide laser for de-epithelialization of periodontal flaps. *J Periodontol* 1997: **68**: 763–769.
47. Cercadillo-Ibarguren I, Espana-Tost A, Arnabat-Dominguez J, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Histologic evaluation of thermal damage produced on soft tissues by CO2, Er, Cr:YSGG and diode lasers. *Med Oral Patol Oral Cir Bucal* 2010: **15**: e912–e918.
48. Choi KH, Im SU, Kim CS, Choi SH, Kim CK. Effect of the carbon dioxide laser on the clinical parameters and crevicular IL-1beta when used as an adjunct to gingival flap surgery. *J Int Acad Periodontol* 2004: **6**: 29–36.
49. Cloutier M, Girard B, Peel SA, Wilson D, Sandor GK, Clokie CM, Miller D. Calvarial bone wound healing: a comparison between carbide and diamond drills, Er:YAG and Femtosecond lasers with or without BMP-7. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010: **110**: 720–728.
50. Cobb CM. Lasers in periodontics: a review of the literature. *J Periodontol* 2006: **77**: 545–564.
51. Cobb CM, Low SB, Coluzzi DJ. Lasers and the treatment of chronic periodontitis. *Dent Clin North Am* 2010: **54**: 35–53.
52. 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.
53. Coffelt DW, Cobb CM, MacNeill S, Rapley JW, Killoy WJ. Determination of energy density threshold for laser ablation of bacteria. An in vitro study. *J Clin Periodontol* 1997: **24**: 1–7.
54. Coluzzi DJ. Fundamentals of lasers in dentistry: basic science, tissue interaction, and instrumentation. *J Laser Dent* 2008: **16**: 4–10.
55. Coluzzi DJ, Convissar RA. *Atlas of laser applications in dentistry*. Hanover Park, IL: Quintessence Publishing Co Inc, 2007.
56. Coluzzi DJ, Convissar RA. Esthetic laser dentistry. In: Coluzzi DJ, Convissar RA, editors. *Atlas of laser applications in dentistry*. Hanover Park, IL: Quintessence Publishing Co, Inc, 2007: 133–151.
57. Coluzzi DJ, Convissar RA. Osseous Recontouring for crown lengthening. In: Coluzzi DJ, Convissar RA, editors.. *Atlas of laser applications in dentistry*. Hanover Park, IL: Quintessence Publishing Co, Inc, 2007: 110–116.
58. Conlan MJ, Rapley JW, Cobb CM. Biostimulation of wound healing by low-energy laser irradiation. A review. *J Clin Periodontol* 1996: **23**: 492–496.
59. Crespi R, Barone A, Covani U, Ciaglia RN, Romanos GE. Effects of CO_2 laser treatment on fibroblast attachment to root surfaces. A scanning electron microscopy analysis. *J Periodontol* 2002: **73**: 1308–1312.
60. Crespi R, Cappare P, Toscanelli I, Gherlone E, Romanos GE. Effects of Er:YAG laser compared to ultrasonic scaler in periodontal treatment: a 2-year follow-up split-mouth clinical study. *J Periodontol* 2007: **78**: 1195–1200.
61. Crespi R, Covani U, Margarone JE, Andreana S. Periodontal tissue regeneration in beagle dogs after laser therapy. *Lasers Surg Med* 1997: **21**: 395–402.
62. Damante CA, Greghi SL, Sant'ana AC, Passanezi E. Clinical evaluation of the effects of low-intensity laser (GaAlAs) on wound healing after gingivoplasty in humans. *J Appl Oral Sci* 2004: **12**: 133–136.
63. Darveau RP, Tanner A, Page RC. The microbial challenge in periodontitis. *Periodontol 2000* 1997: **14**: 12–32.

64. de Mello ED, Pagnoncelli RM, Munin E, Filho MS, de Mello GP, Arisawa EA, de Oliveira MG. Comparative histological analysis of bone healing of standardized bone defects performed with the Er:YAG laser and steel burs. *Lasers Med Sci* 2008: **23**: 253–260.
65. De Micheli G, de Andrade AK, Alves VT, Seto M, Pannuti CM, Cai S. Efficacy of high intensity diode laser as an adjunct to non-surgical periodontal treatment: a randomized controlled trial. *Lasers Med Sci* 2011: **26**: 43–48.
66. de Paula Eduardo C, de Freitas PM, Esteves-Oliveira M, Aranha AC, Ramalho KM, Simoes A, Bello-Silva MS, Tuner J. Laser phototherapy in the treatment of periodontal disease. A review. *Lasers Med Sci* 2010: **25**: 781–792.
67. Dederich DN, Pickard MA, Vaughn AS, Tulip J, Zakariasen KL, Folwaczny M, Aggstaller H, Mehl A, Hickel R, Benner KU, Flasskamp B. Comparative bactericidal exposures for selected oral bacteria using carbon dioxide laser radiation. *Lasers Surg Med* 1990: **10**: 591–594.
68. Deppe H, Horch HH, Henke J, Donath K. Per-implant care of ailing implants with the carbon dioxide laser. *Int J Oral Maxillofac Implants* 2001: **16**: 659–667.
69. Deppe H, Horch HH, Neff A. Conventional versus CO2 laser-assisted treatment of peri-implant defects with the concomitant use of pure-phase beta-tricalcium phosphate: a 5-year clinical report. *Int J Oral Maxillofac Implants* 2007: **22**: 79–86.
70. Dilsiz A, Canakci V, Aydin T. The combined use of Nd:YAG laser and enamel matrix proteins in the treatment of periodontal infrabony defects. *J Periodontol* 2010: **81**: 1411–1418.
71. Dortbudak O, Haas R, Mailath-Pokorny G. Effect of low-power laser irradiation on bony implant sites. *Clin Oral Implants Res* 2002: **13**: 288–292.
72. Dukic W, Bago I, Aurer A, Roguljic M. Clinical effectiveness of diode laser therapy as an adjunct to non-surgical periodontal treatment: a randomized clinical study. *J Periodontol* 2013: **84**: 1111–1117.
73. Dyer B, Sung EC. Minimally Invasive Periodontal Treatment Using the Er, Cr:YSGG Laser. A 2-year Retrospective Preliminary Clinical Study. *Open Dent J* 2012: **6**: 74–78.
74. Eberhard J, Ehlers H, Falk W, Acil Y, Albers HK, Jepsen S. Efficacy of subgingival calculus removal with Er:YAG laser compared to mechanical debridement: an in situ study. *J Clin Periodontol* 2003: **30**: 511–518.
75. el Montaser MA, Devlin H, Sloan P, Dickinson MR. Pattern of healing of calvarial bone in the rat following application of the erbium-YAG laser. *Lasers Surg Med* 1997: **21**: 255–261.
76. el-Montaser M, Devlin H, Dickinson MR, Sloan P, Lloyd RE. Osseointegration of titanium metal implants in erbium-YAG laser-prepared bone. *Implant Dent* 1999: **8**: 79–85.
77. Eltas A, Orbak R. Effect of 1,064-nm Nd:YAG laser therapy on GCF IL-1beta and MMP-8 levels in patients with chronic periodontitis. *Lasers Med Sci* 2012: **27**: 543–550.
78. Enwemeka CS, Parker JC, Dowdy DS, Harkness EE, Sanford LE, Woodruff LD. The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study. *Photomed Laser Surg* 2004: **22**: 323–329.
79. Esposito M, Grusovin MG, Coulthard P, Worthington HV. The efficacy of interventions to treat peri-implantitis: a Cochrane systematic review of randomised controlled clinical trials. *Eur J Oral Implantol* 2008: **1**: 111–125.
80. Euzebio Alves VT, de Andrade AK, Toaliar JM, Conde MC, Zezell DM, Cai S, Pannuti CM, De Micheli G. Clinical and microbiological evaluation of high intensity diode laser adjutant to non-surgical periodontal treatment: a 6-month clinical trial. *Clin Oral Investig* 2013: **17**: 87–95.
81. Featherstone JDB. Caries detection and prevention with laser energy. *Dent Clin North Am* 2000: **44**: 955–969.
82. Feist IS, De Micheli G, Carneiro SR, Eduardo CP, Miyagi S, Marques MM. Adhesion and growth of cultured human gingival fibroblasts on periodontally involved root surfaces treated by Er:YAG laser. *J Periodontol* 2003: **74**: 1368–1375.
83. Fisher SE, Frame JW, Browne RM, Tranter RM. A comparative histological study of wound healing following CO_2 laser and conventional surgical excision of canine buccal mucosa. *Arch Oral Biol* 1983: **28**: 287–291.
84. Folwaczny M, Aggstaller H, Mehl A, Hickel R, Benner KU, Flasskamp B. Removal of bacterial endotoxin from root surface with Er:YAG laser. *Am J Dent* 2003: **16**: 3–5.
85. Friedmann A, Antic L, Bernimoulin JP, Purucker P. In vitro attachment of osteoblasts on contaminated rough titanium surfaces treated by Er:YAG laser. *J Biomed Mater Res A* 2006: **79**: 53–60.
86. Friesen LR, Cobb CM, Rapley JW, Forgas-Brockman L, Spencer P. Laser irradiation of bone. II. Healing response following treatment by CO_2 and Nd:YAG lasers. *J Periodontol* 1999: **70**: 75–83.
87. Fujii T, Baehni PC, Kawai O, Kawakami T, Matsuda K, Kowashi Y. Scanning electron microscopic study of the effects of Er:YAG laser on root cementum. *J Periodontol* 1998: **69**: 1283–1290.
88. Fujimoto K, Kiyosaki T, Mitsui N, Mayahara K, Omasa S, Suzuki N, Shimizu N. Low-intensity laser irradiation stimulates mineralization via increased BMPs in MC3T3-E1 cells. *Lasers Surg Med* 2010: **42**: 519–526.
89. Fukuda M, Minoura S, Ishikawa K, Ogura N, Ueda N, Murase M, Sugihara N, Kato K, Nakagaki H, Noguchi T. Effects of Nd:YAG laser irradiation on endotoxin in exposed cementum. *Jpn J Conserv Dent* 1994: **37**: 711–716 (in Japanese, English abstract).
90. Fukuhara E, Goto T, Matayoshi T, Kobayashi S, Takahashi T. Optimal low-energy laser irradiation causes temporal G2/M arrest on rat calvarial osteoblasts. *Calcif Tissue Int* 2006: **79**: 443–450.
91. Fukuoka H, Daigo Y, Enoki N, Taniguchi K, Sato H. Influence of carbon dioxide laser irradiation on the healing process of extraction sockets. *Acta Odontol Scand* 2011: **69**: 33–40.
92. Galli C, Macaluso GM, Elezi E, Ravanetti F, Cacchioli A, Gualini G, Passeri G. The effects of Er:YAG laser treatment on titanium surface profile and osteoblastic cell activity: an in vitro study. *J Periodontol* 2011: **82**: 1169–1177.
93. Ganz CH. Evaluation of the safety of the carbon dioxide laser used in conjunction with root form implants: a pilot study. *J Prosthet Dent* 1994: **71**: 27–30.
94. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. *J Biomed Sci* 2009: **16**: 4 (http://www.jbiomedsci.com/content/16/11/14).
95. Gaspirc B, Skaleric U. Clinical evaluation of periodontal surgical treatment with an Er:YAG laser: 5-year results. *J Periodontol* 2007: **78**: 1864–1871.
96. Gavish L, Perez LS, Reissman P, Gertz SD. Irradiation with 780 nm diode laser attenuates inflammatory cytokines but

upregulates nitric oxide in lipopolysaccharide-stimulated macrophages: implications for the prevention of aneurysm progression. *Lasers Surg Med* 2008: **40**: 371–378.

97. Giannelli M, Bani D, Viti C, Tani A, Lorenzini L, Zecchi-Orlandini S, Formigli L. Comparative evaluation of the effects of different photoablative laser irradiation protocols on the gingiva of periodontopathic patients. *Photomed Laser Surg* 2012: **30**: 222–230.
98. Giannelli M, Formigli L, Bani D. Comparative evaluation of photoablative efficacy of erbium: yttrium-aluminium-garnet and diode laser for the treatment of gingival hyperpigmentation. A randomized split-mouth clinical trial. *J Periodontol* 2014: **85**: 554–561.
99. Giannelli M, Formigli L, Lorenzini L, Bani D. Combined photoablative and photodynamic diode laser therapy as an adjunct to non-surgical periodontal treatment: a randomized split-mouth clinical trial. *J Clin Periodontol* 2012: **39**: 962–970.
100. Giannini R, Vassalli M, Chellini F, Polidori L, Dei R, Giannelli M. Neodymium:yttrium aluminum garnet laser irradiation with low pulse energy: a potential tool for the treatment of peri-implant disease. *Clin Oral Implants Res* 2006: **17**: 638–643.
101. Goharkhay K, Moritz A, Wilder-Smith P, Schoop U, Kluger W, Jakolitsch S, Sperr W. Effects on oral soft tissue produced by a diode laser in vitro. *Lasers Surg Med* 1999: **25**: 401–406.
102. Gokhale SR, Padhye AM, Byakod G, Jain SA, Padbidri V, Shivaswamy S. A comparative evaluation of the efficacy of diode laser as an adjunct to mechanical debridement versus conventional mechanical debridement in periodontal flap surgery: a clinical and microbiological study. *Photomed Laser Surg* 2012: **30**: 598–603.
103. Gold SI, Vilardi MA. Pulsed laser beam effects on gingiva. *J Clin Periodontol* 1994: **21**: 391–396.
104. Gomez C, Dominguez A, Garcia-Kass AI, Garcia-Nunez JA. Adjunctive Nd:YAG laser application in chronic periodontitis: clinical, immunological, and microbiological aspects. *Lasers Med Sci* 2011: **26**: 453–463.
105. Goultschin J, Gazit D, Bichacho N, Bab I. Changes in teeth and gingiva of dogs following laser surgery: a block surface light microscope study. *Lasers Surg Med* 1988: **8**: 402–408.
106. Gregg RH, McCarthy DK. Laser ENAP for periodontal bone regeneration. *Dent Today* 1998: **17**: 88–91.
107. Gutknecht N, Zimmermann R, Lampert F. Lasers in periodonology: state of the art. *J Oral Laser Applications* 2001: **1**: 169–179.
108. Guzzardella GA, Fini M, Torricelli P, Giavaresi G, Giardino R. Laser stimulation on bone defect healing: an in vitro study. *Lasers Med Sci* 2002: **17**: 216–220.
109. Haina D, Landthaler M, Braun-Falco O, Waidelich W. Comparison of the maximum coagulation depth in human skin for different types of medical lasers. *Lasers Surg Med* 1987: **7**: 355–362.
110. Hale GM, Querry MR. Optical constants of water in the 200-nm to 200-μm wavelength region. *Appl Opt* 1973: **12**: 555–563.
111. Harris DM, Gregg RH 2nd, McCarthy DK, Colby LE, Tilt LV. Laser-assisted new attachment procedure in private practice. *Gen Dent* 2004: **52**: 396–403.
112. Hirata S, Kitamura C, Fukushima H, Nakamichi I, Abiko Y, Terashita M, Jimi E. Low-level laser irradiation enhances BMP-induced osteoblast differentiation by stimulating the BMP/Smad signaling pathway. *J Cell Biochem* 2010: **111**: 1445–1452.
113. Horton JE, Tarpley TM Jr, Wood LD. The healing of surgical defects in alveolar bone produced with ultrasonic instrumentation, chisel, and rotary bur. *Oral Surg Oral Med Oral Pathol* 1975: **39**: 536–546.
114. Ishikawa I, Aoki A, Takasaki A. Potential applications of erbium:YAG laser in periodontics. *J Periodontal Res* 2004: **39**: 275–285.
115. Ishikawa I, Aoki A, Takasaki AA. Clinical application of erbium:YAG laser in periodontology. *J Int Acad Periodontol* 2008: **10**: 22–30.
116. 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.
117. Ishikawa I, Iwata T, Washio K, Okano T, Nagasawa T, Iwasaki K, Ando T. Cell sheet engineering and other novel cell-based approaches to periodontal regeneration. *Periodontol 2000* 2009: **51**: 220–238.
118. Ishikawa I, Okamoto T, Morita S, Shiramizu F, Fuma Y, Ichinose S, Okano T, Ando T. Blue-violet light emitting diode (LED) irradiation immediately controls socket bleeding following tooth extraction: clinical and electron microscopic observations. *Photomed Laser Surg* 2011: **29**: 333–338.
119. Ishikawa K. Effects of Nd:YAG laser irradiation in the periodontal pockets on bacterial adhesion and change of temperature on root surfaces and clinical symptoms. *Aichi-Gakuin J Dent Sci* 1996: **34**: 465–480 (in Japanese, English abstract).
120. Israel M, Cobb CM, Rossmann JA, Spencer P. The effects of CO_2, Nd:YAG and Er:YAG lasers with and without surface coolant on tooth root surfaces. An in vitro study. *J Clin Periodontol* 1997: **24**: 595–602.
121. Israel M, Rossmann JA, Froum SJ. Use of the carbon dioxide laser in retarding epithelial migration: a pilot histological human study utilizing case reports. *J Periodontol* 1995: **66**: 197–204.
122. Izumi Y, Aoki A, Yamada Y, Kobayashi H, Iwata T, Akizuki T, Suda T, Nakamura S, Wara-Aswapati N, Ueda M, Ishikawa I. Current and future periodontal tissue engineering. *Periodontol 2000* 2011: **56**: 166–187.
123. Jin JY, Lee SH, Yoon HJ. A comparative study of wound healing following incision with a scalpel, diode laser or Er, Cr:YSGG laser in guinea pig oral mucosa: A histological and immunohistochemical analysis. *Acta Odontol Scand* 2010: **68**: 232–238.
124. Kamma JJ, Vasdekis VG, Romanos GE. The effect of diode laser (980 nm) treatment on aggressive periodontitis: evaluation of microbial and clinical parameters. *Photomed Laser Surg* 2009: **27**: 11–19.
125. Kang HW, Oh J, Welch AJ. Investigations on laser hard tissue ablation under various environments. *Phys Med Biol* 2008: **53**: 3381–3390.
126. Karu T. Laser biostimulation: a photobiological phenomenon. *J Photochem Photobiol, B* 1989: **3**: 638–640.
127. Karu T. Photobiology of low-power laser effects. *Health Phys* 1989: **56**: 691–704.
128. Karu T, Pyatibrat L, Kalendo G. Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. *J Photochem Photobiol, B* 1995: **27**: 219–223.

129. Kato J, Awazu K, Shinoki T, Moriya K. *A to Z guide to dental laser treatment*. Tokyo: Ishiyaku Pulishers, 2003: 175.
130. Kato T, Kusakari H, Hoshino E. Bactericidal efficacy of carbon dioxide laser against bacteria-contaminated titanium implant and subsequent cellular adhesion to irradiated area. *Lasers Surg Med* 1998: **23**: 299–309.
131. Kawashima Y, Aoki A, Ishii S, Watanabe H, Ishikawa I. Er:YAG laser treatment of gingival melanin pigmentation. In: Ishikawa I, Frame JW, Aoki A, editors. *Lasers in dentistry - revolution of dental treatment in the new millennium*, Amsterdam: Elsevier Science, 2003: 245–248.
132. Kazancioglu HO, Ezirganli S, Aydin MS. Effects of laser and ozone therapies on bone healing in the calvarial defects. *J Craniofac Surg* 2013: **24**: 2141–2146.
133. Kelbauskiene S, Baseviciene N, Goharkhay K, Moritz A, Machiulskiene V. One-year clinical results of Er, Cr:YSGG laser application in addition to scaling and root planing in patients with early to moderate periodontitis. *Lasers Med Sci* 2011: **26**: 445–452.
134. Kesler G, Romanos G, Koren R. Use of Er:YAG laser to improve osseointegration of titanium alloy implants - a comparison of bone healing. *Int J Oral Maxillofac Implants* 2006: **21**: 375–379.
135. Kesler G, Shvero DK, Tov YS, Romanos G. Platelet derived growth factor secretion and bone healing after Er:YAG laser bone irradiation. *J Oral Implantol* 2011: **37**: 195–204.
136. Khadra M, Kasem N, Haanaes HR, Ellingsen JE, Lyngstadaas SP. Enhancement of bone formation in rat calvarial bone defects using low-level laser therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004: **97**: 693–700.
137. Khadra M, Lyngstadaas SP, Haanaes HR, Mustafa K. Effect of laser therapy on attachment, proliferation and differentiation of human osteoblast-like cells cultured on titanium implant material. *Biomaterials* 2005: **26**: 3503–3509.
138. Kim HK, Kim JH, Abbas AA, Kim DO, Park SJ, Chung JY, Song EK, Yoon TR. Red light of 647 nm enhances osteogenic differentiation in mesenchymal stem cells. *Lasers Med Sci* 2009: **24**: 214–222.
139. Kim K, Kim IS, Cho TH, Seo YK, Hwang SJ. High-intensity Nd:YAG laser accelerates bone regeneration in calvarial defect models. *J Tissue Eng Regen Med* 2013: doi: 10.1002/term.1845. [Epub ahead of print].
140. Kim YD, Kim SS, Hwang DS, Kim SG, Kwon YH, Shin SH, Kim UK, Kim JR, Chung IK. Effect of low-level laser treatment after installation of dental titanium implant-immunohistochemical study of RANKL, RANK, OPG: an experimental study in rats. *Lasers Surg Med* 2007: **39**: 441–450.
141. Kimura Y, Yu DG, Fujita A, Yamashita A, Murakami Y, Matsumoto K. Effects of erbium, chromium:YSGG laser irradiation on canine mandibular bone. *J Periodontol* 2001: **72**: 1178–1182.
142. Kiyosaki T, Mitsui N, Suzuki N, Shimizu N. Low-level laser therapy stimulates mineralization via increased Runx2 expression and ERK phosphorylation in osteoblasts. *Photomed Laser Surg* 2010: **28**(Suppl 1): S167–S172. Erratum in: Photomed Laser Surg. 2010: 2028: 2715.
143. Kojima T, Shimada K, Iwasaki H, Ito K. Inhibitory effects of a super pulsed carbon dioxide laser at low energy density on periodontopathic bacteria and lipopolysaccharide in vitro. *J Periodontal Res* 2005: **40**: 469–473.
144. Komatsu Y, Morozumi T, Abe D, Okada M, Nakasone N, Okuda K, Yoshie H. Effects of erbium-doped: yttrium aluminum garnet (Er:YAG) laser on bacteremia due to scaling and root planing. *J Lasers Med Sci* 2012: **3**: 175–184.
145. Kotsakis GA, Konstantinidis I, Karoussis IK, Ma X, Chu H. A systematic review and meta-analysis of the effect of various laser wavelengths in the treatment of peri-implantitis. *J Periodontol* 2014: **85**: 1203–1213.
146. Kranendonk A, van der Reijden W, van Winkelhoff A, van der Weijden G. The bactericidal effect of a Genius Nd:YAG laser. *Int J Dent Hyg* 2010: **8**: 63–67.
147. Krause LS, Cobb CM, Rapley JW, Killoy WJ, Spencer P. Laser irradiation of bone. I. An in vitro study concerning the effects of the CO_2 laser on oral mucosa and subjacent bone. *J Periodontol* 1997: **68**: 872–880.
148. Kreisler M, Al Haj H, d'Hoedt B. Clinical efficacy of semiconductor laser application as an adjunct to conventional scaling and root planing. *Lasers Surg Med* 2005: **37**: 350–355.
149. Kreisler M, Al Haj H, d'Hoedt B. Temperature changes at the implant-bone interface during simulated surface decontamination with an Er:YAG laser. *Int J Prosthodont* 2002: **15**: 582–587.
150. Kreisler M, Al Haj H, Daublander M, Gotz H, Duschner H, Willershausen B, D'Hoedt B. Effect of diode laser irradiation on root surfaces in vitro. *J Clin Laser Med Surg* 2002: **20**: 63–69.
151. Kreisler M, Al Haj H, Gotz H, Duschner H, d'Hoedt B. Effect of simulated CO_2 and GaAlAs laser surface decontamination on temperature changes in Ti-plasma sprayed dental implants. *Lasers Surg Med* 2002: **30**: 233–239.
152. Kreisler M, Christoffers AB, Willershausen B, d'Hoedt B. Effect of low-level GaAlAs laser irradiation on the proliferation rate of human periodontal ligament fibroblasts: an in vitro study. *J Clin Periodontol* 2003: **30**: 353–358.
153. Kreisler M, Gotz H, Duschner H. Effect of Nd:YAG, Ho: YAG, Er:YAG, CO_2, and GaAIAs laser irradiation on surface properties of endosseous dental implants. *Int J Oral Maxillofac Implants* 2002: **17**: 202–211.
154. Kreisler M, Kohnen W, Christoffers AB, Gotz H, Jansen B, Duschner H, d'Hoedt B. In vitro evaluation of the biocompatibility of contaminated implant surfaces treated with an Er: YAG laser and an air powder system. *Clin Oral Implants Res* 2005: **16**: 36–43.
155. 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.
156. Kreisler M, Kohnen W, Marinello C, Schoof J, Langnau E, Jansen B, d'Hoedt B. Antimicrobial efficacy of semiconductor laser irradiation on implant surfaces. *Int J Oral Maxillofac Implants* 2003: **18**: 706–711.
157. Krohn-Dale I, Boe OE, Enersen M, Leknes KN. Er:YAG laser in the treatment of periodontal sites with recurring chronic inflammation: a 12-month randomized, controlled clinical trial. *J Clin Periodontol* 2012: **39**: 745–752.
158. Kushibiki T, Awazu K. Blue laser irradiation enhances extracellular calcification of primary mesenchymal stem cells. *Photomed Laser Surg* 2009: **27**: 493–498.

159. Labanca M, Azzola F, Vinci R, Rodella LF. Piezoelectric surgery: twenty years of use. *Br J Oral Maxillofac Surg* 2008: **46**: 265–269.
160. Lafaurie GI, Mayorga-Fayad I, Torres MF, Castillo DM, Aya MR, Baron A, Hurtado PA. Periodontopathic microorganisms in peripheric blood after scaling and root planing. *J Clin Periodontol* 2007: **34**: 873–879.
161. Lee CY. A new method to harvest ramus bone using the erbium, chromium:yttrium-scandium-gallium-garnet laser. *J Oral Maxillofac Surg* 2005: **63**: 879–882.
162. Lee SY, Piao C, Heo SJ, Koak JY, Lee JH, Kim TH, Kim MJ, Kwon HB, Kim SK. A comparison of bone bed preparation with laser and conventional drill on the relationship between implant stability quotient (ISQ) values and implant insertion variables. *J Adv Prosthodont* 2010: **2**: 148–153.
163. Lewandrowski KU, Lorente C, Schomacker KT, Flotte TJ, Wilkes JW, Deutsch TF. Use of the Er:YAG laser for improved plating in maxillofacial surgery: comparison of bone healing in laser and drill osteotomies. *Lasers Surg Med* 1996: **19**: 40–45.
164. Li WT, Leu YC, Wu JL. Red-light light-emitting diode irradiation increases the proliferation and osteogenic differentiation of rat bone marrow mesenchymal stem cells. *Photomed Laser Surg* 2010: **28**(Suppl 1): S157–S165.
165. Liu CM, Hou LT, Wong MY, Lan WH. Comparison of Nd: YAG laser versus scaling and root planing in periodontal therapy. *J Periodontol* 1999: **70**: 1276–1282.
166. Lopes BM, Theodoro LH, Melo RF, Thompson GM, Marcantonio RA. Clinical and microbiologic follow-up evaluations after non-surgical periodontal treatment with erbium:YAG laser and scaling and root planing. *J Periodontol* 2010: **81**: 682–691.
167. Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg* 2005: **23**: 3–9.
168. Luk K. A Novel technique of laserassisted blood coagulation for tissue regeneration in implant dentistry. *Int Mag Laser Dent* 2009: **1**: 20–21.
169. Luk K, Seto R. A novel technique of Er:YAG laser-enhanced early implant stability for implant dentistry: a pilot clinical case report. *J Laser Dent* 2011: **19**: 162–167.
170. Luomanen M. A comparative study of healing of laser and scalpel incision wounds in rat oral mucosa. *Scand J Dent Res* 1987: **95**: 65–73.
171. Luomanen M, Meurman JH, Lehto VP, Kreisler M, Meyer C, Stender E, Daublander M, Willershausen-Zonnchen B, d'Hoedt B. Extracellular matrix in healing CO_2 laser incision wound. *J Oral Pathol* 1987: **16**: 322–331.
172. Luomanen M, Virtanen I, Willershausen-Zonnchen B, d'Hoedt B. Fibronectins in healing incision, excision and laser wounds. *J Oral Pathol Med* 1991: **20**: 133–138.
173. Mailoa J, Lin GH, Chan HL, Maceachern M, Wang HL. Clinical outcomes of using lasers for peri-implantitis surface detoxification: a systematic review and meta-analysis. *J Periodontol* 2014: **85**: 1194–1202.
174. Martins GL, Puricelli E, Baraldi CE, Ponzoni D. Bone healing after bur and Er:YAG laser ostectomies. *J Oral Maxillofac Surg* 2011: **69**: 1214–1220.
175. Maruyama H, Aoki A, Sasaki KM, Takasaki AA, Iwasaki K, Ichinose S, Oda S, Ishikawa I, Izumi Y. The effect of chemical and/or mechanical conditioning on the Er:YAG laser-treated root cementum: analysis of surface morphology and periodontal ligament fibroblast attachment. *Lasers Surg Med* 2008: **40**: 211–222.
176. Matsuyama T, Aoki A, Oda S, Yoneyama T, Ishikawa I. Effects of the Er:YAG laser irradiation on titanium implant materials and contaminated implant abutment surfaces. *J Clin Laser Med Surg* 2003: **21**: 7–17.
177. Mavrogiannis M, Ellis JS, Seymour RA, Thomason JM. The efficacy of three different surgical techniques in the management of drug-induced gingival overgrowth. *J Clin Periodontol* 2006: **33**: 677–682.
178. McDavid VG, Cobb CM, Rapley JW, Glaros AG, Spencer P. Laser irradiation of bone: III. Long-term healing following treatment by CO_2 and Nd:YAG lasers. *J Periodontol* 2001: **72**: 174–182.
179. McGuire MK, Scheyer ET. Laser-assisted flapless crown lengthening: a case series. *Int J Periodontics Restorative Dent* 2011: **31**: 357–364.
180. Merigo E, Clini F, Fornaini C, Oppici A, Paties C, Zangrandi A, Fontana M, Rocca JP, Meleti M, Manfredi M, Cella L, Vescovi P. Laser-assisted surgery with different wavelengths: a preliminary ex vivo study on thermal increase and histological evaluation. *Lasers Med Sci* 2013: **28**: 497–504.
181. Merli LA, Santos MT, Genovese WJ, Faloppa F. Effect of low-intensity laser irradiation on the process of bone repair. *Photomed Laser Surg* 2005: **23**: 212–215.
182. Mester E, Mester AF, Mester A. The biomedical effects of laser application. *Lasers Surg Med* 1985: **5**: 31–39.
183. Mester E, Spiry T, Szende B, Tota JG. Effect of laser rays on wound healing. *Am J Surg* 1971: **122**: 532–535.
184. Miyazaki A, Yamaguchi T, Nishikata J, Okuda K, Suda S, Orima K, Kobayashi T, Yamazaki K, Yoshikawa E, Yoshie H. Effects of Nd:YAG and CO_2 laser treatment and ultrasonic scaling on periodontal pockets of chronic periodontitis patients. *J Periodontol* 2003: **74**: 175–180.
185. Mizutani K, Aoki A, Takasaki AA, Kinoshita A, Hayashi C, Oda S, Ishikawa I. Periodontal tissue healing following flap surgery using an Er:YAG laser in dogs. *Lasers Surg Med* 2006: **38**: 314–324.
186. Mombelli A, Lang NP. The diagnosis and treatment of peri-implantitis. *Periodontol 2000* 1998: **17**: 63–76.
187. Morimoto Y, Arai T, Kikuchi M, Nakajima S, Nakamura H. Effect of low-intensity argon laser irradiation on mitochondrial respiration. *Lasers Surg Med* 1994: **15**: 191–199.
188. Morlock BJ, Pippin DJ, Cobb CM, Killoy WJ, Rapley JW. The effect of Nd:YAG laser exposure on root surfaces when used as an adjunct to root planing: an in vitro study. *J Periodontol* 1992: **63**: 637–641.
189. Mouhyi J, Sennerby L, Nammour S, Guillaume P, Van Reck J. Temperature increases during surface decontamination of titanium implants using CO_2 laser. *Clin Oral Implants Res* 1999: **10**: 54–61.
190. Mozzati M, Martinasso G, Cocero N, Pol R, Maggiora M, Muzio G, Canuto RA. Influence of superpulsed laser therapy on healing processes following tooth extraction. *Photomed Laser Surg* 2011: **29**: 565–571.
191. Mullarky MB, Norris CW, Goldberg ID. The efficacy of the CO_2 laser in the sterilization of skin seeded with bacteria: survival at the skin surface and in the plume emissions. *Laryngoscope* 1985: **95**: 186–187.

192. Muthukuru M, Zainvi A, Esplugues EO, Flemmig TF. Non-surgical therapy for the management of peri-implantitis: a systematic review. *Clin Oral Implants Res* 2012: **23**(Suppl 6): 77–83.
193. Nagata MJ, de Campos N, Messora MR, Pola NM, Santinoni CS, Bomfim SR, Fucini SE, Ervolino E, de Almeida JM, Theodoro LH, Garcia VG. Platelet-rich plasma, low-level laser therapy or their combination promote periodontal regeneration in fenestration defects: a preliminary in vivo study. *J Periodontol* 2014: **85**: 770–778.
194. Naka T, Yokose S. Application of laser-induced bone therapy by carbon dioxide laser irradiation in implant therapy. *Int J Dent* 2012: **2012**: 409496.
195. Nakamura Y, Hossain M, Hirayama K, Matsumoto K. A clinical study on the removal of gingival melanin pigmentation with the CO_2 laser. *Lasers Surg Med* 1999: **25**: 140–147.
196. Neil ME, Mellonig JT. Clinical efficacy of the Nd:YAG laser for combination periodontitis therapy. *Pract Periodontic Aesthet Dent* 1997: **9**: 1–5.
197. Nelson JS, Orenstein A, Liaw LH, Berns MW. Mid-infrared erbium:YAG laser ablation of bone: the effect of laser osteotomy on bone healing. *Lasers Surg Med* 1989: **9**: 362–374.
198. Nelson JS, Yow L, Liaw LH, Macleay L, Zavar RB, Orenstein A, Wright WH, Andrews JJ, Berns MW. Ablation of bone and methacrylate by a prototype mid-infrared erbium: YAG laser. *Lasers Surg Med* 1988: **8**: 494–500.
199. Nevins M, Kim SW, Camelo M, Martin IS, Kim D. A prospective 9-month human clinical evaluation of Laser-Assisted New Attachment Procedure (LANAP) therapy. *Int J Periodontics Restorative Dent* 2014: **34**: 21–27.
200. Nevins ML, Camelo M, Schupbach P, Kim SW, Kim DM, Nevins M. Human clinical and histologic evaluation of laser-assisted new attachment procedure. *Int J Periodontics Restorative Dent* 2012: **32**: 497–507.
201. Niemz MH. *Laser-tissue interaction. Fundamentals and applications*. Berlin: Springer-Verlag, 1996.
202. Ninomiya T, Miyamoto Y, Ito T, Yamashita A, Wakita M, Nishisaka T. High-intensity pulsed laser irradiation accelerates bone formation in metaphyseal trabecular bone in rat femur. *J Bone Miner Metab* 2003: **21**: 67–73.
203. Noguchi T, Sanaoka A, Fukuda M, Suzuki S, Aoki T. Combined effects of Nd:YAG laser irradiation with local antibiotic application into periodontal pockets. *J Int Acad Periodontol* 2005: **7**: 8–15.
204. Nuss RC, Fabian RL, Sarkar R, Puliafito CA. Infrared laser bone ablation. *Lasers Surg Med* 1988: **8**: 381–391.
205. Ohshiro T, Calderhead RG. Development of low reactive-level laser therapy and its present status. *J Clin Laser Med Surg* 1991: **9**: 267–275.
206. Omasa S, Motoyoshi M, Arai Y, Ejima K, Shimizu N. Low-level laser therapy enhances the stability of orthodontic mini-implants via bone formation related to BMP-2 expression in a rat model. *Photomed Laser Surg* 2012: **30**: 255–261.
207. Oyster DK, Parker WB, Gher ME. CO_2 lasers and temperature changes of titanium implants. *J Periodontol* 1995: **66**: 1017–1024.
208. Ozawa Y, Shimizu N, Kariya G, Abiko Y. Low-energy laser irradiation stimulates bone nodule formation at early stages of cell culture in rat calvarial cells. *Bone* 1998: **22**: 347–354.
209. Ozcelik O, Cenk Haytac M, Kunin A, Seydaoglu G. Improved wound healing by low-level laser irradiation after gingivectomy operations: a controlled clinical pilot study. *J Clin Periodontol* 2008: **35**: 250–254.
210. Ozcelik O, Cenk Haytac M, Seydaoglu G. Enamel matrix derivative and low-level laser therapy in the treatment of intra-bony defects: a randomized placebo-controlled clinical trial. *J Clin Periodontol* 2008: **35**: 147–156.
211. Pang P, Andreana S, Aoki A, Coluzzi D, Obeidi A, Olivi G, Parker S, Rechmann P, Sulewski J, Sweeney C, Swick M, Yung F. Laser energy in oral soft tissue applications. *J Laser Dent* 2011: **18**: 123–131.
212. Papadaki M, Doukas A, Farinelli WA, Kaban L, Troulis M. Vertical ramus osteotomy with Er:YAG laser: a feasibility study. *Int J Oral Maxillofac Surg* 2007: **36**: 1193–1197.
213. Park JB, Ahn SJ, Kang YG, Kim EC, Heo JS, Kang KL. Effects of increased low-level diode laser irradiation time on extraction socket healing in rats. *Lasers Med Sci* 2013: [Epub ahead of print].
214. Park JH, Heo SJ, Koak JY, Kim SK, Han CH, Lee JH. Effects of laser irradiation on machined and anodized titanium disks. *Int J Oral Maxillofac Implants* 2012: **27**: 265–272.
215. Pereira AN, Eduardo CP, Matson E, Marques MM. Effect of low-power laser irradiation on cell growth and procollagen synthesis of cultured fibroblasts. *Lasers Surg Med* 2002: **31**: 263–267.
216. Perry DA, Goodis HE, White JM. In vitro study of the effects of Nd:YAG laser probe parameters on bovine oral soft tissue excision. *Lasers Surg Med* 1997: **20**: 39–46.
217. Persson GR, Roos-Jansaker AM, Lindahl C, Renvert S. Microbiologic results after non-surgical erbium-doped: yttrium, aluminum, and garnet laser or air-abrasive treatment of peri-implantitis: a randomized clinical trial. *J Periodontol* 2011: **82**: 1267–1278.
218. Persson LG, Mouhyi J, Berglundh T, Sennerby L, Lindhe J. Carbon dioxide laser and hydrogen peroxide conditioning in the treatment of periimplantitis: an experimental study in the dog. *Clin Implant Dent Relat Res* 2004: **6**: 230–238.
219. Perussi LR, Pavone C, de Oliveira GJ, Cerri PS, Marcantonio RA. Effects of the Er, Cr:YSGG laser on bone and soft tissue in a rat model. *Lasers Med Sci* 2012: **27**: 95–102.
220. Pick RM, Colvard MD. Current status of lasers in soft tissue dental surgery. *J Periodontol* 1993: **64**: 589–602.
221. Pick RM, Pecaro BC. Use of the CO_2 laser in soft tissue dental surgery. *Lasers Surg Med* 1987: **7**: 207–213.
222. Pinheiro AL, Limeira Junior Fde A, Gerbi ME, Ramalho LM, Marzola C, Ponzi EA, Soares AO, De Carvalho LC, Lima HC, Goncalves TO. Effect of 830-nm laser light on the repair of bone defects grafted with inorganic bovine bone and decalcified cortical osseus membrane. *J Clin Laser Med Surg* 2003: **21**: 301–306.
223. Pourzarandian A, Watanabe H, Aoki A, Ichinose S, Sasaki K, Nitta H, Ishikawa I. Histological and TEM examination of early stages of bone healing after Er:YAG laser irradiation. *Photomed Laser Surg* 2004: **22**: 355–363.
224. Pourzarandian A, Watanabe H, Ruwanpura SM, Aoki A, Ishikawa I. Effect of low-level Er:YAG laser irradiation on cultured human gingival fibroblasts. *J Periodontol* 2005: **76**: 187–193.
225. Pourzarandian A, Watanabe H, Ruwanpura SM, Aoki A, Noguchi K, Ishikawa I. Er:YAG laser irradiation increases prostaglandin E production via the induction of cyclooxygenase-2 mRNA in human gingival fibroblasts. *J Periodontal Res* 2005: **40**: 182–186.

226. Qadri T, Bohdanecka P, Tuner J, Miranda L, Altamash M, Gustafsson A. The importance of coherence length in laser phototherapy of gingival inflammation: a pilot study. *Lasers Med Sci* 2007: **22**: 245–251.
227. Qadri T, Javed F, Poddani P, Tuner J, Gustafsson A. Long-term effects of a single application of a water-cooled pulsed Nd:YAG laser in supplement to scaling and root planing in patients with periodontal inflammation. *Lasers Med Sci* 2011: **26**: 763–766.
228. Qadri T, Miranda L, Tuner J, Gustafsson A. The short-term effects of low-level lasers as adjunct therapy in the treatment of periodontal inflammation. *J Clin Periodontol* 2005: **32**: 714–719.
229. Qadri T, Poddani P, Javed F, Tuner J, Gustafsson A. A short-term evaluation of Nd:YAG laser as an adjunct to scaling and root planing in the treatment of periodontal inflammation. *J Periodontol* 2010: **81**: 1161–1166.
230. Renvert S, Lindahl C, Roos Jansaker AM, Persson GR. Treatment of peri-implantitis using an Er:YAG laser or an air-abrasive device: a randomized clinical trial. *J Clin Periodontol* 2011: **38**: 65–73.
231. Renvert S, Polyzois I, Claffey N. Surgical therapy for the control of peri-implantitis. *Clin Oral Implants Res* 2012: **23** (Suppl 6): 84–94.
232. Reyhanian A, Coluzzi DJ. Peri-Implantitis Therapy with an Er:YAG Laser. *J Laser Dent* 2008: **16**: 69–74.
233. Ribeiro IW, Sbrana MC, Esper LA, Almeida AL. Evaluation of the effect of the GaAlAs laser on subgingival scaling and root planing. *Photomed Laser Surg* 2008: **26**: 387–391.
234. Roberts GJ. Dentists are innocent! “Everyday” bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. *Pediatr Cardiol* 1999: **20**: 317–325.
235. Romanos G, Crespi R, Barone A, Covani U. Osteoblast attachment on titanium disks after laser irradiation. *Int J Oral Maxillofac Implants* 2006: **21**: 232–236.
236. Romanos G, Ko HH, Froum S, Tarnow D. The use of CO_2 laser in the treatment of peri-implantitis. *Photomed Laser Surg* 2009: **27**: 381–386.
237. Romanos G, Nentwig GH. Diode laser (980 nm) in oral and maxillofacial surgical procedures: clinical observations based on clinical applications. *J Clin Laser Med Surg* 1999: **17**: 193–197.
238. Romanos GE. Clinical applications of the Nd:YAG laser in oral soft tissue surgery and periodontology. *J Clin Laser Med Surg* 1994: **12**: 103–108.
239. 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.
240. Romanos GE, Gladkova ND, Feldchtein FI, Karabut MM, Kiseleva EB, Snopova LB, Fomina YV. Oral mucosa response to laser patterned microcoagulation (LPM) treatment. An animal study. *Lasers Med Sci* 2013: **28**: 25–31.
241. Romanos GE, Nentwig GH. Regenerative therapy of deep peri-implant infrabony defects after CO_2 laser implant surface decontamination. *Int J Periodontics Restorative Dent* 2008: **28**: 245–255.
242. Romanos GE, Pelekanos S, Strub JR. A comparative histological study of wound healing following Nd:YAG laser with different energy parameters and conventional surgical incision in rat skin. *J Clin Laser Med Surg* 1995: **13**: 11–16.
243. Romanos GE, Pelekanos S, Strub JR. Effects of Nd:YAG laser on wound healing processes: clinical and immunohistochemical findings in rat skin. *Lasers Surg Med* 1995: **16**: 368–379.
244. Rooney J, Midda M, Leeming J. A laboratory investigation of the bactericidal effect of a NdYAG laser. *Br Dent J* 1994: **176**: 61–64.
245. Rosa DS, Aranha AC, Eduardo Cde P, Aoki A. Esthetic treatment of gingival melanin hyperpigmentation with Er:YAG laser: short-term clinical observations and patient follow-up. *J Periodontol* 2007: **78**: 2018–2025.
246. Rossmann JA, Cobb CM. Lasers in Periodontal therapy. *Periodontol 2000* 1995: **9**: 150–164.
247. Rossmann JA, Gottlieb S, Koudelka BM, McQuade MJ. Effects of CO_2 laser irradiation on gingiva. *J Periodontol* 1987: **58**: 423–425.
248. Rossmann JA, Israel M. Laser de-epithelialization for enhanced guided tissue regeneration. A paradigm shift? *Dent Clin North Am* 2000: **44**: 793–809.
249. Rossmann JA, McQuade MJ, Turunen DE. Retardation of epithelial migration in monkeys using a carbon dioxide laser: an animal study. *J Periodontol* 1992: **63**: 902–907.
250. Rotundo R, Nieri M, Cairo F, Franceschi D, Mervelt J, Bonaccini D, Esposito M, Pini-Prato G. Lack of adjunctive benefit of Er:YAG laser in non-surgical periodontal treatment: a randomized split-mouth clinical trial. *J Clin Periodontol* 2010: **37**: 526–533.
251. Ryu SW, Lee SH, Yoon HJ. A comparative histological and immunohistochemical study of wound healing following incision with a scalpel, CO2 laser or Er, Cr:YSGG laser in the guinea pig oral mucosa. *Acta Odontol Scand* 2012: **70**: 448–454.
252. Safavi SM, Kazemi B, Esmaeili M, Fallah A, Modarresi A, Mir M. Effects of low-level He-Ne laser irradiation on the gene expression of IL-1beta, TNF-alpha, IFN-gamma, TGF-beta, bFGF, and PDGF in rat’s gingiva. *Lasers Med Sci* 2008: **23**: 331–335.
253. Saglam M, Kantarci A, Dundar N, Hakki SS. Clinical and biochemical effects of diode laser as an adjunct to nonsurgical treatment of chronic periodontitis: a randomized, controlled clinical trial. *Lasers Med Sci* 2014: **29**: 37–46.
254. Sakurai Y, Yamaguchi M, Abiko Y. Inhibitory effect of low-level laser irradiation on LPS-stimulated prostaglandin E2 production and cyclooxygenase-2 in human gingival fibroblasts. *Eur J Oral Sci* 2000: **108**: 29–34.
255. Salina S, Maiorana C, Iezzi G, Colombo A, Fontana F, Piattelli A. Histological evaluation, in rabbit tibiae, of osseointegration of mini-implants in sites prepared with Er:YAG laser versus sites prepared with traditional burs. *J Long Term Eff Med Implants* 2006: **16**: 145–156.
256. Sanz-Moliner JD, Nart J, Cohen RE, Ciancio SG. The effect of an 810-nm diode laser on postoperative pain and tissue response after modified Widman flap surgery: a pilot study in humans. *J Periodontol* 2013: **84**: 152–158.
257. Sasaki KM, Aoki A, Ichinose S, Ishikawa I. Ultrastructural analysis of bone tissue irradiated by Er:YAG Laser. *Lasers Surg Med* 2002: **31**: 322–332.
258. Sasaki KM, Aoki A, Ichinose S, Yoshino T, Yamada S, Ishikawa I. Scanning electron microscopy and Fourier transformed infrared spectroscopy analysis of bone removal

using Er:YAG and CO_2 lasers. *J Periodontol* 2002: **73**: 643–652.

259. Sawabe M, Aoki A, Komaki M, Iwasaki K, Ogita M, Izumi Y. Gingival tissue healing following Er:YAG laser ablation compared to electrosurgery in rats. *Lasers Med Sci* 2013: e-pub Nov 16.
260. Saygun I, Karacay S, Serdar M, Ural AU, Sencimen M, Kurtis B. Effects of laser irradiation on the release of basic fibroblast growth factor (bFGF), insulin like growth factor-1 (IGF-1), and receptor of IGF-1 (IGFBP3) from gingival fibroblasts. *Lasers Med Sci* 2008: **23**: 211–215.
261. Schlee M, Steigmann M, Bratu E, Garg AK. Piezosurgery: basics and possibilities. *Implant Dent* 2006: **15**: 334–340.
262. Schoop U, Kluger W, Moritz A, Nedjelik N, Georgopoulos A, Sperr W. Bactericidal effect of different laser systems in the deep layers of dentin. *Lasers Surg Med* 2004: **35**: 111–116.
263. Schultz RJ, Harvey GP, Fernandez-Beros ME, Krishnamurthy S, Rodriguez JE, Cabello F, Folwaczny M, Benner KU, Flasskamp B, Mehl A, Hickel R. Bactericidal effects of the neodymium:YAG laser: in vitro study. *Lasers Surg Med* 1986: **6**: 445–448.
264. Schwarz F, Aoki A, Becker J, Sculean A. Laser application in non-surgical periodontal therapy: a systematic review. *J Clin Periodontol* 2008: **35**: 29–44.
265. Schwarz F, Aoki A, Sculean A, Becker J. The impact of laser application on periodontal and peri-implant wound healing. *Periodontol 2000* 2009: **51**: 79–108.
266. Schwarz F, Aoki A, Sculean A, Georg T, Scherbaum W, Becker J. In vivo effects of an Er:YAG laser, an ultrasonic system and scaling and root planing on the biocompatibility of periodontally diseased root surfaces in cultures of human PDL fibroblasts. *Lasers Surg Med* 2003: **33**: 140–147.
267. Schwarz F, Bieling K, Bonsmann M, Latz T, Becker J. Nonsurgical treatment of moderate and advanced periimplantitis lesions: a controlled clinical study. *Clin Oral Investig* 2006: **10**: 279–288.
268. 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.
269. Schwarz F, Hegewald A, John G, Sahm N, Becker J. Four-year follow-up of combined surgical therapy of advanced peri-implantitis evaluating two methods of surface decontamination. *J Clin Periodontol* 2013: **40**: 962–967.
270. Schwarz F, Jepsen S, Herten M, Aoki A, Sculean A, Becker J. Immunohistochemical characterization of periodontal wound healing following nonsurgical treatment with fluorescence controlled Er:YAG laser radiation in dogs. *Lasers Surg Med* 2007: **39**: 428–440.
271. Schwarz F, Jepsen S, Herten M, Sager M, Rothamel D, Becker J. Influence of different treatment approaches on non-submerged and submerged healing of ligature induced peri-implantitis lesions: an experimental study in dogs. *J Clin Periodontol* 2006: **33**: 584–595.
272. Schwarz F, John G, Mainusch S, Sahm N, Jürgen B. Combined surgical therapy of peri-implantitis evaluating two methods of surface debridement and decontamination. A two-year clinical follow up report. *J Clin Periodontol* 2012: **39**: 789–797.
273. Schwarz F, Nuesry E, Bieling K, Herten M, Becker J. Influence of an erbium, chromium-doped yttrium, scandium, gallium, and garnet (Er, Cr:YSGG) laser on the reestablishment of the biocompatibility of contaminated titanium implant surfaces. *J Periodontol* 2006: **77**: 1820–1827.
274. Schwarz F, Olivier W, Herten M, Sager M, Chaker A, Becker J. Influence of implant bed preparation using an Er:YAG laser on the osseointegration of titanium implants: a histomorphometrical study in dogs. *J Oral Rehabil* 2007: **34**: 273–281.
275. Schwarz F, Rothamel D, Sculean A, Georg T, Scherbaum W, Becker J. Effects of an Er:YAG laser and the Vector ultrasonic system on the biocompatibility of titanium implants in cultures of human osteoblast-like cells. *Clin Oral Implants Res* 2003: **14**: 784–792.
276. Schwarz F, Sahm N, Iglhaut G, Becker J. Impact of the method of surface debridement and decontamination on the clinical outcome following combined surgical therapy of peri-implantitis: a randomized controlled clinical study. *J Clin Periodontol* 2011: **38**: 276–284.
277. Schwarz F, Sculean A, Berakdar M, Georg T, Reich E, Becker J. Clinical evaluation of an Er:YAG laser combined with scaling and root planing for non-surgical periodontal treatment. A controlled, prospective clinical study. *J Clin Periodontol* 2003: **30**: 26–34.
278. Schwarz F, Sculean A, Berakdar M, Georg T, Reich E, Becker J. Periodontal treatment with an Er:YAG laser or scaling and root planing. A 2-year follow-up split-mouth study. *J Periodontol* 2003: **74**: 590–596.
279. Schwarz F, Sculean A, Berakdar M, Szathmari L, Georg T, Becker J. In vivo and in vitro effects of an Er:YAG laser, a GaAlAs diode laser, and scaling and root planing on periodontally diseased root surfaces: a comparative histologic study. *Lasers Surg Med* 2003: **32**: 359–366.
280. Schwarz F, Sculean A, Georg T, Becker J. Clinical evaluation of the Er:YAG laser in combination with an enamel matrix protein derivative for the treatment of intrabony periodontal defects: a pilot study. *J Clin Periodontol* 2003: **30**: 975–981.
281. Schwarz F, Sculean A, Georg T, Reich E. Periodontal treatment with an Er: YAG laser compared to scaling and root planing. A controlled clinical study. *J Periodontol* 2001: **72**: 361–367.
282. 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.
283. Schwarz F, Sculean A, Rothamel D, Schwenzer K, Georg T, Becker J. Clinical evaluation of an Er:YAG laser for nonsurgical treatment of peri-implantitis: a pilot study. *Clin Oral Implants Res* 2005: **16**: 44–52.
284. Sculean A, Schwarz F, Becker J. Anti-infective therapy with an Er:YAG laser: influence on peri-implant healing. *Expert Rev Med Devices* 2005: **2**: 267–276.
285. Sculean A, Schwarz F, Berakdar M, Romanos GE, Arweiler NB, Becker J. Periodontal treatment with an Er:YAG laser compared to ultrasonic instrumentation: a pilot study. *J Periodontol* 2004: **75**: 966–973.
286. Sculean A, Schwarz F, Berakdar M, Windisch P, Arweiler NB, Romanos GE. Healing of intrabony defects following surgical treatment with or without an Er:YAG laser. *J Clin Periodontol* 2004: **31**: 604–608.

287. Seka W, Featherstone JDB, Fried D, Visuri SR, Walsh JT. Laser ablation of dental hard tissue: from explosive ablation to plasma-mediated ablation. *Proc SPIE* 1996: **2672**: 144–158.
288. Seka W, Rechmann P, Featherstone JDB, Fried D. Laser ablation of dental hard tissue. *J Laser Dent* 2007: **15**: 61–72.
289. Sgolastra F, Petrucci A, Gatto R, Monaco A. Efficacy of Er:YAG laser in the treatment of chronic periodontitis: systematic review and meta-analysis. *Lasers Med Sci* 2012: **27**: 661–673.
290. Shimizu N, Mayahara K, Kiyosaki T, Yamaguchi A, Ozawa Y, Abiko Y. Low-intensity laser irradiation stimulates bone nodule formation via insulin-like growth factor-I expression in rat calvarial cells. *Lasers Surg Med* 2007: **39**: 551–559.
291. Shimizu N, Yamaguchi M, Goseki T, Shibata Y, Takiguchi H, Iwasawa T, Abiko Y. Inhibition of prostaglandin E2 and interleukin 1-beta production by low-power laser irradiation in stretched human periodontal ligament cells. *J Dent Res* 1995: **74**: 1382–1388.
292. Shimotoyodome A, Okajima M, Kobayashi H, Tokimitsu I, Fujimura A. Improvement of macromolecular clearance via lymph flow in hamster gingiva by low-power carbon dioxide laser-irradiation. *Lasers Surg Med* 2001: **29**: 442–447.
293. Shin SI, Min HK, Park BH, Kwon YH, Park JB, Herr Y, Heo SJ, Chung JH. The effect of Er:YAG laser irradiation on the scanning electron microscopic structure and surface roughness of various implant surfaces: an in vitro study. *Lasers Med Sci* 2011: **26**: 767–776.
294. Shiozaki H, Yokose S, Saitou M, Suzuki Y, Hirose N, Shimizu H, Masuda K, Hasegawa A, Katayama T, Okumura Y. Carbon dioxide laser irradiation stimulates bone formation in rat tibiae. *J Jpn Soc Laser Dent* 2005: **16**: 23–30 (in Japanese, English abstract).
295. Silva JA, Pinheiro AL, Oliveira MG, Weismann R, Ramalho LM, Nicolau RA. Computerized morphometric assessment of the effect of low-level laser therapy on bone repair: an experimental animal study. *J Clin Laser Med Surg* 2002: **20**: 83–87.
296. Simon BI, Schuback P, Deasy MJ, Kelner RM. The destructive potential of electrosurgery on the periodontium. *J Periodontol* 1976: **47**: 342–347.
297. Sinha UK, Gallagher LA. Effects of steel scalpel, ultrasonic scalpel, CO_2 laser, and monopolar and bipolar electrosurgery on wound healing in guinea pig oral mucosa. *Laryngoscope* 2003: **113**: 228–236.
298. Slot DE, Jorritsma KH, Cobb CM, Van der Weijden GA. The effect of the thermal diode laser (wavelength 808-980 nm) in non- surgical periodontal therapy: a systematic review and meta-analysis. *J Clin Periodontol* 2014: **41**: 681–692.
299. Slot DE, Kranendonk AA, Paraskevas S, Van der Weijden F. The effect of a pulsed Nd:YAG laser in non-surgical periodontal therapy. *J Periodontol* 2009: **80**: 1041–1056.
300. Slot DE, Timmerman MF, Versteeg PA, van der Velden U, van der Weijden FA. Adjunctive clinical effect of a water-cooled Nd:YAG laser in a periodontal maintenance care programme: a randomized controlled trial. *J Clin Periodontol* 2012: **39**: 1159–1165.
301. Small IA, Osborn TP, Fuller T, Hussain M, Kobernick S. Observations of carbon dioxide laser and bone bur in the osteotomy of the rabbit tibia. *J Oral Surg* 1979: **37**: 159–166.
302. Soukos NS, Goodson JM. Photodynamic therapy in the control of oral biofilms. *Periodontol 2000* 2011: **55**: 143–166.
303. Stein A, Benayahu D, Maltz L, Oron U. Low-level laser irradiation promotes proliferation and differentiation of human osteoblasts in vitro. *Photomed Laser Surg* 2005: **23**: 161–166.
304. Stübinger S, Biermeier K, Bachi B, Ferguson SJ, Sader R, von Rechenberg B. Comparison of Er:YAG laser, piezoelectric, and drill osteotomy for dental implant site preparation: a biomechanical and histological analysis in sheep. *Lasers Surg Med* 2010: **42**: 652–661.
305. Stübinger S, Dissmann JP, Pinho NC, Saldamli B, Seitz O, Sader R. A preliminary report about treatment of bisphosphonate related osteonecrosis of the jaw with Er:YAG laser ablation. *Lasers Surg Med* 2009: **41**: 26–30.
306. Stübinger S, Etter C, Miskiewicz M, Homann F, Saldamli B, Wieland M, Sader R. Surface alterations of polished and sandblasted and acid-etched titanium implants after Er:YAG, carbon dioxide, and diode laser irradiation. *Int J Oral Maxillofac Implants* 2010: **25**: 104–111.
307. Stübinger S, Henke J, Donath K, Deppe H. Bone regeneration after peri-implant care with the CO2 laser: a fluorescence microscopy study. *Int J Oral Maxillofac Implants* 2005: **20**: 203–210.
308. Stübinger S, Homann F, Etter C, Miskiewicz M, Wieland M, Sader R. Effect of Er:YAG, COü and diode laser irradiation on surface properties of zirconia endosseous dental implants. *Lasers Surg Med* 2008: **40**: 223–228.
309. Stübinger S, Landes C, Seitz O, Sader R. Er:YAG laser osteotomy for intraoral bone grafting procedures: a case series with a fiber-optic delivery system. *J Periodontol* 2007: **78**: 2389–2394.
310. Stübinger S, Nuss K, Landes C, von Rechenberg B, Sader R. Harvesting of intraoral autogenous block grafts from the chin and ramus region: preliminary results with a variable square pulse Er:YAG laser. *Lasers Surg Med* 2008: **40**: 312–318.
311. Stübinger S, Nuss K, Pongratz M, Price J, Sader R, Zeilhofer HF, von Rechenberg B. Comparison of Er:YAG laser and piezoelectric osteotomy: An animal study in sheep. *Lasers Surg Med* 2010: **42**: 743–751.
312. Stübinger S, von Rechenberg VB, Zeilhofer HF, Sader R, Landes C. Er:YAG laser osteotomy for removal of impacted teeth: Clinical comparison of two techniques. *Lasers Surg Med* 2007: **39**: 583–588.
313. Sugi D, Fukuda M, Minoura S, Yamada Y, Tako J, Miwa K, Noguchi T, Nakashima K, Sobue T, Noguchi T. Effects of irradiation of Er:YAG laser on quantity of endotoxin and microhardness of surface in exposed root after removal of calculus. *Jpn J Conserv Dent* 1998: **41**: 1009–1017 (in Japanese, English abstract).
314. Tajima N. In vitro effects of carbon dioxide laser irradiation on bone formation in rat tibiae. *J Jpn Soc Laser Dent* 2003: **14**: 32–43 (in Japanese, English abstract).
315. Tajima N, Yokose S, Kadokura H, Adachi K, Kakitsubo H, Matsuoka T, Fujieda K, Hasegawa A, Katayama T. The effects of CO_2 laser irradiation on activation of MAPK in rat skeletal muscle cells. *J Jpn Soc Laser Dent* 2002: **45**: 583–590 (in Japanese, English abstract).
316. Takasaki AA, Aoki A, Mizutani K, Kikuchi S, Oda S, Ishikawa I. Er:YAG laser therapy for peri-implant

infection: a histological study. *Lasers Med Sci* 2007: **22**: 143–157.

317. Takasaki AA, Aoki A, Mizutani K, Schwarz F, Sculean A, Wang CY, Koshy G, Romanos G, Ishikawa I, Izumi Y. Application of antimicrobial photodynamic therapy in periodontal and peri-implant diseases. *Periodontol 2000* 2009: **51**: 109–140.
318. Takei HH, Carranza FA. Gingival surgical techniques. In: Newman MG, Takei HH, Klokkevold PR, Carranza FA, editors. *Carranza's clinical periodontology.* 10th edition. St. Louis: Elsevier, 2006: 915.
319. Tal H, Oegiesser D, Tal M. Gingival depigmentation by erbium:YAG laser: clinical observations and patient responses. *J Periodontol* 2003: **74**: 1660–1667.
320. Tang E, Arany P. Photobiomodulation and implants: implications for dentistry. *J Periodontal Implant Sci* 2013: **43**: 262–268.
321. Taniguchi Y, Aoki A, Mizutani K, Takeuchi Y, Ichinose S, Takasaki AA, Schwarz F, Izumi Y. Optimal Er:YAG laser irradiation parameters for debridement of microstructured fixture surfaces of titanium dental implants. *Lasers Med Sci* 2013: **28**: 1057–1068.
322. Ting CC, Fukuda M, Watanabe T, Aoki T, Sanaoka A, Noguchi T. Effects of Er, Cr:YSGG laser irradiation on the root surface: morphologic analysis and efficiency of calculus removal. *J Periodontol* 2007: **78**: 2156–2164.
323. To TN, Rabie AB, Wong RW, McGrath CP. The adjunct effectiveness of diode laser gingivectomy in maintaining periodontal health during orthodontic treatment. *Angle Orthod* 2013: **83**: 43–47.
324. Tomasi C, Schander K, Dahlen G, Wennstrom JL. Short-term clinical and microbiologic effects of pocket debridement with an Er:YAG laser during periodontal maintenance. *J Periodontol* 2006: **77**: 111–118.
325. Tosun E, Tasar F, Strauss R, Kivanc DG, Ungor C. Comparative evaluation of antimicrobial effects of Er:YAG, diode, and CO_2 lasers on titanium discs: an experimental study. *J Oral Maxillofac Surg* 2012: **70**: 1064–1069.
326. Tseng P, Liew V. The potential applivations of a Nd:YAG dental laser in periodontal treatment. *Periodontology (Australia)* 1990: **11**: 20–22.
327. Tuby H, Maltz L, Oron U. Low-level laser irradiation (LLLI) promotes proliferation of mesenchymal and cardiac stem cells in culture. *Lasers Surg Med* 2007: **39**: 373–378.
328. Tucker D, Cobb CM, Rapley JW, Killoy WJ. Morphologic changes following in vitro CO_2 laser treatment of calculus-ladened root surfaces. *Lasers Surg Med* 1996: **18**: 150–156.
329. Vaderhobli RM, White JM, Le C, Ho S, Jordan R. In vitro study of the soft tissue effects of microsecond-pulsed CO_2 laser parameters during soft tissue incision and sulcular debridement. *Lasers Surg Med* 2010: **42**: 257–263.
330. Vescovi P, Manfredi M, Merigo E, Meleti M, Fornaini C, Rocca JP, Nammour S. Surgical approach with Er:YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT). *Lasers Med Sci* 2010: **25**: 101–113.
331. Vescovi P, Meleti M, Merigo E, Manfredi M, Fornaini C, Guidotti R, Nammour S. Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd:YAG low-level laser therapy. *Med Oral Patol Oral Cir Bucal* 2013: **18**: e680–e685.
332. Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC. Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation. *Lasers Med Sci* 2003: **18**: 95–99.
333. Walsh JT Jr, Cummings JP. Effect of the dynamic optical properties of water on midinfrared laser ablation. *Lasers Surg Med* 1994: **15**: 295–305.
334. Walsh JT Jr, Flotte TJ, Deutsch TF. Er:YAG laser ablation of tissue: effect of pulse duration and tissue type on thermal damage. *Lasers Surg Med* 1989: **9**: 314–326.
335. Wang X, Zhang C, Matsumoto K. In vivo study of the healing processes that occur in the jaws of rabbits following perforation by an Er, Cr:YSGG laser. *Lasers Med Sci* 2005: **20**: 21–27.
336. Watanabe H, Ishikawa I, Suzuki M, Hasegawa K. Clinical assessments of the erbium:YAG laser for soft tissue surgery and scaling. *J Clin Laser Med Surg* 1996: **14**: 67–75.
337. White JM, Gekelman D, Shin K, Park J, Swenson T, Rouse B, Tran K, Bullard S, Scott-Beckles B, Oto MG, Buhler JS, Yamamoto A. Laser interaction with dental soft tissues: What do we know from our years of applied scientific research? *Proc SPIE* 2002: **4610**: 39–48.
338. White JM, Goodis HE, Rose CL. Use of the pulsed Nd:YAG laser for intraoral soft tissue surgery. *Lasers Surg Med* 1991: **11**: 455–461.
339. White JM, Goodis HE, Yessik MJ, Myers TD. Histologic effects of a high-repetition pulsed Nd:YAG laser on intraoral soft tissue. *Proc SPIE* 1995: **2394**: 143–153.
340. Williams TM, Cobb CM, Rapley JW, Killoy WJ. Histologic evaluation of alveolar bone following CO_2 laser removal of connective tissue from periodontal defects. *Int J Periodontics Restorative Dent* 1995: **15**: 497–506.
341. Woodruff LD, Bounkeo JM, Brannon WM, Dawes KS, Barham CD, Waddell DL, Enwemeka CS. The efficacy of laser therapy in wound repair: a meta-analysis of the literature. *Photomed Laser Surg* 2004: **22**: 241–247.
342. Wu JY, Wang YH, Wang GJ, Ho ML, Wang CZ, Yeh ML, Chen CH. Low-power GaAlAs laser irradiation promotes the proliferation and osteogenic differentiation of stem cells via IGF1 and BMP2. *PLoS ONE* 2012: **7**: e44027.
343. Yamaguchi H, Kobayashi K, Osada R, Sakuraba E, Nomura T, Arai T, Nakamura J. Effects of irradiation of an erbium:YAG laser on root surfaces. *J Periodontol* 1997: **68**: 1151–1155.
344. Yamamoto A, Tanabe T. Treatment of peri-implantitis around TiUnite-surface implants using Er:YAG laser microexplosions. *Int J Periodontics Restorative Dent* 2013: **33**: 21–30.
345. Yamasaki A, Ito H, Yusa J, Sakurai Y, Okuyama N, Ozawa R. Expression of heat shock proteins, Hsp70 and Hsp25, in the rat gingiva after irradiation with a CO_2 laser in coagulation mode. *J Periodontal Res* 2010: **45**: 323–330.
346. Yamasaki A, Tamamura K, Sakurai Y, Okuyama N, Yusa J, Ito H. Remodeling of the rat gingiva induced by CO_2 laser coagulation mode. *Lasers Surg Med* 2008: **40**: 695–703.
347. Yeh S, Jain K, Andreana S. Using a diode laser to uncover dental implants in second-stage surgery. *Gen Dent* 2005: **53**: 414–417.
348. Yoshino T, Aoki A, Oda S, Takasaki AA, Mizutani K, Sasaki KM, Kinoshita A, Watanabe H, Ishikawa I, Izumi Y. Long-term histologic analysis of bone tissue alteration and healing following Er:YAG laser irradiation compared to electrosurgery. *J Periodontol* 2009: **80**: 82–92.

349. Yousuf A, Hossain M, Nakamura Y, Yamada Y, Kinoshita J, Matsumoto K. Removal of gingival melanin pigmentation with the semiconductor diode laser: a case report. *J Clin Laser Med Surg* 2000: **18**: 263–266.
350. Yu W, Naim JO, McGowan M, Ippolito K, Lanzafame RJ. Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria. *Photochem Photobiol* 1997: **66**: 866–871.
351. Yukna RA, Carr RL, Evans GH. Histologic evaluation of an Nd:YAG laser-assisted new attachment procedure in humans. *Int J Periodontics Restorative Dent* 2007: **27**: 577–587.
352. Yung F. The Use of an Er:YAG laser in periodontal surgery: clinical Cases with Long-Term Follow-Up. *J Laser Dent* 2009: **17**: 13–20.
353. Zitzmann NU, Berglundh T. Definition and prevalence of peri-implant diseases. *J Clin Periodontol* 2008: **35**: 286–291.