
Molecular effects of low-energy laser irradiation during orthodontic tooth movement

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Since orthodontic treatments usually take around 2–3 years, it can be a great burden for both patients and providers. Therefore, shortening the duration of treatment is both desirable and beneficial to the orthodontists as long treatment duration is associated with increased risks of gingival inflammation, decalcification, dental caries, and root resorption. Several novel modalities have been reported to accelerate orthodontic tooth movement including low-level laser therapy, pulsed electromagnetic fields, electrical currents, corticotomy, distraction osteogenesis, and mechanical vibration. Low-level laser therapy (LLLT) is an effective method to prompt wound healing, bone repair, and modeling after surgery. These biostimulatory effects of LLLT have been related to increased fibroblast and osteoblast activities. Similarly, LLLT has been suggested to play a role in accelerated tooth movement. *In vivo* rat studies have demonstrated that low-level laser irradiation (LLLI) increases osteoclastogenesis on the compression side via stimulation of the receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL) and the c-fms/macrophage colony-stimulating factor (M-CSF) during experimental tooth movement. On the tension side, LLLI stimulates bone formation and has been associated with increased expression of type I collagen (COL1), fibronectin (FN), and osteopontin (OPN). Furthermore, *In vivo* studies have shown that LLLI induces differentiation and activation of osteoblasts and osteoclasts. Therefore, LLLI facilitates the turnover of connective tissues and accelerates the bone remodeling process by stimulating osteoblast and osteoclast proliferation and function during orthodontic tooth movement. This article reviews the current knowledge of the biological effects of laser irradiation and its molecular effect on orthodontic tooth movement. (Semin Orthod 2015; 21:203–209.) © 2015 Elsevier Inc. All rights reserved.

Introduction

Prolonged orthodontic treatment may lead to root resorption, caries, and reduced patient compliance. Thus, accelerating orthodontic treatment would be beneficial for both orthodontists and patients.

In an effort to achieve efficient tooth movement, many researchers have employed biochemical agents such as prostaglandin E_2 ,¹ 1,25-dihydroxyvitamin D_3 [$1,25-(OH)_2D_3$],² and parathyroid hormone.³ However, these agents have systemic effects on body metabolism, and as a consequence their application in orthodontics is very limited.⁴

Other methods have been reported to accelerate orthodontic tooth movement such as pulsed electromagnetic fields, electrical currents, corticotomy, distraction osteogenesis, mechanical vibration, and low-level laser irradiation (LLLI).

Various biostimulatory effects of LLLI have been reported including fibroblast proliferation,⁵ collagen synthesis,⁶ and nerve regeneration.⁷ In particular, the acceleration of bone regeneration by laser treatment has been the focus of recent

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studies.⁸ In dentistry, low-level laser therapy (LLLT) has been used to accelerate wound healing and to reduce inflammation.⁹ Lim et al.¹⁰ showed that LLLT is an effective tool to manage orthodontic pain.

Recently LLLT has drawn attention as a non-invasive method to accelerate orthodontic tooth movement,¹¹ although some studies have demonstrated no significant increase in the rate of orthodontic tooth movement after LLLT.¹² The goal of this review is to survey the existing literature on applying LLLT during orthodontic treatment, and its molecular effect on accelerating tooth movement.

Low-level lasers

Laser irradiation has a variety of effects on tissues.¹³ Its effects on tissues depend on the wavelength of the laser. The “biostimulating effects” of laser irradiation on tissues are accompanied by no more than 1°C increase in local temperature. Treatments that utilize the biostimulation potency of laser irradiation are called “low-level laser therapy.”¹⁴

The low-level laser lights from the red and near-infrared regions correspond with the characteristic energy and absorption levels of the respiratory chain in mitochondria. The laser functions by stimulating antenna pigments, the primary photo acceptors of the respiratory chain, thus increasing the mitochondrial ATP production.¹⁵ The primary reaction occurring in the respiratory chain increases the cellular metabolism and as a result increases DNA synthesis and cell proliferation.¹⁶

These events are the basis of the beneficial and therapeutic actions of laser irradiation.¹⁷

LLLT, also known as “soft laser,” stimulates molecules and atoms of cells but does not cause a rapid or significant increase in tissue temperature.¹⁸ Lasers with different wavelengths can penetrate into human tissues at different depths. Red laser penetrates deeper compared with violet, blue, green, or yellow lasers. Infrared and near-infrared lights are invisible but have been demonstrated to penetrate human tissues deeper than the visible red light.¹⁹ While LLLT produces stimulatory effects on cells, high-energy laser irradiation produces inhibitory effects. For this reason, LLLT has been recommended to stimulate wound healing in non-healing ulcers.²⁰

LLLT in dentistry and orthodontics

It has been suggested that application of LLLT in dentistry is an effective method to prompt wound healing,²¹ nerve regeneration, bone repair, and modeling after surgery.²² These effects have been attributed to the biostimulatory effect of LLLT on collagen synthesis, as well as osteoblast and fibroblast proliferation and differentiation.²³ Given this, laser therapy has been suggested for treatment of aphthous ulcers²⁴ and dentinal hypersensitivity, and for use as an oral analgesic. In addition, laser therapy has been used to treat periodontitis as it renders anti-inflammatory effects²⁵ and has been shown to accelerate osseointegration after implant placement.²⁶

In terms of the application of LLLT in orthodontics, current evidence suggests that

Table 1. Literature survey of effect of LLLT on tooth movement in humans

References	Laser type	Wavelength (nm)	Power (mW)	Duration	Acceleration
Cruz et al. ¹¹	GaAlAs	780	20	100 s On days 0, 3, 7, and 14 for 2 monthly spring activations	Yes
Doshi-Mehta and Bhad-Patil ³²	AlGaAr	800	0.25	100 s For days 0, 3, 7, and 14 in the first month and thereafter on every 15th day until space is closed	Yes
Limpanichukul et al. ³⁷	GaAlAs	860	100	25 J/cm ² /site; 184 s On days 0, 1, and 2 for 4 monthly activations	No
Youssef et al. ³⁸	GaAlAs	809	100	80 s On days 0, 3, 7, and 14 after every activation (per 21 days) until space is closed	Yes
Sousa et al. ³⁹	Diode laser	780	20	10 s For 3 days per month for 3 months	Yes
Dominguez et al. ⁴⁰	Diode laser	670	200	9 min On days 0, 1, 2, 3, 4, and 7	Yes
Heravi et al. ⁴¹	GaAlAs	810	200	21.4 J/cm ² /point On days 0, 3, 7, 11, and 15 and repeated after re-activations at the 28th day	No

GaAlAs, a gallium-aluminum-arsenide laser; AlGaAr, an aluminum-gallium-arsenide laser.

Table 2. Literature survey of effect of LLLT on experimental tooth movement in animals

References	Laser type	Wavelength (nm)	Power (mW)	Duration	Animal	Acceleration
Seifi et al. ¹²	Diode laser	805	5	3 min/day for 9 days	Rabbit	No
Fujita et al. ⁴²	GaAlAs	630	10	9 min/day for 7 days	Rat	Yes
Yamaguchi et al. ⁴³	GaAlAs	810	100	9 min/day for 7 days	Rat	Yes
Marquezan et al. ⁴⁴	GaAlAs	830	100	6000 J/cm ² for 7 days	Rat	No
Altan et al. ⁴⁵	GaAlAs	820	100	108 s/day for 3 days	Rat	Yes
Duan et al. ⁴⁶	GaAlAs	830	180	4 s/day for 3 days	Rat	Yes
Shirazi et al. ⁴⁷	InGaAlP	660	25	5 min/day for 14 days	Rat	Yes
Yoshida et al. ⁴⁸	GaAlAs	810	100	9 min/day for 7 days	Rat	Yes
Kim et al. ⁴⁹	GaAlAs	808	96	10 s/day for 7 days	Rat	No
Ohashi et al. ⁵⁰	GaAlAs	810	100	9 min/day for 7 days	Rat	Yes

InGaAlP, an indium-gallium-aluminum-phosphide laser.

LLLT reduces post-adjustment pain,²⁷ stimulates bone regeneration in midpalatal suture area after rapid maxillary expansion,²⁸ enhances the stability of orthodontic mini-implants, and accelerates tooth movement.²⁹

Pain from orthodontic treatment is mostly local and therefore may be controlled more efficiently by locally administered analgesics. Several studies have reported the analgesic effect of tissue-penetrating type lasers, such as He:Ne,³⁰ CO₂,³¹ and semi-conductor lasers.³² These lasers are reported to reduce orthodontic pain by irradiating the teeth and gingiva.

Saito and Shimizu³³ observed that LLLT accelerated bone regeneration in the midpalatal

suture after rapid maxillary expansion (RME) in rats. Several other studies have demonstrated that LLLT can accelerate bone formation by increasing osteoblastic activity, vascularization, and organization of collagen fibers.^{34,35} Omasa et al.²⁹ reported that LLLT enhanced the stability of mini-implants placed in rat tibiae and accelerated peri-implant bone formation by increasing the gene expression of BMP-2 in surrounding cells.

Effect of LLLT on the rate of tooth movement

In physiological bone remodeling, the amounts of bone resorption and formation are almost

Table 3. Literature survey of effect of LLLI on cell function *in vitro*

References	Laser type	Wavelength (nm)	Power (mW)	Duration	Cell	Up-regulated factors
Ozawa et al. ³⁴	GaAlAs	830	500	1, 3, 6, and 10 min/day for 21 days	MC3T3-E1	ALP Osteocalcin
Hamajima et al. ³⁵	GaAlAs	830	500	1, 3, 6, and 10 min/day for 21 days	MC3T3-E1	Osteoglycin
Stein et al. ⁵⁸	He-Ne	632	10	1, 3, 6, and 10 min/day	Human osteoblasts	Proliferation Differentiation
Renno et al. ⁵⁹	He-Ne	670 780 830	50	3 days	Murine osteoblasts (MC3T3) and human osteosarcoma (MG63)	ALP
Hirata et al. ⁶⁰	GaAlAs	830	500	20 min/day	Rat osteoblasts (C2C12 cells)	BMP ALP
Kiyosaki et al. ⁶¹	GaAlAs	830	500	5–20 min	MC3T3-E1	Mineralization
Fujimoto et al. ⁶²	GaAlAs	830	500	5–20 min	MC3T3-E1	BMP
Aihara et al. ⁶³	GaAlAs	810	50	1, 3, 6, and 10 min/day for 8 days	Rat osteoclasts	RANK
Coombe et al. ⁶⁴	GaAlAs	830	90	0.3–4 J for 10 days	Human osteosarcoma (SAOS-2)	No

ALP, alkaline phosphatase; BMP, bone morphogenic protein; RANK, the receptor activator of nuclear factor κB.

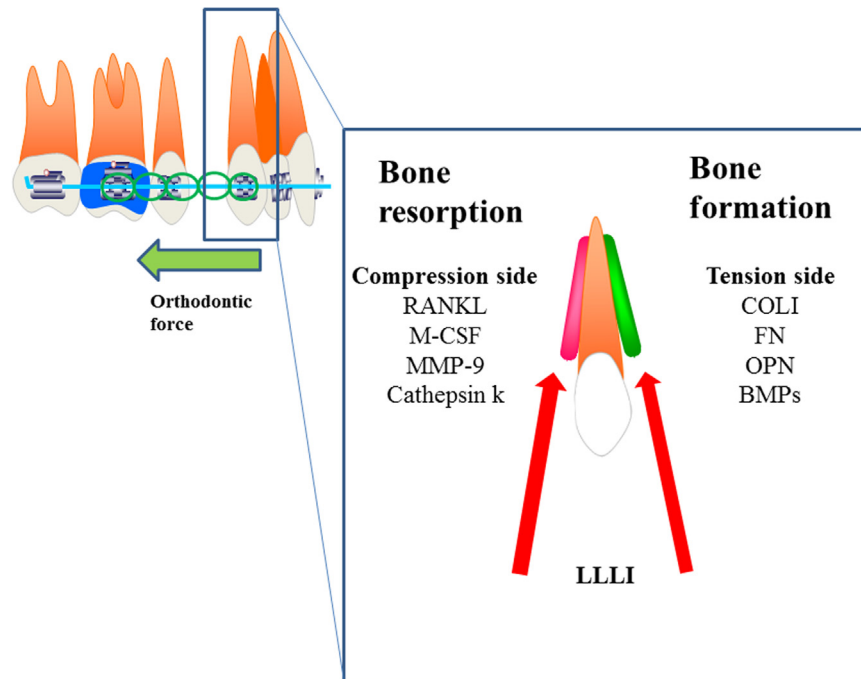


Figure. The schematic diagram shows the molecular effects of LLLT on accelerated tooth movement. Low-level laser irradiation (LLLI) has been suggested to accelerate tooth movement by stimulating osteoclastogenesis on the compression side via stimulating the receptor activator of nuclear factor κ B (RANK)/RANK ligand (RANKL) and the c-fms/macrophage colony-stimulating factor (M-CSF) during orthodontic tooth movement. On the tension side, LLLI also stimulates the bone formation and increases the expression of COL1, FN, and OPN. ALP, alkaline phosphatase; BMP, bone morphogenic protein; RANK, the receptor activator of nuclear factor κ B; RANKL, RANK ligand; M-CSF, the c-fms/macrophage colony-stimulating factor; COL1, type I collagen; FN, fibronectin; OPN, osteopontin; MMP-9, matrix metalloproteinase-9.

equal, and the total bone mass does not change.⁵ This so called “coupling” of bone resorption and formation is the basis for bone remodeling. On the other hand, when orthodontic force is applied to a tooth, osteoclastogenesis is induced on the compression side, while osteogenesis is induced on the tension side. These reactions disrupt the coupling balance resulting in more bone resorption on the compression side, opposing more bone formation on the tension side. This alveolar bone remodeling taking place around the root is the underlying mechanism of tooth movement.³⁶

Recent studies have suggested that LLLT may accelerate orthodontic tooth movement in humans (Table 1)^{11,32,37–41} and animals (Table 2).^{12,42–50} Fujita et al.⁴² and Yamaguchi et al.⁴³ demonstrated that LLLI facilitated osteoclastogenesis on the compression side by stimulating the receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL), and the c-fms/macrophage colony-stimulating factor

(M-CSF) during experimental tooth movement. In response to orthodontic force, RANK, RANKL, and osteoprotegerin (OPG) facilitate the coordination of bone remodeling. An increase in concentration of RANKL in gingival crevicular fluid (GCF) during orthodontic tooth movement has been reported.^{51,52} Moreover, Yamaguchi et al.⁵³ reported that in the rat experimental tooth movement, LLLI stimulated the expression of matrix metalloproteinase-9, cathepsin K, and $\alpha(v)\beta3$ integrin, indicating that LLLI may accelerate the rate of tooth movement by stimulating osteoclastogenesis.

On the tension side, LLLI stimulates bone formation⁴⁸ and has been associated with increased expressions of type I collagen (COL1), fibronectin (FN),⁴⁹ and osteopontin (OPN)⁵⁰ during experimental tooth movement. Type I collagen is abundant in the periodontal ligament, and fibronectin is apparent throughout the mesenchyme.⁵⁴ Fibronectins bind to collagen fibers and support the proliferation and

chemotaxis of the fibroblasts in the periodontal ligament.⁵⁵ OPN, a major member of the noncollagenous extracellular matrix secreted by osteoblasts, has been implicated in bone remodeling upon mechanical stress.⁵⁶ Kim et al.⁵⁷ reported localization of OPN in periodontal tissue during orthodontic tooth movement in rats, suggesting that LLLI may also stimulate osteogenesis during orthodontic tooth movement.

In vitro studies have shown the effects of LLLI on cell proliferation and osteogenesis as shown in Table 3. Hamajima et al.³⁵ reported that the increased expression of OGN (osteoglycin) gene induced by LLLI in the early proliferation stage of cultured osteoblastic cells might play an important role in the stimulation of bone formation. Ozawa et al.³⁴ reported that LLLI administered during the early stages of formation of osteoblast-like cells isolated from fetal rat calvariae significantly stimulated cellular proliferation, alkaline phosphatase (ALP) activity, and osteocalcin gene expression. Furthermore, in the earlier stages of cell cultures, LLLI was shown to significantly stimulate the proliferation of osteoblasts, resulting in a greater number (1.7-fold) and larger area (3.4-fold) of bone nodules developing in culture over 21 days. LLLI was also shown to promote proliferation and maturation of human osteoblasts,^{58,59} stimulate mineralization, and increase bone morphogenic protein (BMP) expression.^{60–62} Meanwhile, Aihara et al.⁶³ reported that LLLI stimulated osteoclast activity *in vitro*.

Fig. shows a schematic acceleration of tooth movement induced by LLLT. LLLI facilitates the turnover of connective tissues and accelerates the bone remodeling process by stimulating osteoblast and osteoclast proliferation and function during orthodontic tooth movement.³⁸ However, many studies have shown no significant increase in the rate of tooth movement after LLLT.^{49,64} Therefore, more studies are needed to identify the optimum energy, wavelength, and duration of usage for laser therapeutics.

Conclusion

According to the findings of this review, LLLT may accelerate orthodontic tooth movement by stimulating the functions of osteoblasts and osteoclasts. However, some studies demonstrate

no significant clinical effects on the rate of tooth movement. Therefore, further studies should be carried out to investigate how to optimize the biological stimuli of LLLI to increase the rate of tooth movement.

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