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REVIEW

Could adverse effects and complications of selective laser trabeculoplasty be decreased by low-power laser therapy?

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Abstract Selective laser trabeculoplasty (SLT) has been used for treatment of primary open-angle glaucoma, ocular hypertension, pigmenter and pseudoexfoliative glaucoma being considered a low-risk procedure. Therefore, transitory and permanent adverse effects have been reported, including corneal changes, subclinical edema, and reduction in endothelial cells and in central corneal thickness. Despite rarer, serious corneal complications after SLT can be permanent and lead to visual impairment, central corneal haze, opacity and narrowing. The mechanism involves increase of vasoactive and chemotactic cytokines causing inflammatory infiltrate, destruction of stromal collagen by fibroblasts and increase of matrix metalloproteinases type 2, which impair reepithelization. SLT also increases free radical production and reduces antioxidant enzymes, resulting in endothelium damages. Low-power laser therapy (LPLT) has been used in regenerative medicine based on its biostimulatory and anti-inflammatory effects. Biostimulation occurs through the interaction of laser photons with cytochrome C oxidase enzyme, which activates intracellular biochemical cascades causing synthesis of a number of molecules related to anti-inflammatory, regenerative effects, pain relief and reduction in edema. It has been showed that LPLT reduces gene expression related to pro-inflammatory cytokines and matrix metalloproteinases, and it increases expression of growth factors related to its proliferative and healing actions. Although radiations emitted by low-power lasers are considered safe and able to induce therapeutic effects, researches based on experimental models for glaucoma could bring important data if LPLT could be an alternative approach to improve acceptation for patients undergoing SLT.

Keywords Biostimulation · Glaucoma · Low-power laser therapy · Regenerative medicine · Selective laser trabeculoplasty

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Introduction

Glaucoma is a multifactorial disease characterized by damage in optic nerve, frequently caused by high

intraocular pressure (IOP). Nowadays, treatment of this disease is based on IOP decrease, being realized by eye drops, therapies based on high-power lasers or surgery. Laser exposure is carried out on trabecular mesh surface (laser trabeculoplasty), and this technique has been successful to decrease IOP since 1970s. Originally, trabeculoplasty was carried out by argon lasers (argon laser trabeculoplasty—ALT), with wavelengths ranging between 488 and 514 nm [1]. Actually, ALT has been substituted by selective laser trabeculoplasty (SLT). The laser used in SLT procedure is a Nd:YAG Q-switched laser, with wavelength at 532 nm, in pulsed wave emission mode, 3 ns time pulse and spot size diameter of 400 μm. The laser selectivity comes from the high absorption of this radiation by pigmented cell in trabecular mesh [2]. SLT is also used for treatment of ocular hypertension, pigmenter and pseudoexfoliative glaucoma [3].

Comparing with ALT, SLT uses lasers at lowest powers; meanwhile, in SLT are used laser beams with energy at approximately 0.9 mJ, and in ALT are used laser beams at 50 mJ, equivalent to 500 mW in 100 ms and energy 55 times higher. The spot size diameter of laser beam used in SLT is 400 μm, while in ALT it is 50 μm; with irradiation areas of 0.13 and 0.002 mm^2, respectively, for example, the energy per mm^2 of biological tissue is 3520 times less in SLT than in ALT [2].

SLT is considered a low-risk procedure, but low secondary and transitory adverse effects could occur [1]. Table 1 lists some studies on the mainly SLT-induced adverse effects. Intraocular pressure picks [2, 4, 10], eye red syndrome, ocular discomfort and anterior chamber inflammatory reaction are relatively common occurrences after SLT procedure [2], but headache, photophobia, corneal abrasion, pigment dispersion and subconjunctival hemorrhage have been also reported [12]. Nagar et al. [11] reported discomfort and pain during the first week in 6% of patients submitted to SLT at 90°, 20% at 180° and 39% at 360°. However, such effects are less evident in patients submitted to SLT, when compared those reported for patients submitted to ALT [10]. As the trabecular meshwork is closer to cornea, clinically imperceptible damages can occur in the structure of this tissue [23].

Intraocular pressure pick

Transitory intraocular pressure picks could occur after laser trabeculoplasty being depended on total energy administered during the procedure, as well as on the energy used in each pulse [2]. However, in SLT are used lowest energies per pulse than in ALT; this complication is less common and less evident after SLT [2, 4, 10].

Discomfort and pain

Discomfort and pain could occur as adverse effect mainly few hours after, but also some patients report pain 1 week after SLT procedure. Percentage of patient complaining pain depends on incidence angle, with highest percentage in patients submitted to SLT at 360° [11]. In another study was reported pain after SLT, but this pain was lower than that after ALT [10]. However, the cause of SLT-induced pain was not explained yet.

Adverse effects and transitory complications in cornea

Endothelial cells and central corneal thickness

Lee et al. [23] performed a study evaluating 111 eyes from patients affected by open-angle glaucoma and submitted to SLT at 360°. The average number of applications per treatment was 166.9, with laser energy of 1.0 mJ. Number of cornea endothelial cells, central corneal thickness (CCT) and refractive error were measured before, 1 week and 1 month after SLT application [23]. Results showed decreasing of 5% in number of endothelial cells 1 week after procedure. This effect was associated with action of inflammatory infiltrate on corneal endothelium or to edema resulting from laser exposure, which separated the endothelial cells from Descemet's membrane, preventing their correct measurement at specular microscopy. The number of endothelial cells increased 1 month after SLT procedure [23]. Also, the CCT decreased 1 week after the procedure. The authors related these results to the dissipation caused by heat from laser beam in corneal stroma, resulting in temporary contractions in collagen fibers, similarly to the effect observed after

Table 1 Summary of some studies on adverse effects caused by selective laser trabeculoplasty

First author	Title	Adverse effect	References
Liu and Birt [4]	Argon versus selective laser trabeculoplasty in younger patients	Intraocular pressure picks	J Glaucoma (2012) 21:112–115
Zhang et al. [5]	Clinical results of selective laser trabeculoplasty in silicone oil-induced secondary glaucoma	Intraocular pressure picks	Graefes Arch Clin Exp Ophthalmol (2014) 252:983–987
Narayanaswamy et al. [6]	Efficacy of selective laser trabeculoplasty in primary angle-closure glaucoma: a randomized clinical trial	Intraocular pressure picks	JAMA Ophthalmol (2015) 133:206–212
Ali Aljasim et al. [7]	Selective laser trabeculoplasty in primary angle-closure glaucoma after laser peripheral iridotomy: a case–control study	Intraocular pressure picks	J Glaucoma (2016) 25:e253–e258
De Keyser et al. [2]	Where does selective laser trabeculoplasty stand now? A review	Intraocular pressure picks/red eye syndrome/ocular discomfort	Eye Vis (2016) 3:10
Bettis et al. [8]	Intraocular pressure spike and corneal decompensation following selective laser trabeculoplasty in patients with exfoliation glaucoma	Intraocular pressure picks/corneal edema/corneal endothelial changes	J Glaucoma (2016) 25:e433–e437
Zhang et al. [9]	Perioperative medications for preventing temporarily increased intraocular pressure after laser trabeculoplasty	Intraocular pressure picks	Cochrane Database Syst Rev (2017) 2:CD010746
Martinez-de-la-Casa et al. [10]	Selective vs argon laser trabeculoplasty: hypotensive efficacy, anterior chamber inflammation, and postoperative pain	Pain/intraocular pressure picks	Eye (2004) 18:498–502
Nagar et al. [11]	A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma	Pain	Br J Ophthalmol (2005) 89:1413–1417
Wong et al. [12]	Systematic review and meta-analysis on the efficacy of selective laser trabeculoplasty in open-angle glaucoma	Pain/headache/photophobia/corneal abrasion/pigment dispersion/subconjunctival hemorrhage	Surv Ophthalmol (2015) 60:36–50
Moubayed et al. [13]	An unusual finding of corneal edema complicating selective laser trabeculoplasty	Corneal edema	Can J ophthalmol (2009) 44:337–338
Huang et al. [14]	Determinants of postoperative corneal edema and impact on goldmann intraocular pressure	Corneal edema	Cornea (2011) 30:962–967
Knickelbein et al. [15]	Acute corneal edema with subsequent thinning and hyperopic shift following selective laser trabeculoplasty	Corneal edema	J Cataract Refract Surg (2014) 40:1731–1735
Ozkok et al. [16]	Corneal decompensation after selective laser trabeculoplasty	Corneal edema	Case Rep Ophthalmol Med (2014) 2014:851971
Chadha et al. [17]	Herpetic stromal keratitis following selective laser trabeculoplasty	Corneal edema	Case Rep Ophthalmol Med (2016) 2016:5768524
Song et al. [18]	Corneal thinning and opacity following selective laser trabeculoplasty: a case report	Corneal thickness decrease/opacity	Br J Med Res (2014) 4:279–287
Guven Yilmaz et al. [19]	Effects of primary selective laser trabeculoplasty on anterior segment parameters	Corneal thickness increase	Int J Ophthalmol (2015) 8:954–959

Table 1 continued

First author	Title	Adverse effect	References
Koc et al. [20]	Effect of selective laser trabeculoplasty on macular thickness	Corneal thickness increase	Clin Ophthalmol (2015) 9:2335–2338
Atalay et al. [21]	Corneal topographic alterations after selective laser trabeculoplasty	Corneal thickness	Int Ophthalmol (2016) 37:905–910
White et al. [22]	Acute transient corneal endothelial changes following selective laser trabeculoplasty	Corneal endothelial changes	Clin Exp Ophthalmol (2013) 41:435–441
Lee et al. [23]	Corneal changes after a single session of selective laser trabeculoplasty for open-angle glaucoma	Reductions in endothelial cell count/central corneal thickness	Eye (2014) 28:47–52

laser thermokeratoplasties. After 1 month, corneal thickness returned to those observed previously to SLT procedure. The increase in keratocyte migration and corneal healing could explain the stromal remodeling. In addition, 1 month after SLT procedure, it was observed that the highest corneal thickness was caused by the highest total laser energy applied, suggesting that high energies cause more intense inflammatory responses and consequent healing and stromal remodeling [23].

On the other hand, Atalay et al. [21] performed a study evaluating 53 eyes from patients affected by open-angle glaucoma and submitted to SLT at 360°, with laser power ranged from 0.8 to 1.3 mJ. CCT was measured, before and 3 months after SLT procedure, by Scheimpflug corneal topography technique. CCT measurements showed significant decrease after 3 months. These findings highlight attention to the fact that CCT measurements can remain reduced even 3 months after SLT, in spite of the findings of Lee et al. [23].

Corneal subclinical edemas could also explain the decrease in intraocular pressure after SLT procedure, since there are alterations in stromal collagen architecture, resulting in modified corneal hysteresis. Therefore, the intraocular pressure levels, dependent on tonometry by corneal applanation, could present false reduction [23].

White et al. [22] performed a study evaluating 19 eyes from patients affected by open-angle glaucoma and submitted to SLT at 180° (laser energy ranging 09–1.3 mJ). Corneal endothelium was evaluated before, 1 h and 6 weeks after SLT application by confocal microscopy. Fifteen eyes showed diffuse or clustered endothelium alterations at 1 h after procedure. Images captured by confocal microscopy showed dysmorphic endothelial cells due to increase in intracellular space, suggesting edema [22]. Pathophysiology of SLT-induced damage in corneal endothelium involves different mechanisms, such as direct light scattering [24] and oxygen free radicals release in the aqueous humor [25]. In addition, it has been shown by an experimental model that SLT triggers releasing of free radicals into aqueous humor for a number of days after the procedure. A toxic insult from the aqueous itself could result in diffuse endothelial changes [22], such as those reported by White et al. [25].

Inflammatory response

Moubayed et al. [13] reported two cases of central corneal edema initiated 1 week after SLT procedure. In one of these cases, which developed beside keratitis caused by simplex herpes virus, there was permanence of residual subepithelial opacity, despite corticosteroid therapy [13]. The triggered inflammatory response by SLT could cause the reactivation of infection by simplex herpes virus [26]. However, a normal herpetic endotheliitis do not follow with stromal narrowing and residual opacity [15].

In another study, Regina et al. [24] reported two cases of central corneal edema with stromal opacity 24 up to 48 h after SLT procedure. Although the edema has been solved, both patients presented corneal cicatrices and narrowing, and one of these patients, previously affected by high myopia, developed significant hypermetropic impairment [24]. A similar

case was reported by Song et al., in which a patient affected by severe myopia developed central corneal edema and opacity 1 day after SLT procedure [18]. This patient presented residual narrowing following the hypermetropic impairment. Knickelbein et al. [15] reported corneal edema and opacity followed by narrowing and hypermetropic impairment in patients affected by severe myopia.

The pathophysiology of SLT-induced damage on corneal stroma collagen could involve direct laser-induced damage and damage by chemical agents. The resulting inflammatory response includes release of vasoactive and chemotactic, as interleukin-1 alpha, interleukin-1 beta and tumor necrosis factor alpha [13, 15, 18]. Hong et al. [27] showed that these mediators, at corneal level, are capable to increase the production of activator and chemotactic factors for monocytes and colony formation-stimulating factor for granulocytes, causing chemotaxis and inflammatory infiltrate in this tissue. This inflammatory cascade could explain corneal edema clinically detectable. In addition, these pro-inflammatory agents stimulate fibroblasts in cornea to destroy and to remove the stromal collagen, explaining the narrowing and opacity of this structure after SLT procedure [15, 18].

Another effect of SLT procedure in cornea is the increase in matrix metalloproteinase expression, mainly of the matrix metalloproteinases type 2 in aqueous humor from irradiated eyes [18]. The increase of metalloproteinases by resident corneal cells results in impairment of reepithelialization after some types of corneal injuries [28].

In parallel, SLT procedure increases the lipid peroxidation and reduces antioxidant enzymes synthesis in aqueous humor, as superoxide dismutase and glutathione *S*-transferase. As a consequence, free radical production increases, and this could be responsible for inflammatory effects in corneal endothelium after SLT procedure, due to high sensibility of this tissue to oxidative stress [16, 18].

Low-power laser therapy

The low-power laser therapy (LPLT) started after the studies reported by Mester et al. [29], who originally had intention to investigate whether low-power lasers are capable to induce cancer in mouse skin and, instead of this, they observed increased hair growth in mouse skin after laser expose.

Thenceforth, LPLT has been widely used for treatment of a number of diseases in regenerative medicine [30], pain relief [31] and to modulate inflammatory process [32]. The modulator effects from LPLT cause increase in regenerative potential in biological tissues, and altogether, they are known as biostimulation (or biomodulation) effect [33]. These effects have been related to decrease in apoptosis, increase in migration, adhesion and proliferation of cells [34, 35]. Table 2 lists some studies on therapeutic applications of low-power lasers.

Physical features of low-power lasers

LPLT is based on a special type of lasers with power output of 0.1 up to 100 mW emitting in red up to near-infrared range of electromagnetic spectrum (wavelength ranging 600 up to 1000 nm), the so-called therapeutic window [36]. This wavelength range is due to absorption and scattering of photons belonging other electromagnetic spectrum ranges by the biological tissue constituents, mainly hemoglobin and melanin, which absorb photons with wavelengths smaller than those in red range and water, which absorbs photons with wavelengths greater than 1000 nm [36]. Also, low-power lasers work in continuous and pulsed (up to 5000 Hz) wave emission mode at low energy densities (0.01 up to 100 J/cm^2) and low power densities (0.01 up to 10 W/cm^2). The energy from low-power lasers in LPLT is not transformed in heat, sound or vibrations at significant power in biological tissues [34]. LPLT-induced effects are not by heating, because the increase in temperature after its application is considered not significant, (approximately 1 °C) [37]. In fact, Boulton et al. [38] demonstrated that exposure to lasers used for LPLT did not alter the temperature in fibroblast cultures. Thus, different from other medical lasers, low-power lasers in LPLT do not have neither ablative and thermal effects, but rather the radiative energy is used to promote photochemical effects, which are involved in the effects induced by these lasers in biological tissues. Table 3 lists physical features of low-power lasers used for LPLT, as well those of lasers for ALT and SLT (Figs. 1, 2).

Table 2 Summary of some studies on low-power laser therapy

First author	Title	Positive effect on	Model	References
Mester et al. [29]	Effect of laser on hair growth of mice	Hair growth	Mouse	Kiserl Orvostud (1967) 19:628–631
Abrahamse [30]	Regenerative medicine, stem cells and low-level laser therapy: future directives	Biostimulation	Cell culture	Photomed Laser Surg (2012) 30:681–682
Lee et al. [51]	Effect of low-level laser therapy on oral keratinocytes exposed to bisphosphonate	Biostimulation/cell migration	Cell culture	Lasers Med Sci (2015) 30:635–643
Engel et al. [53]	Cell lineage responses to photobiomodulation therapy	Biostimulation/free radicals/antioxidant effect	Cell culture	J Biophotonics (2016) 9:1148–1156
Takenori et al. [31]	Immediate pain relief effect of low level laser therapy for sports injuries: Randomized, double-blind placebo clinical trial	Pain	Human	J Sci Med Sport (2016) 19:980–983
Cunha et al. [55]	Evaluation of the effectiveness of diode laser on pain and edema in individuals with cleft lip and palate submitted to secondary bone graft	Pain and edema	Human	Cleft Palate Craniofac J (2013) 50:e92–e97
Ezzat et al. [58]	The effectiveness of low-level laser on postoperative pain and edema in secondary palatal operation	Pain and edema	Human	Int J Pediatr Otorhinolaryngol (2016) 89:183–186
Meneguzzo et al. [56]	Prevention and treatment of mice paw edema by near-infrared low-level laser therapy on lymph nodes	Edema	Mouse	Lasers Med Sci (2013) 28:973–980
Nadur-Andrade et al. [57]	Photobiostimulation reduces edema formation induced in mice by Lys-49 phospholipases A2 isolated from Bothrops moojeni venom	Edema	Mouse	Photochem Photobiol Sci (2014) 13:1561–1567
Prianti et al. [71]	Low-level laser therapy (LLLT) reduces the COX-2 mRNA expression in both subplantar and total brain tissues in the model of peripheral inflammation induced by administration of carrageenan	Inflammation	Rat	Lasers Med Sci (2014) 29:1397–1403
Miranda da Silva et al. [73]	Low level laser therapy reduces the development of lung inflammation induced by formaldehyde exposure	Inflammation	Rat	PLoS One (2015) 10:e0142816
Silveira et al. [74]	Low-level laser therapy attenuates the acute inflammatory response induced by muscle traumatic injury	Inflammation/muscle injury	Rat	Free Radic Res (2016) 50:503–513
de Oliveira et al. [75]	Photobiomodulation therapy in the modulation of inflammatory mediators and bradykinin receptors in an experimental model of acute osteoarthritis	Inflammation	Rat	Lasers Med Sci (2017) 32:87–94
Basso et al. [35]	Biostimulatory effect of low-level laser therapy on keratinocytes in vitro	Biostimulation/ extracellular matrix	Cell culture	Lasers Med Sci (2013) 28:367–374
Trajano et al. [64]	Low-level red laser improves healing of second-degree burn when applied during proliferative phase	Wound healing/ extracellular matrix/ inflammation	Rat	Lasers Med Sci (2015) 30:1297–1304
Sperandio et al. [50]	Low-level laser irradiation promotes the proliferation and maturation of keratinocytes during epithelial wound repair	Wound healing/cell proliferation and maturation		J Biophotonics (2015) 8:795–803
Tatmatsu-Rocha et al. [62]	Low-level laser therapy (904 nm) can increase collagen and reduce oxidative and nitrosative stress in diabetic wounded mouse skin	Wound healing/ extracellular matrix/antioxidant	Mouse	J Photochem Photobiol B (2016) 164:96–102
Yang et al. [65]	Skin healing and collagen changes of rats after fractional erbium:yttrium aluminum garnet laser: observation by reflectance confocal microscopy with confirmed histological evidence	Wound healing/ extracellular matrix	Rats	Lasers Med Sci (2016) 31:1251–1260

Table 2 continued

First author	Title	Positive effect on	Model	References
Gagnon et al. [54]	An in vitro method to test the safety and efficacy of low-level laser therapy (LLLT) in the healing of a canine skin model	Wound healing/cell proliferation and migration	Cell culture	BMC Vet Res (2016) 12:73
de Medeiros et al. [66]	Effect of low-level laser therapy on angiogenesis and matrix metalloproteinase-2 immunoexpression in wound repair	Wound healing/ extracellular matrix	Rat	Lasers Med Sci (2017) 32:35–43
Lemos et al. [67]	Low-level laser therapy stimulates tissue repair and reduces the extracellular matrix degradation in rats with induced arthritis in the temporomandibular joint	Wound healing/ extracellular matrix	Rat	Lasers Med Sci (2016) 31:1051–1059
de Freitas et al. [61]	High final energy of low-level gallium arsenide laser therapy enhances skeletal muscle recovery without a positive effect on collagen remodeling	Muscle injury/ extracellular matrix	Rat	Photochem Photobiol (2015) 91:957–965
Marques et al. [68]	Photobiomodulation therapy on collagen type I and III, vascular endothelial growth factor, and metalloproteinase in experimentally induced tendinopathy in aged rats	Tendon injury/ extracellular matrix	Rat	Lasers Med Sci (2016) 31:1915–1923
Kamal et al. [69]	Radiological and biochemical effects (CTX-II, MMP-3, 8, and 13) of low-level laser therapy (LLLT) in chronic osteoarthritis in Al-Kharj, Saudi Arabia	Extracellular matrix	Human	Lasers Med Sci (2017) 32:297–303

Table 3 Physical features of lasers used in ALT, SLT and LLLT

Physical parameter	Laser therapy		
	ALT	SLT	LLLT
Emitter medium	Argon	Q-switched, frequency-doubled Nd:YAG	InGaAlP, AsGaAl, GaAs
Wavelength (nm)	532	488–514	600–1000
Pulse time (ns)	10	0.3	100–∞
Angle	180°	180° and 360°	90°
Spot size (mm^2)	0.002	0.13	1–10
Energy (J)	0.05	0.0009	1–10
Energy density (J/mm^2)	25	0.007	0.1–10
Power (W)	0.3–1.0	Not obtained	0.001–0.10
Power density (W/mm^2)	150–500	Not obtained	0.01–0.10

Low-power lasers for therapy

The first low-power laser used for LPLT was the helium–neon (He–Ne) laser, which emits in red range (632.8 nm). Actually, low-power He–Ne laser has been substituted by the low-power diode lasers, which attain high efficiency in biostimulation. Diode lasers are more durable, reliable and present simpler and cheaper maintenance than He–Ne laser. Examples of diode lasers available to LPLT are AlGalnP laser (658 nm), AlGaAs laser (830 nm) and GaAs laser (904 nm).

Mechanism of action of low-power lasers

The biological effects induced by the low-power lasers used in LPLT are not completely understood yet, but some mechanisms were proposed to explain the laser-induced increase in cell proliferation (biostimulation effect). Actually, it is almost a consensus that biostimulation occurs by interaction of laser photons with photoacceptors into mitochondria. These photoacceptors (or chromophores) are capable of absorb energy from laser radiation photons, converting them in chemical energy [34, 39]. The main photoacceptor proposed was the cytochrome *C* oxidase for red and

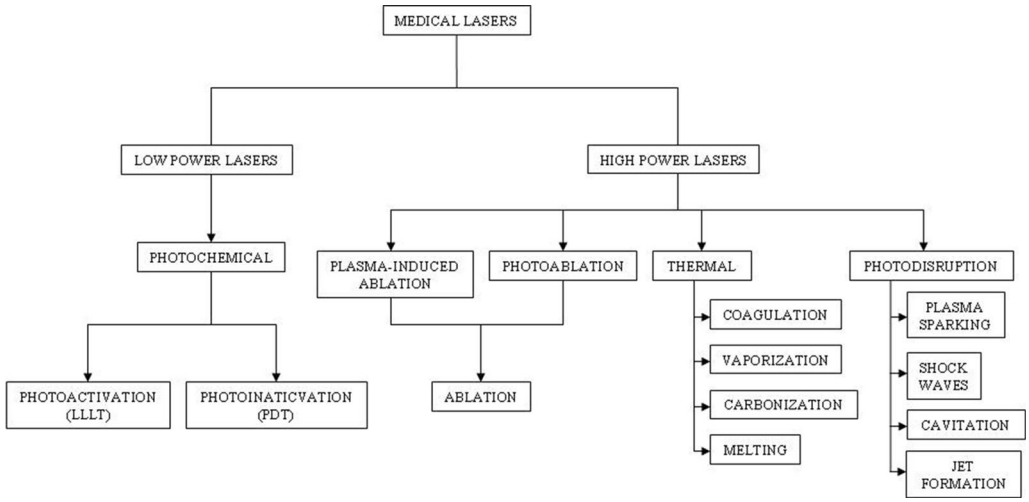

Fig. 1 Schematic representation for medical lasers types

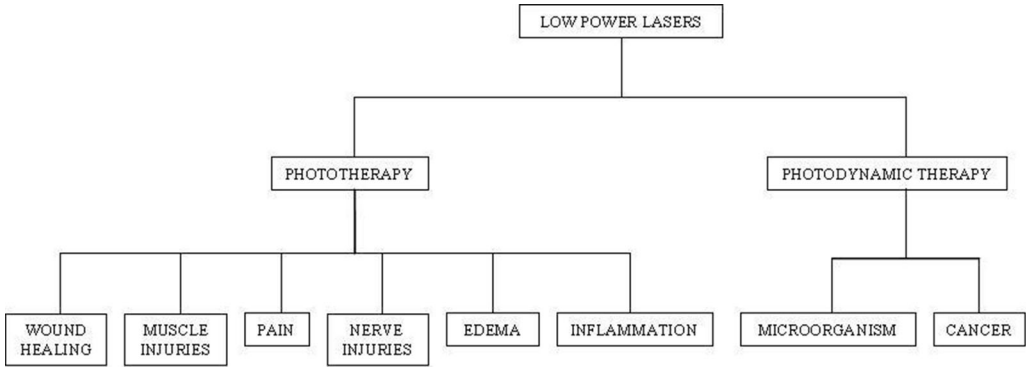

Fig. 2 Schematic representation for low-power lasers applications

near-infrared laser radiations, since this molecule presents absorption spectra matching with the action spectrum for low-power lasers [40]. It was proposed that, after absorption, electron transfer by cytochrome *C* oxidase could be accelerated, increasing the production of ATP, which in turn makes possible nucleic acids and proteins synthesis increase by complex cascades of intracellular signalization. The increase in cellular respiration results in increase in oxygenation, nutrition, metabolism and regeneration capacity in biological tissues exposed to low-power laser radiations [35, 41].

Hypothesis of free radicals action in biostimulation

The hypothesis of free radicals action on laser-induced biostimulation states that cell proliferation by exposure to low-power laser radiations is related to the increase in reactive oxygen species and reactive nitrogen species levels [34]. These chemical species could regulate the activity of a sort of proteins kinases, mainly those belonging to SRC family, which are activated by oxidative damages. SRC play a key role in a number of cellular processes, including modulation of proliferation, adhesion, migration and cell survival [42]. Stadler et al. [43] irradiated leukocytes with LPLT at 660 nm, at fluences ranging of 0.5 up to 5 J/cm^2 and power density of 40 mW/cm^2. The results showed increase in cell proliferation and levels of reactive oxygen species, by increasing superoxide dismutase enzyme, which is an important antioxidant response after oxidative stress [43]. Also, osteoblast proliferation by low-power infrared (980 nm) laser was blocked in the presence of antioxidant agent [44].

In inflammatory responses, there is releasing of reactive oxygen species, which damage cellular components, as lipids, proteins and DNA. Together with pro-inflammatory cytokines, reactive oxygen species could active the nuclear factor kappa-B (NF-kappa-B), which in turn increases enzyme expression and factors related to inflammatory process, as oxide nitric synthase [42]. On the other hand, Rizzi et al. [45] evaluated the effects of diary exposure to infrared laser (904 nm, 45 mW and 5 J/cm^2) on injured muscle tissue. Results showed decreasing of ROS and NF-kappa-B levels. Also, Fillipin et al. [46] irradiated *Wistar* rat calcaneous tendons previously injured and the results showed reduction in reactive oxygen species levels, oxidative stress, synthesis of collagen and fibrosis. A possible explication to reduction in reactive oxygen species levels was the increase in antioxidant defenses, as superoxide dismutase enzyme.

Could LPLT present positive effects on SLT-induced reduction in central corneal thickness?

Lee et al. [23] reported reduction in central corneal thickness 1 week after SLT at 360°, which return to pretreatment levels after 1 month from procedure. This effect was explained by acceleration of cornea healing process and the increase in keratinocyte migration [23]. Could this SLT-induced adverse effect be reduced or prevented by previous LPLT, considering its positive capacity to modulate cell migration, adhesion and proliferation?

Exposure to low-power laser radiation increases gene and protein expression related to a number of growth factors, such as fibroblast (bFGF), platelet-derived growth factor (PDGF) and vascular endothelium growth factor (VEGF) in fibroblast cultures [42, 47]. Gavish et al. [48] and Hu et al. [49] reported that, before increase in keratinocytes growth factor (KGF) expression and releasing of tumor growth factor beta-1 (TGF-beta 1) by melanoma cells, there is increase in mitochondrial membrane potential in cells irradiated with these lasers [48, 49]. This suggests a relationship between photobiostimulation of cytochrome *C* oxidase and the increase in growth factor synthesis, which in turn could induce cell proliferation and differentiation [42]. Other authors reported that exposure to low-power red laser radiation accelerates maturation of the migrating keratinocytes in skin wounds [50] and exposure to low-power infrared laser radiation increases cell viability in keratinocytes incubated with bisphosphonate [51]. Also, exposure to low-power infrared laser does not alter the morphology of human keratinocytes at scanning electron microscopy [52].

However, exposure to low-power infrared laser can be more toxic for keratinocytes than fibroblast at high doses [53], and low-power red laser radiation at highest doses can inhibit cell migration and proliferation [54]. These results suggest that low-power laser radiation should be considered if cell migration and proliferation are aimed.

Could LPLT present positive effects on SLT-induced edema?

SLT at 360° causes transitory corneal edema, evidenced by reduction in endothelial cell number in this tissue at specular microscopy [23]. Subclinical corneal edemas can leave to underestimation of IOP values at tonometry by applanation. Could this SLT-induced adverse effect be reduced or prevented by previous LPLT?

A possible benefit achieved with infrared LPLT could be the faster reestablishment of normal values of corneal central thickness, since there is not reduction in this parameter 1 week after SLT procedure, as reported [23]. Infrared LPLT was not effective to control edema in postoperative period of secondary alveolar bone graft [55]. However, infrared LPLT on lymph nodes reduces paw edema induced by carrageenan in mice [56]. In another study, mouse muscle edema induced by *Bothrops* snake venom was reduced after red LPLT [57]. Also, infrared LPLT was effective for reduction in postoperative edema, minimizing the need of analgesic medication for children after secondary palatal operations [58].

Could LPLT present positive effects SLT-induced disorganization of cornea collagen stromal lamellae?

Pathophysiology responsible for corneal edema has been associated with lowest values of IOP caused by reduction in corneal hysteresis and alterations of the

collagen stromal lamellae [14, 59, 60]. Knickelbein et al. [15] reported activation of matrix metalloproteinases after SLT procedure. These enzymes are involved in destructive inflammatory responses and can enhance collagen degeneration by corneal fibroblasts [2]. Could this SLT-induced adverse effect be reduced or prevented by previous LPLT?

No infrared LPLT-induced changes were observed on collagen remodeling in the muscle extracellular matrix [61], but collagen fibers were more organized in diabetic wound skin after infrared LPLT [61]. Red LPLT increases the expression of type I collagen gene in injured bone tissue [63] and type III collagen gene in burned skin [64], as well the amount of type I and type III collagens in injured skin [65]. Although matrix metalloproteinase expression was increased, red LPLT also increased neocollagenesis in rat skin wounds [66]. However, Lemos et al. [67] reported decreased expression of matrix metalloproteinase expression in temporomandibular joints in rats affected by arthritis after infrared LPLT. In addition, Marques et al. [68] demonstrated downregulation of metalloproteinase expression in rat tendons; as well, Gopal Nambi et al. [69] reported reduction in metalloproteinase expression in articular cartilage of human beings affected by osteoarthritis after infrared LPLT.

Could LPLT prevent SLT-induced inflammatory response?

After SLT procedure, synthesis and releasing of inflammatory cytokines, mainly interleukin-1 alpha, interleukin-1 beta and tumor necrosis factor alpha are increased [13, 15, 18], which stimulate chemotaxis and inflammatory infiltrate at corneal level [27], causing clinical edema by resident fibroblasts in corneal tissue. Simultaneously, metalloproteinases type 2 expression is increased in cornea, which is an important enzyme for this tissue [18]. Taken together, these events could explain opacity and residual thinning [15, 18]. Also, SLT increases lipid peroxidation and reduces the synthesis of antioxidant enzymes in aqueous humor, as superoxide dismutase and glutathione *S*-transferase, resulting in increasing of free radicals levels and oxidative stress in cornea. In view of the high sensibility of cornea to oxidative damages, this mechanism could be an adjuvant of inflammatory process triggered by SLT [16, 18].

Significant reduction in inflammatory cytokines was reported after both infrared and red LPLT [70]. In fact, LPLT reduces prostaglandin E2 and cyclooxygenase mRNA levels in human gingival fibroblasts cultures after induction of inflammatory response [70, 71]. In human keratinocyte cultures, gene expression related to cytokine pro-inflammatory interleukin 1-beta (IL-1-beta), IL-6 and IL-1-alpha reduces after infrared LPLT [48]. In another study, IL-6 level was not modified in gingival crevicular fluid after infrared LPLT [72]. Moreover, the authors observed increase in mitochondrial membrane potential before decreasing of cytokine levels, reinforcing the relationship between the mechanism dependent on mitochondrial photoacceptors and the LPLT action on inflammatory process [48].

The application of LPLT before SLT procedures could reduce and prevent these effects due to its anti-inflammatory effect. In fact, LPLT modulates the gene expression related to pro-inflammatory cytokines, as IL-1-beta and IL-1-alpha, in keratinocyte cultures [48], IL-6 and IL-10 in rat injured lung [73] and muscle [74], as well as TNT-α and CINC-1 in an animal model of osteoarthritis [75]. In addition, LPLT blocks ROS and NF-kappa-B releasing, and LPLT positively modulates expression of growth factors, such as bFGF, VEGF and PDGF in fibroblasts cultures [42], which could explain its proliferative and healing actions [34, 41]. Rezaei et al. [76] evaluated the regenerative and healing potential of infrared LPLT on injured corneas and the results showed reduction in corneal inflammation, a smaller loss of keratinocytes and a higher corneal repair rate.

Based on the effects of LPLT on high inflammatory cytokine levels, but also on the effects of SLT on degradation of stromal collagen and oxidative stress in corneal tissue, the balance of potential LPLT-induced effects in cornea should be taken into account before it is considered as a alternative therapy to prevent or to treat central corneal edema, thinning and residual opacity induced by SLT.

Perspectives of LPLT on SLT-induced adverse effects

LPLT is a vibrant research area with researchers and clinicians developing new therapeutic protocols for treatment of a number of diseases, besides laser

Table 4 Summary of some studies on experimental models for glaucoma

First author	Title	Model	References
Podos [78]	Animal models of human glaucoma	Various	Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol (1976) 81:OP632–OP635
Gelatt [77]	Animal models for glaucoma	Various	Invest Ophthalmol Vis Sci (1977) 16:592–596
Gherezghiher et al. [79]	Laser-induced glaucoma in rabbits	Rabbit	Exp Eye Res (1986) 43:885–894
Lauber [80]	Light-induced avian glaucoma as an animal model for human primary glaucoma	Avian	J Ocul Pharmacol (1987) 3:77–100
Shareef et al. [84]	Chronic ocular hypertension following episcleral venous occlusion in rats	Rat	Exp Eye Res (1995) 61:379–382
Johnson et al. [82]	Developing laser-induced glaucoma in rabbits	Rabbit	Aust N Z J Ophthalmol (1999) 27:180–183
Mabuchi et al. [83]	Optic nerve damage in experimental mouse ocular hypertension	Mouse	Invest OphthalmolVis Sci (2003) 44:4321–4330
Rasmussen and Kaufman [81]	Primate glaucoma models	Primate	J Glaucoma (2005) 14:311–314
Agar et al. [87]	Retinal ganglion cell line apoptosis induced by hydrostatic pressure	Cell culture	Brain Res (2006) 1086: 191–200
Liu et al. [88]	Oxidative stress is an early event in hydrostatic pressure-induced retinal ganglion cell damage	Cell culture	Invest OphthalmolVis Sci (2007) 48:4580–4589
Reigada et al. [91]	Elevated pressure triggers a physiological release of ATP from the retina: possible role for pannexin hemichannels	Bovine eyecup	Neuroscience (2008) 157:396–404
McKinnon et al. [93]	Mouse models of retinal ganglion cell death and glaucoma	Mouse	Exp Eye Res (2009) 88:816–824
Kipfer-Kauer et al. [86]	Distribution of amyloid precursor protein and amyloid-β in ocular hypertensive C57BL/6 mouse eyes	Mouse	Curr Eye Res (2010) 35:828–834
Ishikawa et al. [92]	Effects of acutely elevated hydrostatic pressure in a rat ex vivo retinal preparation	Rat	Invest Ophthalmol Vis Sci (2010) 51:6414–6423
Johnson and Tomarev [94]	Rodent models of glaucoma	Rodent	Brain Res Bull (2010) 81:349–358
Lei et al. [89]	In vitro models for glaucoma research: effects of hydrostatic pressure	Cell culture	Invest Ophthalmol Vis Sci (2011) 52:6329–6339
Steinhart et al. [84]	Mice with an induced mutation in collagen 8A2 develop larger eyes and are resistant to retinal ganglion cell damage in an experimental glaucoma model	Mouse	Mol Vis (2012) 18:1093–1106
You et al. [90]	FTY720 protects retinal ganglion cells in experimental glaucoma	Rat	Invest Ophthalmol Vis Sci (2014) 55:3060–3066

industry, which has manufactured new laser devices, including those based on dichromatic lasers, light-emitting diode (LED) and laser–LED clusters. Despite that, LPLT has been not evaluated to prevent, neither to treat adverse effects induced by SLT.

Since 1870, researchers have submitted animal eyes, and more recently cell cultures, to different insults to induce glaucoma similar to this that occurs in human beings [77]. Although some experimental models failed at the beginning to mimic some features of the human glaucoma, these experimental models were and are useful for understanding of the glaucoma pathophysiology, as well for evaluation of treatment purposes or approaches. Thus, it was developed in vivo [78–86], in vitro [86–89], ex vivo [91, 92] and genetically modified animal models for glaucoma [93, 94]. Table 4 lists some studies on experimental models for glaucoma.

By these experimental models for glaucoma, LPLT effects could be evaluated on adverse SLT-induced effects. In fact, evaluation of therapeutic effects induced by low-power lasers has been carried out by experimental models for a number of other diseases, showing positive effects and becoming an alternative or substituting therapy for these diseases or to soften their adverse effects, to radiation or chemical-induced mucositis [95], brain injury [96] and wounds [97]. Thus, although radiations emitted by low-power lasers are considered safe (class 3B lasers [98]) and able to induce therapeutic effects, researches based on experimental models for glaucoma could bring important data if LPLT could be an alternative approach to improve acceptation for patients undergoing SLT.

Compliance with ethical standards

Conflict of interest The authors declare that they have not conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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