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Original Research

Low-Level Laser Therapy at 635 nm for Treatment of Chronic Plantar Fasciitis: A Placebo-Controlled, Randomized Study

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ABSTRACT

Plantar fasciitis affects nearly 1 million persons in the United States at any one time. Conservative therapies have been reported to successfully treat 90% of plantar fasciitis cases; however, for the remaining cases, only invasive therapeutic solutions remain. This investigation studied newly emerging technology, low-level laser therapy. From September 2011 to June 2013, 69 subjects were enrolled in a placebo-controlled, randomized, double-blind, multicenter study that evaluated the clinical utility of low-level laser therapy for the treatment of unilateral chronic fasciitis. The volunteer participants were treated twice a week for 3 weeks for a total of 6 treatments and were evaluated at 5 separate time points: before the procedure and at weeks 1, 2, 3, 6, and 8. The pain rating was recorded using a visual analog scale, with 0 representing "no pain" and 100 representing "worst pain." Additionally, Doppler ultrasonography was performed on the plantar fascia to measure the fascial thickness before and after treatment. Study participants also completed the Foot Function Index. At the final follow-up visit, the group participants demonstrated a mean improvement in heel pain with a visual analog scale score of 29.6 ± 24.9 compared with the placebo subjects, who reported a mean improvement of 5.4 ± 16.0, a statistically significant difference ($p < .001$). Although additional studies are warranted, these data have demonstrated that low-level laser therapy is a promising treatment of plantar fasciitis.

Plantar fasciitis is the most common cause of heel pain in adults, affecting 1 million persons each year in the United States (1). Plantar fasciitis is an inflammatory response that occurs along the fascia's insertion point (2). The plantar fascia, which is a dense fibrous tissue, originates at the medial calcaneal tuberosity and inserts along the transverse tarsal ligament flexor sheath, plantar plate, and the proximal phalanges of the toes as it extends distally, separating into 5 bands and dividing into a superficial and deep layer (3). The plantar fascia frames the structure of the medial arch of the foot and, as a result, endures substantial mechanical stresses when the foot bears weight. Over time, repetitive tension can weaken the fascia, which can present clinically as persistent heel pain. Terms such as "sharp" and "stabbing" often describe the type of pain reported by patients (4). Additional symptoms may include weakness, swelling, numbness, and/or tingling over the plantar aspect of the foot.

Plantar fasciitis treatment ranges from rest to surgical intervention. According to several studies, 90% of plantar fasciitis cases will be cured with conservative methods that include rest, a change in activity levels, stretching, physical therapy, foot orthotics, night splinting, nonsteroidal anti-inflammatory agents (NSAIDs), oral analgesics, and corticosteroid injections (1,5). Patients unresponsive to conservative therapies can undergo treatment that is more aggressive, including extracorporeal shock wave therapy and endoscopic or open plantar fasciotomy.

A newly emerging noninvasive therapy for plantar fasciitis is low-level laser therapy (LLLT). Numerous histologic and clinical investigations have reported LLLT to be a possible treatment of multiple medical ailments, including acute and chronic pain, osteoarthritis, lymphedema, oral mucositis, peripheral nerve degeneration, ligament or tendon injury, and ischemic stroke (6–24). LLLT operates on the

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principles of photochemistry, which uses a discrete wavelength (color) of light to initiate a signal transduction cascade by stimulating a protein capable of absorbing light energy, also known as a photoreceptor protein. According to several studies, activation of specific photoreceptor proteins initiates secondary cascades linked to protein and growth factor synthesis, cell proliferation, downregulation of inflammatory cytokines, and expression of transcription factors (7–11,13–26).

With its ability to modulate specific secondary cascades, LLLT may promote a diverse clinical response depending on the specific wavelength and intensity parameters used. Studies evaluating LLLT have reported suppression of cyclooxygenase-2, enhancement of peripheral endogenous opioids, collagen synthesis in tendon and ligament repair, a reduction in the extent of fibrosis, suppression of conduction along unmyelinated C fibers, angiogenesis, and inhibition of histamine release (7,27–41). We hypothesized that the use of LLLT could serve as an effective treatment of plantar fasciitis. Accordingly, we conducted a placebo-controlled, randomized, double-blind, multicenter study to evaluate the effectiveness of LLLT at 635 nm with a mean output intensity of 17.0 mW for the treatment of chronic plantar fasciitis.

Patients and Methods

A total of 69 participants aged ≥18 years were consecutively qualified, enrolled, treated, and observed from September 2011 to June 2013. All 69 participants had satisfied all inclusion and exclusion criteria and participated to the study endpoint. Of the 69 subjects, 37 were randomized to the active treatment group and 32 to the placebo group. The Saint Alphonsus Regional Medical Center institutional review board and the Western institutional review board approved the study, which was also registered at clinicaltrials.gov (NCT01835743).

All participants who were deemed eligible for participation satisfied all the following inclusion criteria: unilateral chronic plantar fasciitis; a primary complaint of heel pain on weightbearing after a period of rest; pain that dissipated after a few minutes of walking but returned after prolonged periods of walking or standing; pain located along the medial process of the calcaneal tuberosity and/or medial plantar band of the plantar fascia; pain that developed on palpation of the medial calcaneal tuberosity with passive dorsiflexion of the foot; chronic heel pain that persisted ≥3 months with no evidence of acute trauma to the heel; an average self-rating pain score of ≥50 using a 100-point visual analog scale (VAS) after taking some initial steps following a period of rest both on the day of study qualification and at baseline; and heel pain that was unresponsive to any conservative form of plantar fasciitis care (ie, rest, taping, stretching, orthotics, shoe modifications, night splinting, casting, physical therapy, prescription NSAIDs when taken for a minimum period of 2 weeks, or local corticosteroid injections). In addition, the subjects were required to be willing and able to refrain from participating in any other over-the-counter and/or prescription medications indicated for pain relief (ie, NSAIDs, topical analgesics, anti-inflammatory drugs, and corticosteroid medications) 48 hours before the start of the study until completion. They were also required to be willing and able to refrain from participating in nonstudy treatment or therapy for the relief of plantar fasciitis (including rest, taping, stretching, orthotics, shoe modifications, night splinting, casting, physical therapy, prescription NSAIDs when taken over a minimum period of 2 weeks, or local corticosteroid injections) 48 hours before the start of the study until completion of the individual clinical study course. If a patient had undergone a corticosteroid injection, they were not enrolled until they were again experiencing pain (VAS score >50).

The study participants met none of the following exclusion criteria: mechanical posterior heel pain categorized as insertional Achilles tendonitis or bursitis; neurologic heel pain resulting from nerve entrapment (eg, posterior tibial nerve, medial calcaneal branch of the posterior tibial nerve, abductor digiti quinti nerve, lumbar spine disorder, neuropathy) as determined by the physical evaluation; arthritic heel pain (eg, seronegative arthritides, psoriatic arthritis, reactive arthritis, diffuse idiopathic skeletal hyperostosis, rheumatoid arthritis, fibromyalgia, and/or gout); traumatic heel pain (acute calcaneus trauma, stress fractures of the calcaneus, and/or soft tissue trauma); bilateral plantar fasciitis; heel pain for ≤3 months; skin ulceration surrounding the heel and treatment area; sciatica; benign and/or malignant tumors; acute infection of soft tissue and bone; type 1 diabetes; sensory neuropathy; peripheral vascular disease or autoimmune disease; fibromyalgia; chronic fatigue syndrome; significant heart conditions (ie, congestive heart failure); unable or unwilling to consume the study-selected rescue medication, acetaminophen; photosensitivity disorder; and pregnant or lactating.

All participants were recruited from the senior authors' (M.J.C. and K.Z.) pool of participants who had presented for treatment of unilateral plantar fasciitis, signed the informed consent form, and satisfied all the study eligibility criteria. The participants were not offered any form of compensation to participate in the clinical trial nor were they charged for the cost of the laser procedure or related evaluations. The participants were financially responsible for any component of a session in which the clinical protocol was not performed.

Randomization and Blinding

The clinical study was a prospective, controlled, double-blind, parallel group, multicenter design. A computer program was used to perform the participant group assignment. The double-blind component of the study was established by including a treatment investigator and an assessment investigator. The treatment investigator was responsible for administering the active and placebo interventions. That investigator was the only individual present in the room during the treatment phase and did not participate in the pre- or post-treatment evaluation activities. The assessment investigator was responsible for conducting the pre- and post-procedure evaluations and determining the diagnosis and eligibility of the participants for study participation. The assessment investigator was never aware of the participants' group allocation. Additionally, the study participants were never informed of their group assignment and wore darkened protective glasses designed to filter out the laser light during the treatment procedure.

Intervention

The participants assigned to the test group were treated with a multihead, low-level, diode laser emitting a divergent 635-nm (red) laser light generating a 17-mW output (MLS laser, Erchonia Corp, McKinney, TX). The device was fitted with 2 modes: active and placebo. However, the modes were labeled as A and B, and no study personnel, except for the study monitor, knew which letter corresponded with which treatment mode. Accordingly, the placebo and treatment group participants were treated using the same multihead device, but the placebo group instead received treatment from placebo light-emitting diodes rather than LLLT. Each subject received 6 total procedure administrations with the laser (active or placebo) across a consecutive 3-week period: 2 procedures per week, each procedure separated by 3 or 4 days. The exposure time to the laser was 10 minutes across the top of the foot (dorsal aspect), the myofascial junction of the heel, and the plantar aspect of the heel, simultaneously, for each procedure administration. Each procedure administration occurred at the investigator's test site.

Study Outcomes

The patients were asked to record a preprocedure pain rating using the VAS, with 0 representing "no pain" and 100 representing "worst pain." The VAS has been previously validated in the published data (42). The pain rating was calculated as the average VAS score reported by the patient over a 2-day period. They were asked to record the VAS score immediately after taking their first steps in the morning or after a period of prolonged sedentary behavior (eg, sitting at a desk for 6 hours). They were asked to refrain from taking the rescue medication (acetaminophen) before scoring the VAS.

The study participants also completed the Foot Function Index (FFI), a self-administered questionnaire measuring the foot pain's impact on the patient's quality of life (43). The FFI has 3 distinct subsets, which evaluate pain, disability, and activity limitation.

Additionally, Doppler ultrasonography was performed on the plantar fascia to measure the fascial thickness. The plantar fascia was measured at the point of plantar fascial insertion into the calcaneus. The measurements were recorded in millimeters.

Complications were also assessed. A priori, any complication that might develop in association with treatment, at any time during the observation period, was to be identified and recorded for comparison between the 2 groups. The participants were evaluated across 6 time points: before the procedure and at weeks 1, 2, 3, 6, and 8. The preprocedure and final follow-up subjective scores were used to assess the efficacy of the procedure. The Doppler evaluation was performed only at the preprocedure and final follow-up visits (8 weeks).

Statistical Analysis

The primary efficacy outcome measure was predetermined as a statistically significant difference in the pain rating from the preprocedure baseline score to the final follow-up score between the treatment and placebo groups. Overall, the study success criterion was defined as at least a 35% difference in the statistically significant decrease in the VAS score between the treatment groups, comparing the proportion of individual successes in each group. A 35% difference in the pain scores for the study groups was suggested as a minimum criterion for success in the present trial, with the expectation that the results would be reviewed by the Food and Drug Administration. Fisher's exact test was conducted to test the association of success between the treatment and placebo groups. A paired samples t test was used to compare the change in pain ratings from study baseline to study endpoint within each treatment group. At the final follow-up visit, the subjects were asked to complete a 5-point satisfaction questionnaire, rating their level of satisfaction concerning any perceived overall change in heel pain as very

Table 1
Duration of heel pain before treatment

Duration of Heel Pain (mo)	Mean
Test (n = 37)	12.3 ± 11.0
Placebo (n = 32)	12.2 ± 12.4
Difference	0.1 ± 11.6
Significance	$p = .97$*

* Student's *t* test.

satisfied, satisfied, neutral, dissatisfied, and very dissatisfied. The statistical significance was defined at the 5% ($p \leq .05$) level.

Results

Of the total study population, 61% were female and 39% were male, with a mean age of 56.7 (range 31 to 75) years. The mean difference of 0.1 ± 11.6 months in the duration of heel pain between the study groups was not statistically significant (Table 1). Additionally, comparing the mean plantar fascial thickness in the baseline Doppler ultrasound-determined plantar fascial thickness between the 2 study groups did not demonstrate a statistically significant difference (Table 2). A comparison of the reported baseline FFI subscale scores between treatment groups revealed no statistically significant differences (Table 3).

For the test subjects, a baseline VAS heel pain rating of 69.2 ± 12.7 was reported. The placebo participants reported a VAS heel pain rating of 67.7 ± 11.8 (Table 4). The difference of 1.5 between the study groups was not statistically significant ($p = .36$).

For the test subjects, the reported heel pain mean VAS rating at the study endpoint was 39.6 ± 27.9. Compared with the baseline score, a mean reduction of 29.6 ± 24.9 points (44.2%) was reported, a statistically significant difference ($p < .001$). In contrast, the placebo group reported a study endpoint VAS heel pain rating of 62.3 ± 18.2. Compared with the baseline score, a mean difference of 5.4 ± 16.0 (7.5%) was reported, not a statistically significant difference ($p = .67$). The difference in the reduction of heel pain of 24.2 ± 4.98 points between the treatment and placebo cohorts was statistically significant ($p < .001$; Fig.).

After the treatment administration phase, 23 of the test subjects (62%) and 4 of the placebo subjects (12.5%) met the individual success criteria, a statically significant difference in the proportion of study success between the treatment groups ($p < .001$).

The plantar fascial thickness between the baseline and final measurements for the test subjects revealed a mean decrease in thickness of 0.4 ± 1.3 mm, a statistically significant difference ($p = .003$; Table 5). During the same period, the placebo participants showed a mean change of 0.1 ± 1.0 mm, not a statistically significant difference ($p = .072$).

Concerning the change in the FFI scores, both groups reported improvement in the total scores and all the subscores from the baseline to the final follow-up assessment. No statistically significant difference was found between the treatment and placebo groups in the improvement in the total or subscore FFI scores (Table 3).

Table 2
Preprocedure plantar fascial thickness

Baseline Measurements	Plantar Fascia Thickness (mm)
Test (n = 37)	6.0 ± 1.2
Placebo (n = 32)	5.7 ± 1 0.9
Difference	0.26
Significance	$p = .34$*

* Student's *t* test.

Table 3
Comparison of baseline and final FFI scores between test and placebo cohorts*

Foot Function Index Domain	Test Group (n = 37)	Placebo (n = 32)	*p* Value
Pain subscale			
Baseline	55.9 ± 16.2	55.0 ± 11.9	.80
Endpoint	40.8 ± 21.2	42.8 ± 20.2	.68
p Value	<.01	<.01	
Disability subscale			
Baseline	43.0 ± 18.4	43.7 ± 20.7	.87
Endpoint	31.5 ± 19.6	33.5 ± 20.3	.68
p Value	<.01	<.01	
Activity limitation subscale			
Baseline	13.1 ± 6.8	12.1 ± 5.2	.48
Endpoint	9.7 ± 7.9	9.8 ± 7.1	.97
p Value	<.01	<.01	
Total FFI score			
Baseline	111.9 ± 34.2	110.8 ± 32.3	.89
Endpoint	82.0 ± 43.6	86.1 ± 43.2	.70
p Value	<.01	<.01	

Abbreviation: FFI, Foot Function Index.
Data presented as mean ± standard deviation.
* One-way analysis of variance.

At the final follow-up visit, all subjects completed the subject satisfaction questionnaire (Table 5). The test group reported a much greater level of satisfaction than the placebo group. The results of the Fisher exact test to evaluate the proportion of "satisfied" responses between the treatment groups found a statistically significant difference ($p < .001$). Finally, complications were recorded at each visit; however, no adverse events were reported throughout the study.

Discussion

These data demonstrate the utility of LLLT for the reduction of chronic heel pain arising from plantar fasciitis. The difference of 49.5% exceeded the pre-established target of a 35% difference between the treatment groups by 14.5%. The test group participants demonstrated a significant reduction in pain between the baseline and study endpoint observations. The observed reduction in heel pain was associated with a statistically significant higher number of satisfied test participants than placebo participants. With these results, we have substantiated LLLT as a successful therapy for plantar fasciitis.

Few studies have evaluated LLLT for the treatment of plantar fasciitis; therefore, we do not know the exact mechanism of action. We used the MLS laser for the present study, which has a wavelength of 635 nm and 17 mW output. Basford et al (44) used an 830-nm laser with an output intensity of 30 mW 3 times per week for 1 month. The investigators failed to report a statistically significant difference in the outcome measures between the groups (44). Kiritsi et al (45) administered laser therapy using a 904-nm gallium-arsenide infrared laser with an output intensity of 0.16 W/cm^2 and 0.08 W/cm^2 3 times weekly for 6 weeks for 18 total treatment sessions. They reported a statistically significant difference in the VAS pain scores between the study groups (45).

According to Cardinal et al (46), plantar fasciitis induces proximal fascial hypertrophy, based on ultrasound evaluation (7 to 8 mm; normal is 3 to 4 mm). In the study by Kiritsi et al (45), the investigators

Table 4
Change in heel pain VAS ratings from baseline to study endpoint stratified by group

VAS Heel Pain Ratings	Test (n = 37)	Placebo (n = 32)	*p* Value
Baseline	69.1 ± 12.7	67.6 ± 11.8	.36
Study endpoint	39.5 ± 27.9	62.3 ± 18.2	<.001

Abbreviation: VAS, visual analog scale.
Data presented as mean ± standard deviation.

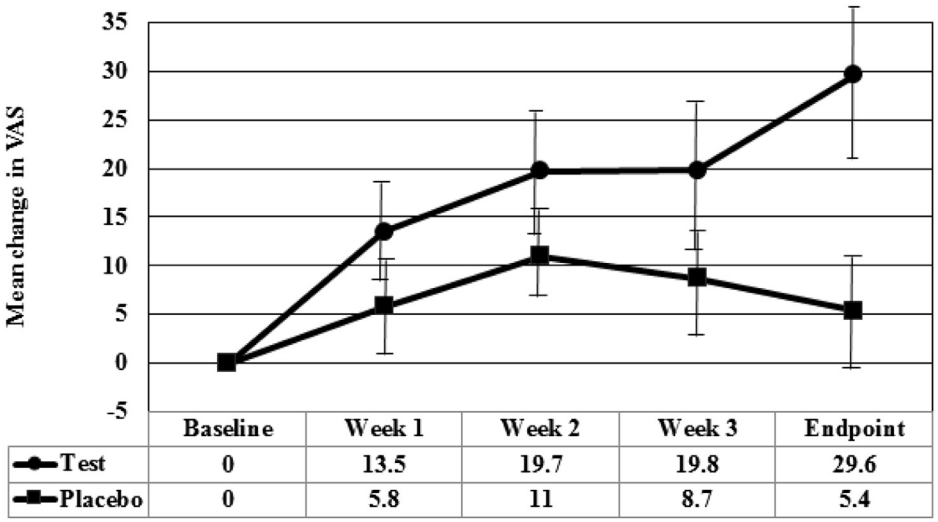

Fig. Change in visual analog scale across the study time points. Whiskers represent 95% confidence interval.

failed to show a statistically significant difference in the observed plantar fascial thickness between the study groups at endpoint; however, both groups did have a mean reduction in the plantar fascial thickness at the final follow-up visit. In the present study, at the final follow-up visit, we observed a reduction of 0.4 mm in the plantar fascial thickness for the test group and an increase in the fascial thickness of 0.1 mm for the placebo group. These measurements of the plantar fascia are subject to both intra- and interobserver reliability issues, because the measurement was performed using Doppler ultrasonography, which is operator dependent. Although a statistically significant change was seen in the plantar fascial thickness, it would be difficult to determine whether that would correlate with a clinically significant change owing to the short duration of our study and the small reduction (0.4 mm) in thickness. Long-term follow-up studies would be helpful to determine whether the plantar fascia would continue to decrease in size.

Although the results are promising, 1 limitation in the present study was the lack of long-term follow-up data. Our aim, however, was to ascertain the primary efficacy within a period that we thought would be consistent with a reasonable clinical response to treatment. Thus, our primary efficacy endpoint was set at 6 weeks after intervention. A study with 6- and 12-month postprocedure evaluations is currently underway. Other limitations of the present study were the measurements of the plantar fascial thickness using Doppler ultrasonography, which is a very user dependent modality. However, Doppler ultrasonography has the benefit of being relatively inexpensive and noninvasive and can easily be performed in the clinic (in contrast to computed tomography or magnetic resonance imaging).

In conclusion, LLLT is a promising therapy for heel pain resulting from plantar fasciitis. We were able to demonstrate a statistically significant reduction in pain for patients undergoing the laser therapy compared with those who received placebo treatment. In addition to the reduction in pain, we did not see any complications, demonstrating the safe and efficacious nature of LLLT. Although additional studies are warranted, the noninvasive nature of LLLT enables this technology to serve as a treatment of plantar fasciitis.

Table 5
Satisfaction scores at study endpoint

	Test Group (n = 37)	Placebo Group (n = 32)	*p* Value
Very satisfied	14 (38)	1 (3)	<.001
Somewhat satisfied	8 (22)	3 (9)	.17
Neither satisfied nor dissatisfied	9 (24)	7 (22)	.81
Not very satisfied	5 (13)	15 (47)	.002
Not at all satisfied	1 (3)	6 (19)	.28

Data presented as n (%).

References

1. Goff JD, Crawford R. Diagnosis and treatment of plantar fasciitis. Am Fam Physician 84:676–682, 2011.
2. McBryde AM, Hoffman JL. Injuries to the foot and ankle in athletes. South Med J 97:738–741, 2004.
3. Karr SD. Subcalcaneal heel pain. Orthop Clin North Am 25:161–174, 1994.
4. Pasquina PF, Foster LS. Plantar fasciitis. In: *Musculoskeletal Disorders: Foot and Ankle*, pp. 469–473, edited by WR Frontera, JK Silver, TDRizzo Jr, WB Saunders, Philadelphia, 2008.
5. Chacko K. Heel pain: diagnosis and treatment. Primary Care Case Rev 6:50–56, 2003.
6. Bjordal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RA. Photoradiation in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. Photomed Laser Surg 24:158–168, 2006.
7. Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain: a systematic review and meta-analysis of randomized placebo-controlled trials. BMC Musculoskelet Disord 8:51, 2007.
8. Carati CJ, Anderson SN, Gannon BJ, Piller NB. Treatment of postmastectomy lymphedema with low-level laser therapy: a double blind, placebo-controlled trial. Cancer 98:1114–1122, 2003.
9. Chow RT, Johnson MI, Lopes-Martins RAB, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systemic review and meta-analysis of randomized placebo or active-treatment controlled trials. Lancet 374:1897–1908, 2009.
10. Fillipin LI, Mauriz JL, Vedovelli K, Moreira AJ, Zettler CG, Lech O, Marroni NP, Gonzalez-Gallego J. Low-level laser therapy (LLLT) prevents oxidative stress and reduces fibrosis in rat traumatized Achilles tendon. Lasers Surg Med 37:293–300, 2005.
11. Genot MT, Klastersky J. Low-level laser for prevention and therapy of oral mucositis induced by chemotherapy or radiotherapy. Curr Opin Oncol 17:236–240, 2005.
12. Greco M, Guida G, Perlino E, Marra E, Quagliariello E. Increase in RNA and protein synthesis by mitochondria irradiated with helium-neon laser. Biochem Biophys Res Commun 163:1428–1434, 1989.
13. 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 30:353–358, 2003.
14. Lampl Y, Zivin JA, Fisher M, Lew R, Welin L, Dahlof B, Borenstein P, Andersson B, Perez J, Caparo C, Ilic S, Oron U. Infrared laser therapy for ischemic stroke: a new treatment strategy. Results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1). Stroke 38:1843–1849, 2007.
15. Moore P, Ridgway TD, Higbee RG, Howard EW, Lucroy MD. Effect of wavelength on low intensity laser irradiation-stimulated cell proliferation in vitro. Lasers Surg Med 36:8–12, 2005.

16. Ohno T. Pain suppressive effect of low power laser irradiation: a quantitative analysis of substance P in the rat spinal dorsal root ganglion. Nihon Ika Daigaku Zasshi 64:395–400, 1997.
17. Oron A, Oron U, Streeter J, de Taboada L, Alexandrovich A, Trembovler V, Shohami E. Low-level laser therapy applied transcranially to mice following traumatic brain injury significantly reduces long-term neurological deficits. J Neurotrauma 24:651–656, 2007.
18. Sakihama H. Effect of a helium-neon laser on cutaneous inflammation. Kurume Med J 42:299–305, 1995.
19. Saltmarche AE. Low level laser therapy for healing acute and chronic wounds—the extendicare experience. Int Wound J 5:351–360, 2008.
20. Schindl M, Kerschan K, Schindl A, Schon H, Heinzl H, Schindl L. Induction of complete wound healing in recalcitrant ulcers by low-intensity laser irradiation depends on ulcer cause and size. Photodermatol Photoimmunol Photomed 15:18–21, 1999.
21. Schindl A, Schindl M, Schindl L, Jurecka W, Honigsmann H, Breier F. Increased dermal angiogenesis after low-intensity laser therapy for a chronic radiation ulcer determined by a video measuring system. J Am Acad Dermatol 40:481–484, 1999.
22. Walker-Bone K, Palmer KT, Reading I, Copper C. Soft-tissue rheumatic disorders of the neck and upper limb: prevalence and risk factors. Semin Arthritis Rheum 33:185–203, 2003.
23. Wu S, Xing D, Gao X, Chen WR. High fluence low-power laser irradiation induces mitochondrial permeability transition mediated by reactive oxygen species. J Cell Physiol 218:603–611, 2009.
24. Yamaguchi N, Tsukamoto Y. The effects of semiconductor laser irradiation on the immune activities of human lymphocytes in vitro. Lasers Life Sci 6:143–149, 1994.
25. Ad N, Oron U. Impact of low level laser irradiation on infarct size in the rat following myocardial infarction. Int J Cardiol 80:109–116, 2001.
26. Hawkins D, Abrahamse H. Biological effects of helium-neon laser irradiation on normal and wounded human skin fibroblast. Photomed Laser Surg 23:251–259, 2005.
27. Abergel RP, Lyons RF, Castel JC, Dwyer RM, Uitto J. Biostimulation of wound healing by lasers: experimental approaches in animal models and in fibroblast cultures. J Dermatol Surg Oncol 13:127–133, 1987.
28. Calkhoven CF, Ab G. Multiple steps in the regulation of transcription factor level and activity. Biochem J 317:329–342, 1996.
29. Fork RL. Laser stimulation of nerve cells in aplysia. Science 171:907–908, 1971.
30. Funk JO, Kruse A, Neustock P, Kirchner H. He-Ne laser irradiation induces effects of cytokine production at the protein and the mRNA level. Exp Dermatol 2:75–83, 1993.
31. Gavish L, Perez L, Gertz SD. Low-level laser irradiation modulates matrix metalloproteinase activity and gene expression in porcine aortic smooth muscle cells. Lasers Surg Med 38:779–786, 2006.
32. Haddad JJ. Oxygen-sensing mechanisms and the regulation of redox responsive transcription factors in development and pathophysiology. Respir Res 3:26–53, 2002.
33. Morrone G, Guzzardella GA, Torricelli P, Rocca M, Tigani D, Brodano GB, Fini M, Giardino R. Osteochondral lesion repair of the knee in the rabbit after low-power diode Ga-Al-As laser biostimulation: an experimental study. Artif Cells Blood Substit Immobil Biotechnol 28:321–336, 2000.
34. Rochkin S, Nissan M, Lubart R, Avram J, Bartal A. The in vivo nerve response to direct low-energy laser irradiation. Acta Neurochir 94:74–77, 1988.
35. Rusakov DA, Klering PG. Structural and functional changes in spinal cord neurons after low-intensity laser irradiation. Radiobiology 29:130–133, 1988.
36. 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 23:331–335, 2008.
37. Shao XH, Yang YP, Dai J, Wu JF, Bo AH. Effects of He-Ne laser irradiation on chronic atrophic gastritis in rats. World J Gastroenterol 11:3958–3961, 2005.
38. Shefer G, Partridge TA, Heslop L, Gross JG, Oron U, Halevy O. Low-energy laser irradiation promotes the survival and cell cycle entry of skeletal muscle satellite cells. J Cell Sci 115:1461–1469, 2002.
39. Vizi ES, Mester E, Tisza S, Mester A. Acetylcholine releasing effect of laser irradiation on Auerbach's plexus in guinea-pig ileum. J Neural Transm 40:305–308, 1997.
40. Walker JE, Akhanjee LK. Laser-induced somatosensory evoked potentials: evidence of photosensitivity in peripheral nerves. Brain Res 344:281–285, 1985.
41. Yaakobi T, Shoshany Y, Levkovitz S, Rubin O, Ben Haim SA, Oron U. Long-term effect of low energy laser irradiation on infarction and reperfusion injury in the rat heart. J Appl Physiol 90:2411–2419, 2002.
42. Wessel J. The reliability and validity of pain threshold measurements in osteoarthritis of the knee. Scand J Rheumatol 24:238–242, 1995.
43. Budiman-Mak E, Conrad KJ, Roach KE. The foot function index: a measure of foot pain and disability. J Clin Epidemiol 44:561–570, 1991.
44. Basford JR, Malanga GA, Krause DA, Harmsen WS. A randomized controlled evaluation of low-intensity laser therapy: plantar fasciitis. Arch Phys Med Rehabil 79:249–254, 1998.
45. Kiritsi O, Tsitas K, Malliaropoulos N, Mikroulis G. Ultrasonographic evaluation of plantar fasciitis after low-level laser therapy results of a double-blind, randomized, placebo-controlled, trial. Lasers Med Sci 25:275–281, 2010.
46. Cardinal E, Chhem RK, Beauregard CG, Aubin B, Pelletier M. Plantar fasciitis: sonographic evaluation. Radiology 201:257–259, 1996.