

## Effects of low level laser therapy on grades II and III of diabetic foot ulcers

Nooshafarin Kazemi khoo<sup>1</sup>, Mitra Hajizade<sup>2</sup>, Fataneh Hashem Dabaghian<sup>3</sup>

<sup>1</sup> MD, Medical Genetics, PhD Candidate, Department of Medical Genetics, Tehran University of medical sciences, Tehran, Iran.

<sup>2</sup> MD, Internal Medicine, Department of Internal Medicine Milad Hospital, Tehran, Iran.

<sup>3</sup> MD, community Medicine, Tehran University of medical sciences, Research Institute for Islamic and Complementary Medicine, Tehran, Iran.

Corresponding Author: N. Kazemi khoo, E-mail: kazemikho@razi.tums.ac.ir

### Abstract

**Objective:** To evaluate the effect of Low Level laser Therapy on foot ulcers in diabetic type II based on photographic assessment.

**Background data:** Researchers have been used low level lasers to enhance wound healing. Ulcers in diabetic patients are in risk of compromised healing, due to reduced microcirculation and the other disorders that may affect wound healing.

**Material and Methods:** Thirty diabetic type 2 patients, with grade II and III diabetic foot ulcers were treated by low level laser therapy. The mean duration of diabetes was 14.3 years and ulcers were present since average 3.4 months ago. Treatment sessions were performed every other day for 10-15 sessions and then continued two times a week until complete healing or achieving grade I.

**Results:** Mean of wounds surface was 43.5 cm<sup>2</sup> (range 0.09- 62.5) before treatment, and was 0.3 cm<sup>2</sup> (range 0-1.7) after about 18 treatment sessions (range 8-46), P<0.001. There was no relapse or other problem with ulcers during three months of follow-up. There were no reported side-effects by the patients.

**Conclusion:** Low level laser therapy could be a safe and effective method for treatment of diabetic foot ulcers. Clinical trials with higher sample size are proposed to evaluate more details about low level laser therapy effectiveness on diabetic wound healing process.

**Key words:** Low level Laser Therapy, Diabetic Foot Ulcer, Laser Acupuncture, Intravenous Laser

### Introduction

According to the American Diabetes Association in 2009, about 23.6 million people in America suffer from diabetes [1]. Diabetic foot ulcers are one of the most common health problems with 1.0-4.1% annual population-based incidence and 4-10% prevalence suggest that the life time incidence may be as high as 25% among patients with diabetes mellitus [2–3]. These ulcers cause considerable morbidity and care expenses, and their significance for the individual and society, is apparent [4-7].

The pathophysiological mechanisms lead to foot ulceration in diabetic patients is not completely clear. Structural deformities, peripheral neuropathy, ischemia, infection, edema, and callus formation are some of the most identified causes lead to diabetic ulcers [8]. Peripheral neuropathy is one of the most important causes [9] which affects more than 50% of diabetic patients older than 60 years [10]. Endothelial dysfunction, reduction of vessel elasticity due to the sclerosis of media and dysfunction of the autonomic vasomotor are the other causal pathways [11-14].

Several surgical and medical options are provided for treatment of diabetic foot ulcers [15]. Low level laser therapy (LLLT) has been suggested as a promising treatment option for open wounds. However, there are few reports on LLLT effectiveness on diabetic wounds.

During past 30 years, low-level lasers have been broadly used in medical fields. Recently, there has been an increase in the clinical applications of low-

level laser irradiation in various therapeutic fields. One of the most important functional aspects of laser therapy is photobiostimulatory effects on various biological systems especially microcirculation. The photobiostimulatory effects is reported based on the effects of low intensity lasers which are described as lasers with less than 500 mW average power [16-19].

Researchers have been tried to use Helium Neon (He-Ne), CO<sub>2</sub>, and Potassium Titanyl Phosphate. (KTP) lasers in encouraging wound healing in diabetic patients [20]. Carvalho et al (2006) evaluated the effect of He-Ne laser on wound healing in diabetic and non diabetic rats. They showed significant effect of laser on the amount of collagen fibers [21]

In another study, Kawalec et al (2004) used infra red low level laser on diabetic and non diabetic rats [22]. Hawkins et al (2005) showed the effect of LLLT on synthesis of protein and prostaglandins, ATP and fibroblasts, cellular growth and secretion of neurotransmitters. LLLT had significant effect on wound healing in diabetic rats but not on non diabetic ones [23].

Hopkins et al (2004) in triple blinded study with sham laser showed the effect of LLLT on human fibroblast proliferation [24].

Low-level laser irradiation has been shown to accelerate collateral circulation, enhance microcirculation [25] as well as relaxation of vascular smooth muscle [26]. Furthermore, LLLT was reported effective to improve skin circulation in patients with diabetic microangiopathy [27].

Schindle et al. (1999) reported the first diabetic foot which was treated by LLLT. He suggested that this therapeutic method might represent a useful side-effect-free alternative treatment modality for the induction of wound healing in neuropathic diabetic ulcers [28]. Since then, some researchers have been applied low-intensity lasers for treatment of diabetic foot ulcers. But contradictory results have been achieved through different research plans. Cullum et al. (2001) systemically reviewed the available published articles and reported there were no sufficient reliable evidences on contribution of laser therapy in chronic wound healing [29].

There are several methods for laser irradiation, local, intravenous, acupuncture and etc. Unlike the treatment mechanisms of local laser therapy, the medical effects of intravenous laser therapy are determined by predominance of systemic mechanisms as increasing the efficacy of vascular,

immune, respiratory, other systems and organs as a whole [30,31].

Apart from standard needle acupuncture, other methods of stimulating acupuncture points are also applied. Due to invention of low power lasers, irradiation laser acupuncture has been introduced into routine treatment methods which are a painless and aseptic technique [32-33].

In our pilot study on seven diabetic foot patients, with grade 2-3 ulcers, we used combination of local LLLT, intravenous laser and laser acupuncture. All patients healed completely after mean 19 sessions of therapy [34].

We report herein a case series of 30 patients with grade II and III diabetic foot ulcers treated with LLLT as an alternative therapeutic method to routine medical conservative treatment.

## Material and Methods

Thirty type 2 diabetic (T2DM) patients with grade II and III diabetic foot ulcers, who had conventional therapy and came to laser clinic of Milad Hospital, were recruited voluntarily for this study. Patients with pregnancy, epilepsy, photosensitivity and pacemaker were excluded because of laser contraindication [34]. The ulcers were graded as follow: 1-Epidermal ulcers. 2- Dermal ulcers. 3- Muscle involvement [5]. Glycosylated hemoglobin (HbA1C), Fasting Blood Sugar (FBS), Triglyceride (TG), Low-density Lipoprotein (LDL), High-density Lipoprotein (HDL),: LDL-to-HDL ratio (LDL/HDL), Body Mass Index (BMI), Hip-to-waist ratio (HWR) were measured for all patients before treatment( Table 1).

Table 1: Patients overall data

| Patients overall data       | Mean(SD)                   | Range                   |
|-----------------------------|----------------------------|-------------------------|
| TG                          | (79)147                    | 50-430                  |
| HDL/LDL                     | (.0.1)0.3                  | 0.17-0.49               |
| HbA1C                       | (1.3)8.4                   | 6-11                    |
| FBS                         | (57.4)193                  | 71-300                  |
| BMI                         | (3.5)27.6                  | 21.4-38.4               |
| H/W ratio                   | (0.00)1.07                 | 0.9-1.24                |
| Ulcer area before treatment | (11.11)4.35cm <sup>2</sup> | 0.9-62.5cm <sup>2</sup> |
| Ulcer area after treatment  | (0.3)0.00cm <sup>2</sup>   | 0-1.7cm <sup>2</sup>    |
| Ulcer duration              | (2.9)3.4 months            | 0.5-12                  |
| Diabetes duration           | (7.8)14.3 years            | 2-30                    |
| Treatment sessions          | (7.85)17.78                | 8-46                    |

All patients were under classic conventional treatment for wound including daily wash with normal saline and routine dressing. Wound secretion culture was done before treatment and antibiotic was prescribed according to the antibiogram result. Wound culture was repeated every 2-3 weeks according to the secretions. Debridement was done if needed.

The length and width of the ulcers were measured by one person before and after treatment. Photographs were taken before and after treatment by digital camera.

We applied LLLT through local contact irradiation of ulcer bed with red light (660 nm, power 25 mW, 1.5 J/cm<sup>2</sup>) and ulcer margins with infrared laser (980 nm, power 200 mW, 6 J/cm<sup>2</sup>). We used sterile translucent covers to avoid direct contact of probe and ulcer, along with intravenous laser irradiation with red light laser (650 nm, power 1.5 mW) for 15 to 20 minutes, in addition to laser acupuncture with infrared laser (1 J/cm<sup>2</sup>) for LI-11, LI-4 SP-6, Pe-6, ST-36 and GB-34 points. Based on the authors past experiences, combination of these three methods (local laser therapy, intravenous laser and laser acupuncture) can be more effective to accelerate wound healing, especially in chronic and non healing wounds.

The LLLT intervention were performed every other day for 10-15 sessions and after that continued two times a week until complete healing were achieved. In total, treatment period was about 1.5-2 months.

## Results

Thirty diabetic T2DM patients with grade II and III diabetic foot ulcers were recruited for this study (mean age 61.77, range 46-76). The mean period of diabetes was 14.3 years (range 2-30, SD 7.8) and the mean value for glycosylated hemoglobin (HbA<sub>1c</sub>) also was 8.4mg/dl (range: 6-11, SD: 1.3). The ulcers were emerged from average 3.4 months ago (range 0.5-12, SD 2.9). Mean wound's area before treatment was 43.5 cm<sup>2</sup> (range 0.09-62.5), and after about 18 sessions of treatment 0.3 cm<sup>2</sup> (range 0- 1.7), Wilcoxon-signed test showed P<0.001. Total outcome measures can be reached by table 1. All ulcers were completely healed with exception of three patients who quitted from the study. Mean of therapeutic sessions in these three patients were 19. The surface of their ulcers was about 1.5-2.64 cm<sup>2</sup> at the ending session but all of these ulcers reduced to grade I. The lower extremity blood supply was assessed by doppler sonography. 17 patients (53.1%)

normal, in 10 patients (31.3%) decreased and in 5 patients (15.6%) cut off. There was no significant difference between three groups based on doppler report (normal flow, decreased, and cut off) and number of therapeutic sessions.

There was no relapse or other problem with ulcers during three months of follow-up. There was no compliance reported by the patients.

In Spearman's rho test for evaluating the relation between laser sessions with HbA<sub>1c</sub> ( as blood sugar control indicator ), BMI ( as body mass indicator ), diabetes duration, ulcer duration, age and wound surface before treatment ,P>0.05 which is statistically insignificant.



A: before treatment



B: After treatment

## Discussion

Low Level Lasers have been evaluated as a non-invasive treatment for wound healing. This effect, called “photostimulation” or “biostimulation”, produces non-destructive effects on tissues at the cellular level [32]. The exact pathophysiological

mechanisms for this treatment have not yet been elucidated. However, ATPase activity changes, long-term erythrocytes membrane proteins as well as lipid bi-layer structural changes, changes in membrane ion pumps activities [35], changes in neutrophils through activation of tyrosine kinase and phospholipase C [22], dose-dependent priming of polymorphonuclear leukocytes [36] have all been mentioned as cellular mechanisms for application of low intensity laser irradiation.

It seems that laser irradiation increases cell and fibroblast proliferation, collagen synthesis, stimulates macrophages, releases cytokines, modulates the production of growth factors and develops new blood vessels [19, 37-38].

In a randomized control trial by Ataie-Fashtami et al on 16 diabetic foot patients, healing rate in laser group was reported 70% versus 33.3% in placebo group. The difference between the groups in Javid study was not statistically significant, which might happen because of small numbers in each group [39].

Laser clinical trials in wound healing have lots of structural and methodological defects [40]. There is no evidence for positive effect of LLLT on wound healing in some studies which may due to defect in the study designs, sample sizes or insufficient irradiated dosage. [29, 41, 42]. For example in two studies by Lagan and Fernando, chronic ulcers were categorized too [43, 44].

Our study is new because of combination of three laser therapy methods including: local LLLT, intravenous laser and laser acupuncture.

For better evaluation of the relationship between the parameters, more studies with control group and more sample size are necessary.

## Conclusion

Effective cure of all diabetic ulcers in 1.5-2 months give a magnificent approach to open a new horizon in treatment of diabetic foot ulcers as already known to be refractory chronic ulcers.

This study is a case series report and lack of control group is a limitation for this research. More clinical and experimental studies may necessary to describe a distinct laser profile for treatment of diabetic foot ulcers.

Although the aim of our study was not evaluating the effect of LLLT on resistant ulcers, but it affect the surface area and grading of the ulcers. Our patients had chronic diabetic foot ulcers and had received several kind of treatment, but the exact kind of therapies was not cleared. According to the results, the grading of the ulcers for all patients after nearly 18 sessions were 0 (complete healing) to 1 (small epidermal ulcers). Patients with ulcer grade 1 were those that stopped their treatment because the ulcer was so small.

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## References

1. American Diabetes Association "Total Prevalence of Diabetes & Pre-diabetes". 2009, Retrieved on 2010-03-17.
2. International Working Group on the Diabetic Foot. Epidemiology of diabetic foot infections in a populationbased cohort. Paper presented at: International Consensus on the Diabetic Foot. 2003. Noordwijkerhout, the Netherlands.
3. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. *Diabetes Care*. 2003; 26: 1435-8.
4. Saar WE, Lee TH, Berlet GC. The economic burden of diabetic foot and ankle disorders. *Foot Ankle Int*. 2005; 26: 27-31.
5. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA*. 2005; 293(2): 217-28.
6. Ramachandran A. Specific problems of the diabetic foot in developing countries. *Diabetes Metab Res Rev*. 2004; 20 Suppl 1: S19-22.
7. The Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. *JAMA* 1996; 276: 1409-15.

8. Reiber GE, Vileikyte L, Boyko EJ. Pathways for incident lower-extremity ulcers in patients with diabetes from two settings.; *Diabetes Care* 1999; 22: 157-62.
9. Reiber GE. The epidemiology of diabetic foot problems. *Diabet Med.* 1996; 13(suppl 1): S6-S11.
10. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia.* 1993; 36: 150-4.
11. Dinh T, Veves A. Microcirculation of the diabetic foot. *Curr Pharm.* 2005; 11(18): 2301-9.
12. Pataky Z, Assal JP, Conne P, Vuagnat H, Golay A. Plantar pressure distribution in Type 2 diabetic patients without peripheral neuropathy and peripheral vascular disease. *Diabet Med.* 2005; 22: 762-7.
13. Hile C, Veves A. Diabetic neuropathy and microcirculation. *Curr Diab Rep.* 2003; 3: 446-51.
14. Eicke BM, Bauer J, Mink S, Kuhl V, Hlawatsch A, Kustner E, Victor A. Sympathetic vasomotor response of the radial artery in patients with diabetic foot syndrome. *Diabetes Care.* 2003; 26: 2616-21.
15. Frykberg RG. A summary of guidelines for managing the diabetic foot. *Adv Skin Wound Care.* 2005; 18: 209-14.
16. Passarella S, Casamassima E, Molinari S, Pastone D. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by He-Ne laser. *FEBS Lett* 1984; 175: 95-9.
17. Lubart R, Wollman Y. Effects of visible and near-infrared lasers on cell cultures. *J Photochem Photobiol B Biol* 1991; 12: 305-10.
18. Grossman N, Schneid N, Reuveni H, Halevy S, Lubart. 780 nm low power diode laser irradiation stimulates proliferation of keratinocyte cultures: involvement of reactive oxygen species. *Lasers Surg Med* 1998; 22: 212-8.
19. Yu M, Naim JO, Lauzafama RJ. The effects of photo-irradiation on the secretion of TGF and PDGF from fibroblasts in vitro. *Lasers Surg Med Suppl* 1994; 6: 8.
20. Forney R, Mauro T. Using lasers in diabetic wound healing. *Diabetes Technol Ther.* 1999; 1: 189-92.
21. Carvalho p, Mazzer N, Ries F. Analysis of influence of low-power He-Ne laser on the healing of skin wounds in diabetic and non-diabetic rats. *Acta Cirurgica Brasileira* 2006; 21(3); 177.
22. Kawalec JS, Hetherington VJ, Pfennigwerth TC. Effect of a Diode Laser on Wound Healing by Using Diabetic and Non Diabetic Mice. *The Journal of Foot and Ankle Surgery.* 2004; 43(4): 214-20.
23. Hawkins D, Abraham H. Laboratory Methods for Evaluating the Effect of Low Level Laser Therapy in Wound Healing. *African Journal of Biomedical Research.* 2005; 8: 1-14.
24. Hopkins J Ty, Mc Lodat A Todd, Seegmillert G. Jeff. Low Level laser Therapy Faciliates Superficial Wound Healing in Human: a triple-Blind, Sham-Controlled Study. *Journal of Athletic Training.* 2004; 39(3): 223-9.
25. Ihsan FR. Low-level laser therapy accelerates collateral circulation and enhances microcirculation. *Photomed Laser Surg.* 2005; 23(3): 289-94.
26. Gal D, Chokshi SK, Mosseri M, Clarke RH, Isner JM. Percutaneous delivery of low-level laser energy reverses histamine-induced spasm in atherosclerotic Yucatan microswine. *Circulation.* 1992; 85(2): 756-68.
27. Schindl A, Schindl M, Schon H, Knobler R, Havelec L, Schindl L. Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. *Diabetes Care.* 1998; 21(4):580-4.
28. Schindl A, Schindl M, Pernerstorfer-Schon H, Kerschman K, Knobler R, Schindl L. Diabetic neuropathic foot ulcer: successful treatment by low-intensity laser therapy. *Dermatology.* 1999; 198(3): 314-6.
29. Cullum N, Nelson EA, Flemming K, Sheldon T. Systematic reviews of wound care management: (5) beds; (6) compression; (7)laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess.* 2001; 5(9): 1-221.
30. Gasparian, L. Laser irradiation of blood. *Laser World Guest Editorial.* 2000; Nr 14.
31. Babushkina, GV, Kartelische AV. Kinetic of blood lipoprotein spectrum indices in patients with angina pectoralis during and after low intensity laser therapy as a paraclinical criterion for treatment efficiency. *Proceeding of SPIE.* 2001;4422: 1-5.
32. Milojevic M., Kuruc V. Low power laser biostimulation in treatment of bronchial asthma. *Med Pregl.* 2003; 56: 413-8.
33. Yuan, H.T.. Acupuncture at five Shu points for treating of 126 cases of numbness of hands and feet induced by peripheral diabetic neuropathies. *Hongguo Zhen Jiu.* 2006; 6: 225-6.
34. Kazemi-khoo N. Successful treatment of diabetic foot ulcers with low-level laser therapy. *The Foot* 2006; 16 : 184-7.
35. Kujawa J, Zavodnik L, Zavodnik I, Buko V, Lapshyna A, Bryszewska M. Effect of low-intensity

- (3.75-25 J/cm<sup>2</sup>) near-infrared (810 nm) laser radiation on red blood cell ATPase activities and membrane structure. *J Clin Laser Med Surg*. 2004; 22: 111-7.
36. Duan R, Liu TC, Li Y, Guo H, Yao LB. Signal transduction pathways involved in low intensity He-Ne laser-induced respiratory burst in bovine neutrophils: a potential mechanism of low intensity laser biostimulation. *Lasers Surg Med*. 2001; 29: 174-8.
37. Klebanov GI, Kreinina MV, Poltanov EA, Khristoforova TV, Vladimirov YA. Mechanism of therapeutic effect of low-intensity infrared laser radiation. *Bull Exp Biol Med*. 2001; 131(3): 239-41.
38. Yu W, Naim JO, Lanzafame RJ. Effects of photostimulation on wound healing in diabetic mice. *Lasers Surg Med*. 1997; 20(1): 56-63.
39. Ataie-Fashtami L, Djavid GE, Kaviani A, Larijani B, Razavi L, Salami M, Fateh M, Fatemi SM, Mortazavi SMJ. Low level laser therapy in treatment of diabetic foot ulcers: double blind controlled clinical trial. *Lasers in Medicine*. 2008; 5(3,4): 6-11.
40. Hawkins D, Houreld N, Abrahamse H. Low Level Laser Therapy (LLLT) as an Effective Therapeutic Modality for Delayed Wound Healing. *Ann. N.Y. Acad. Sci*. 2005; 1056: 486-93.
41. Flemming K, Cullum N. laser therapy for venous leg ulcers. *Coherent Database Syst Rev* 2000; (2): CD001182.
42. Flemming KA, Cullum NA, Nelson EA. A systemic Review for laser therapy for venous leg ulcers. *J Wound Care* 1999; 8(3): 111-4.
43. Lagan KM, Clements BA, McDonough S. Low intensity laser therapy (830nm) in the management of minor post surgical wounds: a controlled clinical study. *Lasers Surg Med* 2001; 28(1): 27-30.
44. Fernando S, Hill CM, Walker R. A randomized double blind comparative study of low level laser therapy following surgical extraction of lower third molar teeth. *Br J Oral Maxillofac Surg* 1993; 31(3): 170-2.