

Healing of Diabetic Ulcers Using Photobiomodulation

Nicolette N. Houreld, DTech

AT THE END OF 2013, The United Nations (UN) General Assembly 68th Session proclaimed 2015 to be the International Year of Light (IYL). Various scientific organizations, institutions, and societies are to all be brought together to raise global awareness about light (and lasers) and its uses in technology, including medicine, and everyday use. This worldwide program will highlight our dependence on light, and its importance to our lives. John Dudley, Chairman of the IYL 2015 Steering Committee stated that “An International Year of Light is a tremendous opportunity to ensure that international policymakers and stakeholders are made aware of the problem-solving potential of light technology. We now have a unique opportunity to raise global awareness of this.”¹ The IYL has given us all a unique opportunity to showcase our research and the importance and usefulness of light in medicine.

Since the development of the first laser, the use of lasers and light in medicine has made great strides; new technologies have since been developed and continue to advance. Today, photomedicine is practiced in a wide variety of fields, including but not limited to ophthalmology, dermatology, dentistry, veterinary science, somatology, regenerative medicine, physiotherapy, surgery, and oncology. One area of research that has been receiving much attention is the use of light [both lasers and light emitting diodes (LED)] in improving and speeding up wound healing. A wound is a pathological state in which tissue integrity has been lost. Wound healing is an intricate process aimed at reversing the loss of this tissue integrity, and is directed toward closure of the defect, usually by replacement with scar-forming connective tissue, and is highly coordinated and controlled at the wound site. If there is a delay or disruption to this process, delayed wound healing ensues; a complication that is frequently seen in diabetes.

As defined by the International Diabetes Federation (IDF), diabetes mellitus (DM) is a chronic disease that occurs as a result of the pancreas failing to make insulin, or when the body can no longer make use of the insulin that is produced.² DM is a threat to global development and has been declared as a global burden, with 382,000,000 cases worldwide in 2013.³ Because of the damage inflicted on the blood vessels (angiopathy) and nerves (neuropathy), diabetic patients often experience sensory loss in the lower extremities, and as a result, small sores go unnoticed and develop into non-healing chronic ulcers. The ulcer recurrence rate over 5 years is as high as 70%, and these ulcers

often require amputation.⁴ Diabetic foot ulcers are one of the most costly complications of the disease, accounting for 50% of all nontraumatic amputations.⁵ Diabetic foot ulcers require extensive long-term treatment by clinicians, and they impact heavily on the quality of life of the patient, comparable with that of a patient with breast cancer.⁶ The treatment of diabetic foot ulcers includes wound dressing, debridement, off-loading, corrective shoe wear, infection control, and surgery. New advances in the treatment of diabetic foot ulcers have been developed, such as hyperbaric oxygen therapy (HBOT), and dressings that have growth factors incorporated into them. Advances in the area of photonics and photobiomodulation have led to the use of lasers and LEDs in the treatment of diabetic ulcers.

A number of clinical studies in animal models and humans have shown the beneficial effects of photobiomodulation in speeding up the healing process in slow-to-heal diabetic foot ulcers.^{7–17} There is an increase in wound closure,^{7,13–15} collagen production,^{8,9} epithelization, and granulation tissue,¹¹ and a decrease in inflammatory cells and oxidative stress.⁹ Al-Watban⁷ conducted a large study on Sprague–Dawley rats ($n=893$) using various wavelengths at 532 (20.4 mW/cm²), 633 (15.56 mW/cm²), 810 (22.22 mW/cm²), 980 (22.22 mW/cm²), and 10,600 nm (66.37 mW/cm²), as well as LED clusters (510–872 nm, 13.6 mW/cm²). A full-thickness wound or burn was created and treated three times a week at incident doses of 5, 10, 20, and 30 J/cm². The best results were seen with the 633 nm laser, and it was recommended that a dose of 4.71 J/cm², three times per week be used for diabetic burn wounds, and a dose of 2.35 J/cm² three times per week be used for diabetic wounds for human clinical trials.

Another study showed that daily irradiation with a 660 nm (80 mW) diode laser at a dose of 1.6 J/day (3.7–5.0 J/cm²) for 7 days resulted in healing of splinted wounds in genetic diabetic mice, and that healing was mainly caused by re-epithelization and granulation tissue formation.¹¹ Another study looked at the effect of laser irradiation on oxidative stress in diabetic rats. Diabetic (streptozotocin) induced male Wistar rats ($n=42$) were wounded with a 3 mm punch biopsy and irradiated at 940 nm at a dose of 10 J/cm² (0.1 W) immediately after surgery and again on days 2, 4, and 6 post-surgery.⁹ On day 14, there was a significant decrease in inflammatory cells and increased collagen synthesis and vascularization in the irradiated group compared with the unirradiated, control group as determined by

histology. No significant differences were found in oxidant and antioxidant status between the groups.⁹

Minatel and colleagues¹⁴ showed that combined LED at 660 and 890 nm (3 J/cm², 100 mW/cm²) applied twice a week for a maximum of 90 days promoted rapid granulation of wounds and healing of ulcers in 14 diabetic patients. In a similar study, 20 diabetic patients with chronic non-healing ulcers were treated using the same device and protocol.¹⁷ Medium- and large-sized ulcers healed significantly faster with photobiomodulation than placebo-irradiated ulcers or control ulcers (cleaned and dressed only). In another study that involved 23 diabetic patients, foot ulcers were treated at 685 nm, (10 J/cm², 50 mW/cm²) six times per week, for 2 successive weeks and then every other day until the ulcers were healed.¹⁵ By the 4th week, ulcers in the treated group ($n=13$) showed a reduction in size compared with the placebo group ($n=9$). The same was seen at the 20th week; however, these results were not significant.¹⁵

A study conducted in India on 68 type 2 diabetic patients showed a reduction in ulcer size by 40.24% as compared with 11.87% in the control group.¹⁸ The effects of light on diabetic cells in culture has also been demonstrated and has shown favorable effects.^{19–27} Exposure of diabetic cells has led to increased cellular migration,^{20–23} proliferation and viability,^{20,22–25} collagen production,¹⁹ adenosine triphosphate (ATP) mitochondria concentration, and cytochrome c oxidase activity,²⁶ and a decrease in apoptosis and pro-inflammatory cytokines.^{20,27}

Advances in the area of photonics and photobiomodulation continue to revolutionize and transform our world, and, more specifically, the medical industry. The advancement of photobiomodulation is the result not of one individual's efforts, but of the work of a number of researchers and clinicians over the years. If this treatment modality is to become better recognized for the healing of diabetic ulcers, larger, well controlled clinical studies with statistically significant results are required. There is a definite need to generate new treatment modalities to improve diabetic wound healing, and photobiomodulation has an unmistakable place in this. It would be ignorant to emasculate a multidisciplinary approach, and photobiomodulation needs to be adequately and critically studied alongside existing treatments in a clinical environment for its benefits to be properly recognized.

References

1. International Year of Light 2015. Available at: <http://www.light2015.org/Home.html> (Last accessed January 23, 2015).
2. International Diabetes Federation 2014. Available at: <http://www.idf.org/about-diabetes> (Last accessed January 26, 2015).
3. International Diabetes Federation. IDF Diabetes atlas, 6th ed. 2013. Available at: www.idf.org/diabetesatlas (Last accessed November 25, 2013).
4. Dorresteijn JAN, Kriegsman DMW, Valk GD. Complex interventions for preventing diabetic foot ulceration. *Cochrane Database Syst Rev* 2010;1:CD007610.
5. Page J. Critiquing clinical research of new technologies for diabetic foot wound management. *J Foot Ankle Surg* 2002; 41:251–259.
6. Nabuurs-Franssen MH, Huijberts MS, Nieuwenhuijzen-Kruseman AC, Willems J, Schaper NC. Health-related quality of life of diabetic foot ulcer patients and their caregivers. *Diabetologia* 2005;48:1905–1910.
7. Al-Watban FAH. Laser therapy converts diabetic wound healing to normal healing. *Photomed Laser Surg* 2009;27: 127–135.
8. Aparecida Da Silva A, Leal-Junior EC, Alves AC, et al. Wound-healing effects of low-level laser therapy in diabetic rats involve the modulation of MMP-2 and MMP-9 and the reduction of collagen types I and III. *J Cosmet Laser Ther* 2013;15:210–216.
9. Firat ET, Dağ A, Günay A, et al. The effects of low-level laser therapy on palatal mucoperiosteal wound healing and oxidative stress status in experimental diabetic rats. *Photomed Laser Surg* 2013;31:315–321.
10. França CM, de Loura Santana C, Takahashi CB, et al. Effect of laser therapy on skeletal muscle repair process in diabetic rats. *Lasers Med Sci* 2013;28:1331–1338.
11. Chung TY, Peplow PV, Baxter DG. Laser photobiostimulation of wound healing: defining a dose response for splinted wounds in diabetic mice. *Lasers Surg Med* 2010;42:656–664.
12. Peplow PV, Chung TY, Baxter GD. Laser photostimulation (660 nm) of wound healing in diabetic mice is not brought about by ameliorating diabetes. *Lasers Surg Med* 2012;44: 26–29.
13. 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;198:314–316.
14. Minatel DG, Frade AC, Franca SC, Enwemeka CS. Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. *Lasers Surg Med* 2009;41:433–441.
15. Kaviani A, Djavid GE, Ataie-Fashtami L, et al. Randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. *Photomed Laser Surg* 2011;29:109–114.
16. Kılık R, Lakyová L, Sabo J, et al. Effect of equal daily doses achieved by different power densities of low-level laser therapy at 635nm on open skin wound healing in normal and diabetic rats. *BioMed Res Int* 2014;2014:269253.
17. Caetano KS, Frade MAC, Minatel DG, Santana LA, Enwemeka CS. Phototherapy improves healing of chronic venous ulcers. *Photomed Laser Surg* 2009;27:111–118.
18. Kajagar BM, Goghi AS, Pandit A, Khatri S. Efficacy of low level laser therapy on wound healing in patients with chronic diabetic foot ulcers – a randomized control trial. *Indian J Surg* 2012;74:359–363.
19. Ayuk SM, Houreld NN, Abrahamse H. Collagen production in diabetic wounded fibroblasts in response to low-intensity laser irradiation at 660 nm. *Diabetes Technol Ther* 2012;14:1110–1117.
20. Sekhejane PR, Houreld NN, Abrahamse H. Irradiation at 636 nm positively affects diabetic wounded and hypoxic cells in vitro. *Photomed Laser Surg* 2011;29:521–530.
21. Houreld N, Abrahamse H. In vitro exposure of wounded diabetic fibroblast cells to a helium-neon laser at 5 and 16 J/cm². *Photomed Laser Surg* 2007;25:78–84.
22. Zungu IL, Hawkins Evans D, Houreld N, Abrahamse H. Biological responses of injured human skin fibroblasts to assess the efficacy of in vitro models for cell stress studies. *African J Biochem Res* 2007;1:60–71.
23. Esmacelinedjad M, Bayat M, Darbandi H, Bayat M, Mosaffa N. The effects of low-level laser irradiation on cellular viability and proliferation of human skin fibroblasts cultured

- in high glucose mediums. *Lasers Med Sci* 2014;29:121–129.
24. Houreld N, Abrahamse H. Irradiation with a 632.8nm helium-neon laser with 5 J/cm² stimulates proliferation and expression of interleukin-6 in diabetic wounded fibroblast cells. *Diabetes Technol Ther* 2007;9:451–459.
25. Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC. Green light emitting diode irradiation enhances fibroblast growth impaired by high glucose level. *Photomed Laser Surg* 2005;23:167–171.
26. Houreld NN, Masha RT, Abrahamse H. Low-intensity laser irradiation at 660 nm stimulates cytochrome c oxidase in stressed fibroblast cells. *Lasers Surg Medi* 2012;44:429–434.
27. Houreld NN, Sekhejane PR, Abrahamse H. Irradiation at 830 nm stimulates nitric oxide production and inhibits proinflammatory cytokines in diabetic wounded fibroblast cells. *Lasers Surg Med* 2010;42:494–502.

Address correspondence to:
Nicolette Houreld
Laser Research Centre
Faculty of Health Sciences
University of Johannesburg
P.O. Box 17011
Doornfontein
Johannesburg, 2028
South Africa

E-mail: nhoureld@uj.ac.za