

## Laser therapy in wound healing associated with diabetes mellitus - Review\*

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**Abstract:** The article discusses the results of a literature review on the application of low intensity laser therapy on the healing of wounds associated diabetes mellitus in the last 10 years. Objective: To determine the most effective parameter in healing wounds related to diabetes mellitus, as well as the most widely used type of laser. Methodology: consisted of bibliographic searching the databases Bireme, SciELO, PubMed/Medline and Lilacs by using the keywords related to the topic. Were selected from these keywords, papers discussing the use of laser on wounds associated with diabetes, published in the period 2005-2014, in Portuguese or English. Results: After analyzing the research, 12 studies consistent with the theme were selected. Conclusion: Based on this review, the studies that showed more satisfactory results in healing diabetic wounds were those who applied energy densities in the range of 3-5 J/cm<sup>2</sup>, power densities equal to or below 0.2 W/cm<sup>2</sup> and continuous emission. The He-Ne laser with a wavelength of 632.8 nm was used more often.

**Keywords:** Diabetic foot; Foot ulcer; Laser therapy, low-level; Wound healing

### INTRODUCTION

Diabetes mellitus (DM) comprises a set of metabolic diseases resulting from changes in the secretion and/or action of insulin produced by the pancreas. Its main feature is the hyperglycemia associated with dysfunction of various systems, such as cardiovascular, renal and nervous.<sup>1</sup>

After tissue injury, scarring occurs through four phases: hemostasis, inflammation, proliferation and remodeling. These phases involve a cascade of events that will add and promote the repair of the lesion. The action of growth

factors such as VEGF (Vascular Endothelial Growth Factor), FGF (fibroblast growth factor) and TGF- $\beta$  (Transforming Growth Factor  $\beta$ ) is essential since it stimulates fibroblast proliferation and collagen, as well as the neovascularization, important for scar formation. When any of these components is changed, there is a commitment of tissue repair and the wound becomes chronic.<sup>2</sup>

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In diabetic subjects, there is an endothelial dysfunction, which alters the performance of these cells, such as the proliferation, migration and angiogenesis ability, hampering the consolidation of this process.<sup>3</sup> This dysregulation, associated with the presence of neuropathy and consequent reduction in sensitivity, predisposes the emergence of ulcers.<sup>4</sup>

The deficiency in the wound healing process is a complex problem not only for the diabetic patient and family, but also for the government, since the high-risk of the existing infection may culminate in the patient's limb and own life impairment, burdening the system with social security expenses.<sup>5-6</sup>

Due to this dysfunction, several studies have been conducted aiming to assist in wound healing of patients and to reduce morbidity and mortality caused by them. Among the reported therapeutic methods, there is the Low Level Laser Therapy (LLLT).

The low level laser therapy is considered an effective therapeutic method in wound healing when certain factors are properly observed, such as dosage, power input, time and interval between sessions.<sup>7</sup> It promotes the reduction of the inflammatory phase, favoring the angiogenesis and the production of extracellular matrix components, as well as its organization.<sup>8-9</sup>

In addition to reducing the lesion area and accelerating the healing process, laser therapy has the advantage of being easily administered. These benefits assist in promoting patient quality of life and minimizing possible complications.<sup>10-11</sup>

Research conducted *in vitro* and *in vivo*, aiming at wound healing by LLLT, have different protocols. The types of low intensity lasers often found in the literature are Helium and Neon (He-Ne), Gallium-Aluminum-Arsenide (GaAlAs) Aluminum-Gallium-Indium-Phosphorous (AlGaInP) and Gallium-Arsenide (GaAs).<sup>12</sup> Parameters such as energy density, power, wave shape and length, beam and application time show wide divergence between studies. Dosage appears as one of the most disparate, ranging from 0.04 to 30 J/cm<sup>2</sup>.<sup>12,13</sup>

The densities used can often be inappropriate for the phase in which the wound is. In wound healing in diabetes, different doses will promote the stimulation or inhibition of this process. Thus, it is important to note, among the most commonly used protocols, which ones proved to be beneficial, so the effectiveness of photostimulation is not compromised.<sup>14</sup>

The random use of these parameters for the same purpose highlights the need for standardization in laser therapy. The objective of this study, therefore, was to check the most effective parameter in the healing of wounds associated with diabetes mellitus, as well as the most commonly used type of laser.

## METHODOLOGY

We conducted a literature search in the databases Bireme, Scielo, Pubmed/ Medline and Lilacs through the combination of descriptors *laser therapy*, *low level*, *diabetic foot*, *foot ulcer* and *wound healing*. From these keywords, we selected articles addressing the use of low intensity laser in wounds associated with diabetes, published between 2005-2014, in Portuguese or English, with full text available for access. All articles that did not meet the above inclusion criteria, as well as literature reviews and studies analyzing laser therapy by light emitting diodes (LEDs), were excluded from this research.

## RESULTS

After analysis of the research, we selected 12 studies compatible with the theme, depicted in table 1.

## DISCUSSION

Among the selected studies, five presented experiments with He-Ne laser. Results obtained by the authors showed improvement in the healing process of wounds associated with DM, with increased collagen synthesis, fibroblast proliferation, angiogenesis and re-epithelialization. However, the parameters used were quite diverse, including studies using GaAlAs (4), AlGaInP (2) and GaAs (1).

Maiya *et al* (2005) used He-Ne laser at a dose of 4.8 J/cm<sup>2</sup> and a distance of 6 mm from the wound, applied for five days a week until complete healing in diabetic rats, and found an increase in the tissue repair rate.<sup>15</sup> Moreover, Carvalho *et al* (2006), using daily an approximate dose (4 J/cm<sup>2</sup>), showed that laser therapy can influence the percentage of collagen fibers, increasing their quantity both in diabetic and in control groups.<sup>16</sup>

In the study by Houreld and Abrahamse (2007), two energy densities were tested: 5 J/cm<sup>2</sup> for 37 minutes or 16 J/cm<sup>2</sup> for 2 hours.<sup>17</sup> They found that the irradiation of 5 J/cm<sup>2</sup> is capable of stimulating the expression of IL-6 (interleukin-6) and cell proliferation and migration of fibroblasts of diabetic wounds. On the other hand, diabetic wounds cells irradiated with 16 J/cm<sup>2</sup> demonstrated signs of cell damage, presenting inhibitory effect.

Maiya *et al* (2009) also compared the effect of different dosages (3-9 J/cm<sup>2</sup>) and found that healing was significantly accelerated in the groups receiving irradiation of 3-6 J/cm<sup>2</sup> per day, being even more effective in the group irradiated with 4-5 J/cm<sup>2</sup>.<sup>14</sup> Doses between 7 and 9 J/cm<sup>2</sup> showed mild deceleration of the healing process and are considered bio-inhibitory in diabetic wounds. Similarly, Hegde *et al* (2011) applied energy densities of 1-5 J/cm<sup>2</sup> and elected 3 J/cm<sup>2</sup> as the best one for wound healing.<sup>18</sup>

In contrast, Gungormus and Akyol (2009), using GaAlAs diode at a dose of 10 J/cm<sup>2</sup> with power density of

TABLE 1: Low-intensity laser use in wounds associated with diabetes mellitus (2005-2014)

Study	Author(s)/Year	Sample	Diabetic group treated	Type of laser	Power density	Energy density	Application time	Emission form	Wavelength	Beam
1	Maiya et al., 2005 <sup>15</sup>	Total sample: 48 male Wistar mice	N=24	He-Ne	_____*	4.8 J/cm <sup>2</sup>	_____*	Continuous	632.8 nm	Visible
2	Carvalho et al., 2006 <sup>16</sup>	Total sample: 48 male Wistar mice	N=12	He-Ne	0.2 W/cm <sup>2</sup>	4 J/cm <sup>2</sup>	60s	Continuous	632.8 nm	Visible
3	Hourelid, Abrahamse, 2007 <sup>17</sup>	Sample: Cell culture of human skin fibroblasts Diabetic cells	_____*	He-Ne	2.206 mW/cm <sup>2</sup>	5 J/cm <sup>2</sup> 16 J/cm <sup>2</sup>	37min 2h	Continuous	632.8 nm	Visible
4	Gungormus, Akyol, 2009 <sup>19</sup>	Total sample: 36 female Wistar mice	N=18	GaAIA	0.1W/cm <sup>2</sup>	10 J/cm <sup>2</sup>	_____*	Continuous	808nm	Invisible
5	Maiya et al., 2009 <sup>14</sup>	Total sample: 192 male Wistar mice	N=168	He-Ne	0.01 W/cm <sup>2</sup>	3-9 J/cm <sup>2</sup>	3 - 27 min	Continuous	632.8 nm	Visible
6	Carvalho et al., 2010 <sup>8</sup>	Total sample: 30 male Wistar mice	N=15	GaAIA	_____*	10 J/cm <sup>2</sup>	24 s	Continuous	660 nm	Visible
7	Noudeh et al., 2010 <sup>24</sup>	Total sample: 19 male Wistar mice	N=5	AlGaInP GaAIA	_____*	10 J/cm <sup>2</sup> 1.33 J/cm <sup>2</sup>	48 s 50 s	Continuous	670nm 810nm	Visible Invisible
8	Hegde et al., 2011 <sup>18</sup>	Total sample: 105 male Swiss mice	N=35	He-Ne	4.02 mW/cm <sup>2</sup>	1-5 J/cm <sup>2</sup>	4-21 min	Continuous	632.8 nm	Visible
9	Ayuk et al., 2012 <sup>22</sup>	Sample: Cell culture of human skin fibroblasts	_____*	_____*	10.22 mW/cm <sup>2</sup>	5 J/cm <sup>2</sup>	8 min 9 s	Continuous	660nm	Visible
10	Rocha et al., 2012 <sup>21</sup>	Total sample: 30 non-obese diabetic mice (NOD)	N=7	GaAs	15mW/cm <sup>2</sup>	3.8 J/cm <sup>2</sup>	20 s	Pulsed	780 nm	Invisible
11	Khoo et al., 2014 <sup>23</sup>	Total sample: 14. Cell culture of the skin of diabetic and non-diabetic mice	N=7	GaAIA	10 mW/cm <sup>2</sup>	1 J/cm <sup>2</sup>	1 min and 40 s	Continuous	810 nm	Invisible
12	Kilik et al., 2014 <sup>20</sup>	Total sample: 48 male mice	N=24	GaAIA	1 mW/cm <sup>2</sup> 5mW/cm <sup>2</sup> 15mW/cm <sup>2</sup>	5 J/cm <sup>2</sup>	83 min 20 s 16 min 40 s 5 min 33 s	Continuous	635 nm	Visible

0.1 W/cm<sup>2</sup>, demonstrated an increase in re-epithelialization rate in the diabetic group treated with an interval of two days between applications.<sup>19</sup> Benefits such as increased collagen and macrophages of diabetic wounds were also obtained with the same dosage in the study by Carvalho *et al* (2010),<sup>8</sup> but using AlGaInP and application of 24 s.

In order to verify the action of different power densities in the wound healing of diabetic and nondiabetic mice, Kilik *et al* (2014), after irradiation with GaAlAs and daily dose of 5 J/cm<sup>2</sup>, observed a significant neovascularization in the groups irradiated with power densities of 5 and 15 mW/cm<sup>2</sup>, as well as synthesis and organization of collagen fibers and reduced inflammatory response.<sup>20</sup>

Rocha *et al* (2012), also using a power of 15 mW/cm<sup>2</sup>, but with GaAs diode at a dose of 3.8 J/cm<sup>2</sup>, showed that low-intensity laser irradiation at an interval of 48 hours is able to downmodulate the expression of the enzyme cyclooxygenase 2, contributing to the control of the inflammatory response in skin lesions of NOD mice.<sup>21</sup>

The stimulation of the healing process has also been demonstrated in studies by Ayuk *et al* (2012) and Khoo *et al* (2014).<sup>22,23</sup> Both used low-dose (5:01 J/cm<sup>2</sup>), with approximate power densities (10.22 mW/cm<sup>2</sup> and 10 mW/cm<sup>2</sup>), but there was a wide variation in other parameters, such as application time and wavelength.

However, the study by Noudeh *et al* (2010), a combination of the AlGaInP and GaAlAs diodes, with a dose of 10 J/cm<sup>2</sup> (48 s) and 1.33 J/cm<sup>2</sup> (50 s), respectively, with an interval of three days between sessions, did not achieve significant results in the control group.<sup>24</sup>

## CONCLUSION

Based on this review, the studies that presented better results in diabetic wounds healing were those that applied energy densities in the range of 3-5 J/cm<sup>2</sup>, power densities  $\leq 0.2$  W/cm<sup>2</sup>, and continuous emission. He-Ne laser with a wavelength of 632.8 nm was the most widely used. □

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