Wound healing in diabetic: a review of photobiomodulation therapy applications

Cicatrização de feridas em diabético: uma revisão das aplicações da terapia de fotobiomodulação

Curación de heridas diabéticas: una revisión de las aplicaciones de la terapia de fotobiomodulación

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Abstract

Objective: In order to identify the available scientific production regarding photobiomodulation therapy in wound repair associated with diabetes mellitus. Methodology:

This is an integrative review seeking primary studies conducted in the databases MEDLINE, LILACS, and SCOPUS, from 2015 to 2020. Results: It was analyzed 18 articles. The year that most published articles related to the theme was 2016 and 2018 with 28 % of articles each. Regarding the place of study 72 % of them were international and 28 % national. Regarding the analysis of the evidence levels of the articles, 94 % of the articles were in level 2 of evidence. As for the samples used in the studies, 50% of the studies used *in vivo* samples, 39 % clinical samples and 11 % were *in vitro*. 83 % used laser, 11 % used LED and 6 % used two (laser and LED). At about the power density used, it ranged from 1.08 mW / cm^2 to 1920 mW/cm^2. Energy density ranged from 0.2 J/cm^2 to 6 J/cm^2. The power ranged from 5 mW to 80000 mW. Application time ranged from 12 to 1066 seconds. The most commonly used wavelength was 660 nm. Conclusion: Studies rectify the efficacy of photobiomodulation therapy alone or in combination with other treatments, humans as well as animals or in vitro, in wound repair associated with diabetes mellitus.

Keywords: Diabetes mellitus; Low-level light therapy; Lasers; Wounds and injuries; Wound healing.

Resumo

Objetivo: Identificar a produção científica disponível a respeito da terapia de fotobiomodulação na correção de feridas associadas ao diabetes mellitus. Metodologia: trata-se de uma revisão integrativa buscando estudos primários realizados nas bases de dados MEDLINE, LILACS e SCOPUS, no período de 2015 a 2020. Resultados: Foram analisados 18 artigos. O ano que mais publicou artigos relacionados ao tema foi 2016 e 2018 com 28% dos artigos cada. Quanto ao local de estudo 72% deles eram internacionais e 28% nacionais. Em relação à análise dos níveis de evidência dos artigos, 94% dos artigos estavam no nível 2 de evidência. Quanto às amostras utilizadas nos estudos, 50% dos estudos utilizaram amostras in vivo, 39% amostras clínicas e 11% foram in vitro. 83% usaram laser, 11% usaram LED e 6% usaram dois (laser e LED). Mais ou menos na densidade de potência usada, ela variou de 1,08 mW / cm2 a 1920 mW / cm2. A densidade de energia variou de 0,2 J / cm2 a 6 J / cm2. A potência variou de 5 mW a 80000 mW. O tempo de aplicação variou de 12 a 1.066 segundos. O comprimento de onda mais comumente usado foi 660 nm. Conclusão: Os estudos retificam a eficácia da terapia de fotobiomodulação isolada ou em combinação com outros tratamentos, tanto em humanos quanto em animais ou in vitro, no reparo de feridas associadas ao diabetes mellitus.

Palavras-chave: Diabetes mellitus; Terapia de luz de baixo nível; Lasers; Feridas e lesões; Cicatrização de feridas.

Resumen

Objetivo: Identificar la producción científica disponible sobre la terapia de fotobiomodulación en la corrección de heridas asociadas a la diabetes mellitus. Metodología: es una revisión integradora que busca estudios primarios realizados en las bases de datos MEDLINE, LILACS y SCOPUS, en el período de 2015 a 2020. Resultados: Se analizaron 18 artículos. El año que más artículos publicados relacionados con el tema fue 2016 y 2018 con el 28% de los artículos cada uno. En cuanto al lugar de estudio, el 72% de ellos eran internacionales y el 28% nacionales. En cuanto al análisis de los niveles de evidencia de los artículos, el 94% de los artículos se encontraban en el nivel 2 de evidencia. En cuanto a las muestras utilizadas en los estudios, el 50% de los estudios utilizaron muestras in vivo, el 39% muestras clínicas y el 11% in vitro. El 83% utilizó láser, el 11% utilizó LED y el 6% utilizó dos (láser y LED). Acerca de la densidad de potencia utilizada, osciló entre 1,08 mW / cm2 y 1920 mW / cm2. La densidad de energía osciló entre 0,2 J / cm2 y 6 J / cm2. La potencia osciló entre 5 mW y 80.000 mW. El tiempo de aplicación osciló entre 12 y 1066 segundos. La longitud de onda más utilizada fue de 660 nm. Conclusión: Los estudios rectifican la eficacia de la terapia de fotobiomodulación sola o en combinación con otros tratamientos, tanto en humanos como en animales o in vitro, en la reparación de heridas asociadas a la diabetes mellitus.

Palabras clave: *Diabetes mellitus*; Terapia de luz de bajo nivel; Láseres; Heridas y lesiones; Cicatrización de la herida.

1. Introduction

Diabetes mellitus (DM) as a growing condition worldwide, demonstrates its worrying characteristic through the ability to generate high morbidity and mortality and significantly reduce the quality of life of individual. DM is predicted to be the seventh leading cause of morbidity and mortality worldwide by 2040. Worldwide, more than 415 million people are affected by DM, with an incidence rate of 51.9% in men and 48,1% in women (Dagogo-Jack, 2016).

The increase in the number of people with DM has resulted in a rapid increase in the number of individuals with complications from this disease such as microangiopathy (nephropathy, retinopathy, and neuropathy) and macroangiopathy (ischemic heart disease, stroke, and peripheral vascular disease). These complications can result in poor wound healing and consequently chronic ulceration and limb amputation (Katsuda *et al*., 2014; Okonkwo & Dipietro, 2017)

Concerning the pathogenesis of a diabetic wound, the literature highlights a complex process, as unlike patients without the disease who have defined and ordered tissue repair phases, an inadequate function is highlighted in all patients with DM. stages of this process (Okonkwo & Dipietro, 2017; Sakata *et al*., 2014). In individuals with DM, there is endothelial dysfunction and this dysfunction alters the normal performance of cells such as migration, proliferation and angiogenesis capacity, which makes the repair process difficult (Houreld, 2014). Due to this complexity of the wound healing process in DM patients, several studies are being conducted to help repair wounds and reduce the morbidity and mortality caused by them. Among the reported therapeutic methods is photobiomodulation therapy which includes the use of laser or light-emitting diode (LED) (de Sousa & Batista, 2016).

Photobiomodulation is a method considered effective in wound repair when parameters are adequately employed such as dosage, potency, irradiation time and interval between sessions. This method promotes the modulation of the inflammatory phase, favors angiogenesis and the production of extracellular matrix components, as well as their organization (Colombo *et al*., 2013). Photobiomodulation accelerates the repair process and thus promotes the reduction of the lesion area and is easily administered. They also help to promote the patient's quality of life (Bonini-Domingos & Valente, 2012).

The LED differs from a laser by forming light, whereas while the laser provides coherent light beams, the LED uses the non-coherent light source. It is noteworthy that it is possible to influence angiogenesis with laser and LED light sources by employing low energy doses, that is, light therapy is independent of light coherence, but rather its absorption in a certain spectral band (Hosseini-Zijoud, 2016). Therefore, it is important to highlight that energy absorption is the primary mechanism that allows LED or laser light to produce biological effects on tissues, ie the mechanism of light action at the cellular level is based on photobiological reactions, these reactions. involve the absorption of a specific wavelength of light by photoreceptor molecules that are present, for example, in the mitochondrial respiratory chain (Chaves, Piancastelli, Araujo & Pinotti, 2014). Mitochondrial photobiomodulation can enhance respiratory metabolism and membrane electrophysiological properties and promote changes in cell physiology. Also, energy increases ATP synthesis within the mitochondria that impacts the speed of cellular mitosis (release of growth factors and collagen synthesis) (Karu, 2010). However, studies investigating the effects of

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ohotobiomodulation therapy on wound repair have different protocols, highlighting the variation of parameters such as energy density, power, shape and wavelength, beam and application time when using laser or LED (de Sousa & Batista, 2016; Beckmann, Meyer-Hamme & Schröder, 2014) Given the above, the study aimed to identify the available scientific literature regarding the effects of photobiomodulation therapy on wound repair associated with diabetes mellitus.

2. Methodology

This is an integrative literature review, which makes it possible to systematically gather and synthesize the evidence from multiple relevant studies, which encompass different methodological designs, on a given theme. For the operationalization of this review, the following steps were used: identification of the theme and elaboration of the research question, establishment of criteria for inclusion and exclusion of studies, definition of the information to be extracted from the selected studies, evaluation of the studies included in the integrative review, interpretation of results and synthesis of knowledge and presentation of the review (Mendes, Silveira & Galvão, 2008).

Structure the guiding question of the research and the selection of studies, the PICO strategy was adopted (Table 1). The PICO strategy stands for Population, Intervention, Comparison, and Outcome (Santos, Pimenta & Nobre, 2007).

Table 1 - PICO Strategy for the construction of the guiding question.

1. POPULATION (PATIENT/PROBLEM)	2. INTERVENTION	3. CONTROLE (COMPARISION)	4. OUTCOME
Patient diabetes mellitus with cutaneous wounds	Photobiomodulation Therapy	Not applicable	Diabetes mellitus-associated wound repair
QUESTION: What is the available scientific production regarding photobiomodulation in wound; repair associated with diabetes mellitus?			

Source: Author (2020).

In order to make the selection of studies, the time frame from 2015 to 2020 (was delimited, more updated articles on the subject and important database systems were used in the health context. Through online access, the following databases were used: US National Library of Medicine National Institutes of Health (MEDLINE / PubMed), Latin American and Caribbean Health Sciences Literature (LILACS) and Scopus.

Search of the primary studies in the MEDLINE / PubMed database, MesH descriptors were used: Diabetes mellitus AND Low-Level Light Therapy AND Wound Healing AND LED AND PBM (photobiomodulation). To search the LILACS database, the following controlled descriptors were used (Health Sciences Descriptors - DeCS): (diabetes mellitus OR diabetic foot) AND (lasers OR laser therapy OR low-intensity light therapy OR laser) AND (injuries and injuries OR healing). For the Scopus database, we used the keywords: diabetes mellitus AND low-level light therapy AND wound healing.

In order to establish the sample of the studies selected for this integrative review, the following inclusion criteria were established: scientific articles that presented research using photobiomodulation therapy in the repair of wounds associated with diabetes mellitus; scientific articles indexed in the databases: MEDLINE / PubMed, LILACS and Scopus, scientific articles published from 2015 to April 2020, in the languages: English, Portuguese and Spanish; and as exclusion criteria: informal case reports, book chapters, dissertations, theses, reports, news, editorials, non-scientific texts / scientific articles without full text availability online, duplicates and articles that did not specifically address the use of photobiomodulation in wound repair associated with diabetes mellitus. The search for scientific articles was conducted in April 2020.

From the results found after the search of the studies and rigorously obeying the inclusion and exclusion criteria presented, the title and abstract of each scientific article were exhaustively read to verify its adequacy with the guiding question of the study. Thus, in order to present relevant information about the selected scientific articles, the characteristic description of the\articles was performed in a table representing the numeric code, title, year, place of study, type of study, study design and Level of Evidence. (NE) (Table 1).

Evidence levels are classified as: level 1 - meta-analysis or systematic reviews; level 2 - Randomized Controlled Clinical Trial; level 3 - Clinical Trial without Randomization; Level 4 - Cohort and case-control studies; Level 5 - Systematic reviews of descriptive and qualitative studies; level 6 - descriptive or qualitative studies; and level 7 - expert opinion (Burns, Rohrich & Chung, 2011).

3. Results

In the MEDLINE / PubMed database, after combining the descriptors, 276 articles were identified. By selecting the articles according to the time frame, 47 articles were listed. After reading the titles and abstracts, 13 articles and 19 excluded articles were selected, of which four were review and 15 articles that did not fit the theme (related to infection, the immune system or using therapy other than photobiomodulation). in skin repair). After reading the full articles, ten articles were selected and three excluded, of which one was duplicated and two were case studies. Flowchart 1.

Using the descriptors in health sciences in LILACS, a total of 14 articles were surveyed. By selecting the articles according to the time frame, three articles were listed. After reading the titles and abstracts, the three articles were selected. After reading the full articles, two articles were selected and one per duplicate deleted. Flowchart 1

In the Scopus database, a total of 61 articles were surveyed. By selecting the articles according to the time frame, six articles were listed. After reading the titles and abstracts, five articles were selected. After reading the full articles, four articles were selected and one was excluded because it is a duplicate (Flowchart 1).

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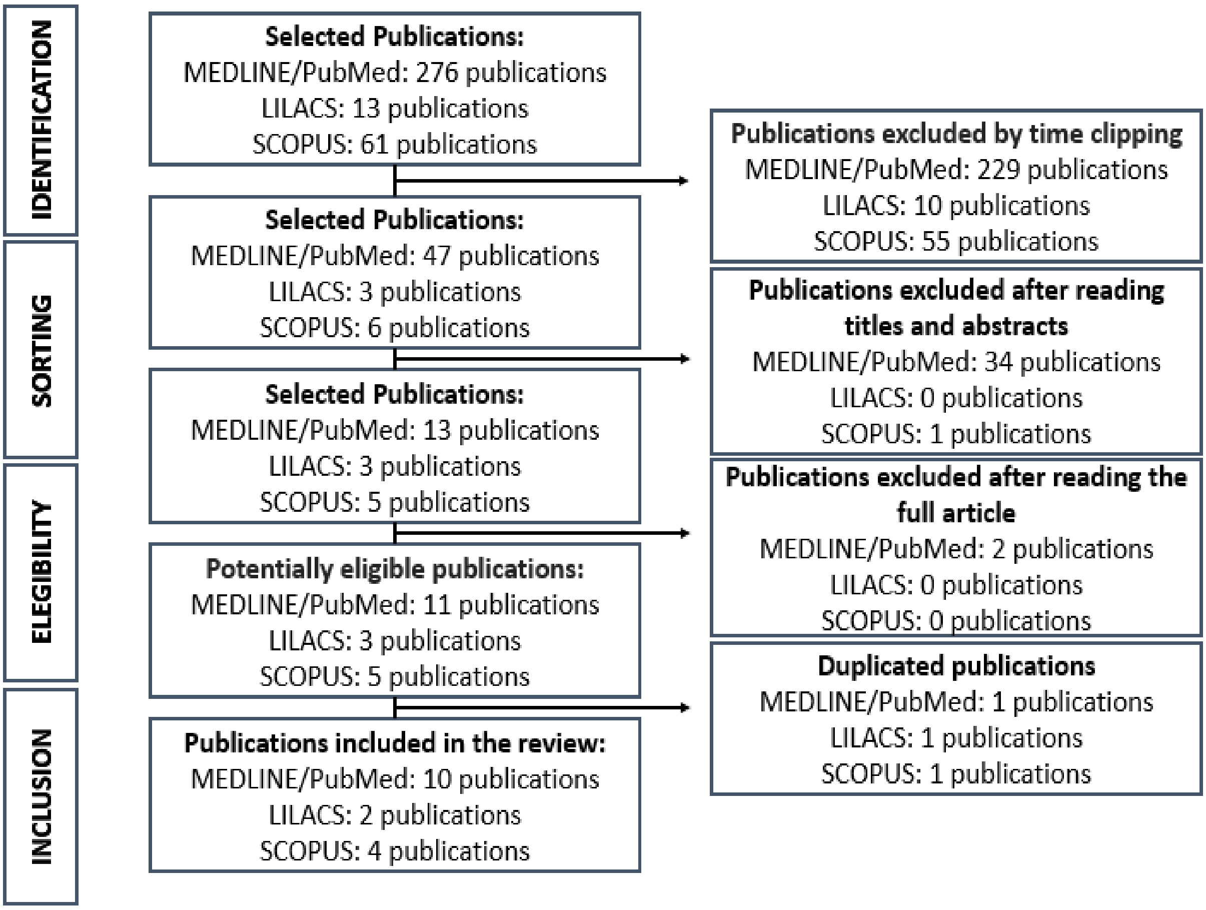
Flowchart 1 - Flowchart of identification, selection, and inclusion of integrative review studies. Teresina, PI, Brazil, 2018.



Source: Author (2020).

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Of the 18 articles analyzed, 6 % of the articles were published in 2019; 28 % 2018 and 2016; 22 % in 2017 and 17 % in 2015. Regarding the study site, 72% were international

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and 28 % national. Of the international ones, 25% were held in Iran and the others were: South Africa, India, Slovenia, Sudan, United States, Malaysia, and Poland. Among the nationals, two were held in Teresina, Brasilia, São Paulo and Paraná one each (Table 2).

Regarding the analysis of the levels of evidence of the articles. 94% of the articles were at level 2 of evidence and one at level 3, demonstrating maximum methodological rigor and a considerable level of evidence (Table 2).

Table 2 - Summary of studies compiled in the review according to numerical code, author (s), title, year, place of study, type of study, design, and level of evidence (2015-2020) (n = 18).

N°	Author (s)	Title	Year	Place of study	Study type	Study delimitation	LE*
A1	Amini *et al.*,[15]	Stereological and gene expression examinations on the combined effects of photobiomodulation and curcumin on wound healing in type one diabetic rats	2019	Tehran, Iran	*in vivo*	Randomized controlled study	2
A2	Santos *et al.*,[16]	Effects of Low-Power Light Therapy on the Tissue Repair Process of Chronic Wounds in Diabetic Feet	2018	São Paulo, Brazil	Clinical	Randomized controlled study	2
A3	Delis *et al.*,[17]	Characterization of the Cicatrization Process in Diabetic Foot Ulcers Based on the Production of Reactive Oxygen Species	2018	Brasilia, Brazil	Clinical	Randomized controlled study	2
A4	Ayuk, Houreld,	Effect of 660 nm visible red light on cell proliferation and viability in diabetic models *in vitro* under stressed conditions	2018	Johannesburg,	*in vitro*	Randomized controlled	2

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	Abrahamse[18]			South Africa		study	
A5	Ruh *et al.*,[19]	Laser photobiomodulation in pressure ulcer healing of human diabetic patients: gene expression analysis of inflammatory biochemical markers	2018	Paraná, Brazil	Clinical	Study without randomization	3
A6	Soleimani *et al.*,[20]	The effect of combined photobiomodulation and curcumin on skin wound healing in type I diabetes in rats	2018	Tehran, Iran	*in vivo*	Randomized controlled study	2
A7	Mathur *et al.*,[21]	Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers	2017	Indore, India	Clinical	Randomized controlled study	2
A8	Asghari *et al.*,[22]	The effect of combined photobiomodulation and metformin on open skin wound healing in a non-genetic model of type II diabetes	2017	Tehran, Iran	*in vivo*	Randomized controlled study	2
A9	Frangez *et al.*,[23]	The effect of LED on blood microcirculation during chronic wound healing in diabetic and non-diabetic patients—a prospective, double-blind randomized study	2017	Ljubljana, Slovenia	Clinical	Randomized controlled study	2
A10	Eissa e Salih[24]	The influence of low-intensity He-Ne laser on the wound healing in diabetic rats	2017	Khartoum, Sudan	*in vivo*	Randomized controlled study	2
A11	Mao *et al.*,[25]	Additive enhancement of wound healing in diabetic mice by low-level light and topical CoQ10	2016	Massachusetts, United	*in vivo*	Randomized controlled	2

				States		study	
A12	Góralczyk *et al.*,[26]	Low-level laser irradiation effect on endothelial cells under conditions of hyperglycemia	2016	Bydgoszcz, Polonia	*in vitro*	Randomized controlled study	2
A13	Carvalho *et al.*,[27]	Low-level laser therapy and Calendula officinalis in repairing diabetic foot ulcers	2016	Teresina, Brazil	Clinical	Randomized controlled study	2
A14	Pouriran *et al.*,[28]	The Effect of Combined Pulsed Wave Low-Level Laser Therapy and Human Bone Marrow Mesenchymal Stem Cell-Conditioned Medium on Open Skin Wound Healing in Diabetic Rats	2016	Tehran, Iran	*in vivo*	Randomized controlled study	2
A15	Fahimipour *et al.*,[29]	The effect of He–Ne and Ga–Al–As lasers on the healing of oral mucosa in diabetic mice	2016	Tehran, Iran	*in vivo*	Randomized controlled study	2
A16	Feitosa *et al.*,[30]	Effects of the Low-Level Laser Therapy (LLLT) in the process of healing diabetic foot ulcers	2015	Teresina, Brazil	Clinical	Randomized controlled study	2
A17	Wu *et al.*,[31]	Organic light-emitting diode improves diabetic cutaneous wound healing in rats	2015	Bethesda, United States	*in vivo*	Randomized controlled study	2
A18	Lau *et al.*,[32]	Photobiostimulation effect on diabetic wound at different power density of near-infrared laser	2015	Johor, Malaysi	*in vivo*	Randomized controlled	2

			a	study

Legend: *LE: level of evidence. Source: Author (2020).

Table 2 shows the study numeric codes and the synthesis of studies compiled in the sample review, laser type, power density, energy density, power, application time, wavelength, and result.

Regarding the samples used in the studies, 11 % of the studies were in vitro, 50% of the studies used in vivo samples and finally 39 % were clinical samples. Regarding the type of photobiomodulation used in the studies, the results show that 83 % used laser while only 11% used LED in the treatment of skin wounds. Still, 6 % of the studies used the association of two non-ionizing light sources (laser and LED). The power density used ranged from 1.08 mW/cm^2 to 1920 mW/cm^2. Energy density ranged from 0.2 J/cm^2 to 6 J/cm^2. The power ranged from 5 mW to 80000 mW. Application time ranged from 12 to 1066 seconds. The length in the spectral region is 52.2% in the visible region and 47.8% in infrared. The most commonly used length was 660 nm (Table 3).

Table 3 - Study numeric codes and the synthesis of studies compiled in the sample review, laser type, power density, energy density, power, application time, wavelength, and result.

Nº	Sample	Photobiomodulation	Power density	Energy Density	Power	Application Time	Wavelength	Result
A1	90 rats were randomly divided into: : (1) healthy control group (untreated), (2) control (diabetic) groups (untreated), (3) vehicle (diabetic) group that received sesame oil, (4) PBM (diabetic) group, (5) curcumin (diabetic) group, and (6) PBM + curcumin (diabetic) group. On days 4, 7, and 15	Laser	1.08 mW/cm^2	0.2 J/cm^2	75000 mW (peak) Pulse duration 180 ns	200 s	Infra-red 890 nm	Positive
A2	18 patients 30–59 years of age, chronic wounds on their foot. 2 groups of equal number (n = 9/group):	Laser	0.49	6 J/cm^2	30 mW	13 s	Visible	Positive

	Control and Laser.		mW/cm^2				660 nm	
A3	15 participants. Group 1 (GI): 5 participants attended by qualified nurses with dressings in the outpatient clinic with latex applications associated with the LED circuit. Control group (GII): 5 participants treated at home by nurses, following standard wound care recommendations (with silver alginate dressing). Group 3 (GIII): 5 participants self-treat at home with the bandage associated with the natural latex patch and the LED circuit.	LED	-	-	-	1050 s	Infra-red 890 nm	Positive
A4	*In vitro* diabetic fibroblast: normal-normal (N) and stressed normal (NW), diabetic (DW), hypoxic (HW) and diabetic hypoxic injured (DHW)	Laser	11,23 mW/cm^2	5 J/cm^2	102 mW	445 s	Visible 660 nm	Positive
A5	8 volunteers (seven male, one female) aged 30 to 70 years: one with grade III calcaneus and seven with grade III or IV sacral	Laser	-	2 J/cm^2	100 mW	12 s	Visible 660 nm	Positive
A6	30 rats (induction of type 1 diabetes mellitus tensiometric lesions). 5 groups: 1 - control; 2 - placebo (received sesame oil by gastric tube); 3 - photobiomodulation (890 nm, 80 Hz, 0.2 J / cm^2); 4 - curcumin (40 mg/kg); 5 - photobiomodulation + curcumin.	Laser	1,08 mW/cm^2	0,2 J/cm^2	75000 mW (peak) Pulse duration 180 ns	200 s	Infra-red 890 nm	Positive
A7	30 type 2 DM patients with grade I Meggitt-Wagner foot ulcers, with negative culture results. The 15 patients were divided into two groups, each with 15 patients. Patients in the study group received PBM + conventional therapy. Control group: were treated with conventional therapy alone.	Laser	~50 mW/cm^2	3 J/cm^2	-	60 s	Visible 660 nm	Positive

A8	20 rats were randomly divided into 4 groups of 5 animals per group. The G1: placebo group (control) that received vehicle control means and a laser off. G2: Received pulsed wave laser. G3: received metformin. G4: laser + metformin.	Laser	1920 mW/cm^2	0,324 J/cm^2	80000 mW (peak) e 1920 mW (mean) Pulse duration 180 ns	300s	Infra-red 890 nm	Positive
A9	40 diabetic patients (20 patients in the treated group and 20 patients in the placebo group) and 39 non-diabetic patients (19 patients in the treated group and 20 patients in the placebo group). The treated group received LED photobiomodulation three times a week for 8 weeks, and the control group received 580-900 nm broadband photobiomodulation and power density 0.72 J/cm^2.	LED	-	2,4 J/cm^2	-	300 s	Visible 625 nm 660 nm Infra-red 850 nm	Positive
A10	14 rats, 6 males and 8 females (induced diabetics) were divided into two groups: control group (N = 7) and study group (N = 7). The He-Ne laser was used to radiate the study group five times a week until the wound completely healed and the control group was maintained untreated.	Laser	4,00 mW/cm^2	-	-	240 s	Visible 632,8 nm	Positive
A11	24 rats divided into 4 groups, each with six rats. Control group: received simulated light + be oil; LLLT Group: LLLT + soybean oil; CoQ10 group: received simulated light + topical coenzyme Q10 (CoQ10); LLLT + CoQ10 group: received topical LLLT + coenzyme Q10 (CoQ10).	Laser	14 mW/cm^2	4,2 J/cm^2	-	300 s	Infra-red 830 nm	Positive
A12	Endothelial cells - HUVEC strain umbilical vein endothelial cells) - under conditions of hyperglycemia. Group 1 (control): no glucose in	Laser	1,875 mW/cm^2	2 J/cm^2	30 mW	1066 s	Visible	Positive

	culture medium, no irradiation; Group 2: glucose, without irradiation; Group 3: glucose + AlGaAlP (635 nm); Group 4: glucose + GaAlAs (830 nm).						635 nm	
			3,75 mW/cm^2	2 J/cm^2	60 mW	533 s	Infra-red 830 nm	Positive (superior)
A13	32 patients with type II diabetes randomly divided into 4 groups: 1. Control (C), 2. Low-intensity Laser Therapy (L), 3. Essential Fatty Acids (EFA), and 4. EFA-associated TLBI (LEFA).	Laser	-	2 J/cm^2	30 mW	80 s	658 nm	Positive
A14	28 adult male rats were divided into 4 groups. Group 1: control; Group 2: received mesenchymal bone marrow stem cells (HBM-MSC-CM); Group 3: received laser therapy and Group 4: HBMMSC-CM + Laser.	Laser	1,08 mW/cm^2	0,2 J/cm^2	75000 mW (peak) e 1080 mW (mean) Pulse duration 180 ns	200s	Infra-red 890 nm	Positive
A15	90 adult male rats were divided into six groups. Type 1 diabetes mellitus was induced in three groups. Of these, one group was irradiated with He-Ne laser (DH group), one with Ga-Al-As laser (DG group) and one had no LLLT (DC group). The remaining groups were non-diabetic, who were allocated to He-Ne laser therapy (NH group) or Ga-Al-As laser therapy (NG group) or without PBM (NC group).	Laser	-	2J/ cm^2	5 mW	16 s	Visible 632,8 nm	Positive (superior)
			-	2 J/cm^2	25 mW	16 s	Infra-red 830 nm	Positive

A16	16 randomly selected uncontrolled type II diabetic patients with lower limb ulcers. Two groups at random. Group 1, Control Group: 8 patients; Group 2: patients treated with PBM.	Laser	-	4 J/cm²	30 mW (pico)	80 s	Visible 632,8 nm	Positive
A17	24 male diabetic rats were used in this study. They underwent full-thickness skin wound surgery. Two wounds were made on each rat, one on the left and one on the right, using 8 mm diameter sterile biopsy punctures. The right side wounds were treated with the organic LED or laser and the left side were the untreated control wounds.	LED Laser	10 mW/cm² 10 mW/cm²	5 J/cm² 5 J/cm²	- -	260 s 260 s	Visible 623 nm 635 nm	Positive Positive
A18	A total of 120 adult male rats were used in the study. The rats were divided into four groups, one serving as a control group and the other three serving as experimental groups, each group had 30 mice. Control group: received no irradiation and their wound received only phosphate-buffered saline (PBS). G1: Laser irradiation with 5 J/cm² energy density, 100 mW output power, 0.1 W/cm² output power density and 50 s exposure time. G2: Laser irradiation with 5 J/cm² energy density, 200 mW output power, 0.2 W/cm² output power density and 25 s exposure time. G3: Laser irradiation with 5 J/cm² energy density, 300 mW output power, 0.3 W/cm² output power density and 17 s exposure time. For all laser groups, the exposure area was 1 cm².	Laser	100 mW/cm² 200 mW/cm² 100 mW/cm²	5 J/cm² 5 J/cm² 5 J/cm²	100 mW 200 mW 300 mW	50 s 25 s 17 s	Infra-red 808 nm 808 nm 808 nm	Positive (Superior) Positive Positive

Legend: mW/cm² (Miliwatts per square centimeter); J/cm² (Joule per square centimeter); s (seconds); m (minutes); nm (nanometer). A1: Amini *et al*., [15], A2: Santos *et al*., [16], A3: Delis *et al*.. [17], A4: Ayuk, Houreld, Abrahamse[18], A5: Ruh *et al*..[19], A6: Soleimani *et al*.. [20], A7: Mathur *et al*.. [21], A8: Asghari *et al*.. [22], A9: Frangez *et al*.. [23], A10: Eissa and Salih[24], A11: Mao *et al*.. [25], A12: Góralczyk *et al*.. [26], A13: Carvalho *et al*.. [27], A14: Pouriran *et al*.. [28], A15: Fahimipour *et al*.. [29], A16: Feitosa *et al*.. [30], A17: Wu *et al*.. [31], A18: Lau *et al*.. [32]. Source: Author (2020).

4. Discussion

Hyperglycemia is associated with several factors, including the formation of advanced glycation end products and reactive oxygen species. These factors can directly or indirectly impact wound repair by disrupting normal cell function, leading to impaired diabetic healing (Ayuk, Houreld & Abrahamse, 2018).

At the molecular level, failure to repair wounds can result in poor or functional inhibition of growth factors such as: Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor Beta (TGF-β) and Interleukin cytokines (IL6), Alpha Tumor Necrosis Factor (TNF-α). What happens in diabetic patients is that these growth factors are elevated, which have been associated with the development of insulin resistance and mild systemic chronic inflammation, in addition to other factors such as reduced neutrophil chemotactic and phagocytic activity (infection-prone wounds), T-cell dysfunction, decreased phagocytosis, chemotaxis and leukocyte bactericidal capacity, fibroblast, and epidermal cell dysfunction, ie in normal wound repair inflammation occurs sequentially and regulated, inflammation in diabetic wounds is prolonged leading to poor healing (Ruh *et al*., 2018).

The articles analyzed in this review converge when considering the use of laser and LED photobiomodulation in the repair of diabetic wounds. The studies present research with a high level of evidence and reliability through the use of protocols that, although different from each other, demonstrate the efficacy of this method (alone or in combination with another therapeutic method, in vitro or in vivo or clinical) wound repair.

Regarding the description of the two articles that conducted in vitro research, the most recent was the study by Ayuk, Houreld, and Abrahamse[18] who used human skin fibroblasts, and demonstrated that laser photobiomodulation alters cell behavior. stress associated with both hypoxia and high glucose. It is worth noting that to create stressed models, cells were introduced under different growth conditions. For the hypoxic cell model, cells were incubated in fetal bovine serum (FBS) deprived media in an anaerobic vial for 4 hours to deprive the cells of oxygen. For diabetic cell models, an additional 17 mm/L glucose was added to the basal medium. A diabetic hypoxic model had an anaerobic incubation and additional glucose.

The study described above used 660 nm visible red light with 5 J/cm^2, 102 mW output power and 11.23 mW/cm^2 power density and observed increased cell migration in normal wound, diabetic wound cells, hypoxic wounds, and diabetic hypoxia wounds compared to non-irradiated controls. The more stress cells are exposed, the better the photobiomodulation effect. Photobiomodulation increased cell viability and proliferation in extremely stressed models such as the diabetic hypoxic wound model with increased glucose. Thus, the study showed that photobiomodulation can be very effective in repairing diabetic wounds in patients under multiple stress conditions (Ayuk, Houreld & Abrahamse, 2018).

Another *in vitro* study was performed with human umbilical vein derived endothelial cells under hyperglycemic conditions. Group 1 (control): no glucose in culture medium, no irradiation; Group 2: glucose, without irradiation; Group 3: glucose + AlGaAlP (635 nm); Group 4: glucose + GaAlAs (830 nm). The research revealed that the level of TNF-α in the group of cells grown in medium containing high glucose concentration decreased under the influence of GaAlAs laser irradiation (Group 4) when compared to the non-irradiated group. Importantly, TNF-α is considered a proinflammatory cytokine, a powerful inducer of interleukin production, generation of reactive oxygen species and apoptosis. Diabetic patients and non-healing wounds have abnormally higher TNF-α levels. Overproduction of TNF-α is believed to affect wound healing, as this increase contributes to various pathological processes associated with persistent inflammation, tissue destruction (fibroblast apoptosis) and decreased collagen production which makes tissue repair difficult (Góralczyk *et al.*, 2016).

The study described above also revealed a significant increase in hyperglycemia-induced IL-6. In the acute inflammatory response, IL-6 has regulatory properties and limits the production of proinflammatory cytokines such as TNF-α. IL-6 may, therefore, suppress the development of diabetes. However, when produced in excess and long term, it promotes the passage of inflammation to the chronic phase and contributes to the development of many diseases. These findings indicate that the adverse effects of hyperglycemia on vascular endothelial cells can be corrected by laser photobiomodulation treatment, especially at the wavelength of 830 nm. The use of photobiomodulation caused a reduction in TNF-α concentration and increased cell proliferation (Góralczyk *et al*., 2016).

Similarly, articles that have developed *in vivo* research using mice demonstrate the positive effects of photobiomodulation. The study conducted in Khartoum, Sudan evaluated the effect of He-Ne laser (Power density 4.00 mW/cm^2, application time 240 s and wavelength: 632.8 nm) on the wound healing rate of diabetic rats. The study reveals that the group treated with laser photobiomodulation therapy promoted wound healing on average on day 21 (fully closed wounds), while the control group recovered after 40 days or even 60 days in some cases. This confirms that photobiomodulation therapy promotes the process of tissue repair of diabetic wounds and halves the healing period. It is noteworthy that the effect of He-

Ne laser irradiation on collagen production was observed from the fourth session of laser irradiation and the reduction in wound area in the laser group was 19.625 cm^2 compared to the control group (Eissa & Salih, 2017).

The study conducted in Tehran, Iran with 90 adult male rats used a different approach, evaluated the effectiveness of two different types of low-intensity laser (He-Ne and Ga-Al-As laser) in the hard palate wound healing process. in diabetic and non-diabetic mice. It is emphasized that the edges of a hard palate ulcer are dense and the healing process is long. In addition, other factors, such as decreased cell capacity, altered growth factor response, and decreased angiogenesis and blood flow, impair the wound healing process in diabetic patients (Fahimipour *et al.*, 2016).

In the inflammatory phase of healing, laser photobiomodulation therapy acted by modulating the inflammatory response and inducing an increase in collagen formation. In the proliferative phase, the number of fibroblasts and new blood vessels in the diabetic groups receiving laser photobiomodulation therapy were significantly compared to the control groups. The amount of fibroblast proliferation and neovascularization in the He-Ne groups was significantly higher compared to the groups using Ga-Al-As in diabetic and non-diabetic mice (Fahimipour *et al.*, 2016).

The Malaysian study compared the effect of diabetic wound photostimulation at different power densities (0.1 W/cm^2, 0.2 W/cm^2 and 0.3 W/cm^2), output power (100 mW, 200 mW and 300 mW) and exposure times of 50, 25 and 17 seconds, respectively, groups G1, G2 and G3. For the study 120 rats were used, distributed in four groups, groups G1, G2 and G3 that received irradiation with the same energy density of 5 J/cm^2 and different power densities, output powers and exposure time as presented above. and 1 a control group that received no irradiation, only phosphate-buffered saline. The results of the study observed that the irradiated groups showed positive results concerning the control group in the healing progress. The rate of wound contraction healing for all irradiated groups increased on the third and sixth day. The cure rate in G1 was 1.6 to two times higher compared to the control group on the third and sixth day. G3 showed progressive healing on the third day but delayed healing on the ninth day (Lau *et al.*, 2015)

In the irradiated group, epithelium proliferated near the wound surface. In the underlying layer of the dermis, there was a denser connective tissue than the control group. In addition, intense infiltration of inflammatory cells was noted. New blood vessels were formed in the laser group wound. Apparently, G1 revealed advanced performance in repairing the damaged area, and collagen fibers were observed in the dermis on the third day. On the sixth

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day, the epithelialization control group was underdeveloped and the connective tissue was still loose, G1 the epithelialization process had already occurred, G2 and G3 presented epithelial cell formation and connective tissue, differing only in the organization and density, since G2 connective tissue was more organized and dense. The authors concluded that positive stimulation effects were detected in the irradiated group throughout the experiment. Generally, the effects were dose-dependent based on power density, ie the lowest power density with power of 0.1 W/cm^2 was the one that obtained the best results compared to others (Lau *et al*., 2015).

Regarding the description of articles that underwent clinical research, all describe, in some way, the improvement in wound repair. A nonrandomized study conducted in Paraná - Brazil with eight volunteers aged 30 to 70 years (one participant with grade III calcaneal pressure injury and seven participants with grade III or IV sacral pressure lesion) used After photobiomodulation therapy through the laser around the lesion area, the laser was positioned perpendicularly and 0.5 cm from the tissue, the irradiated points were 2 cm apart and the irradiation time at each point was 12 cm. 100 mW of output power (Ruh *et al*., 2018). The size of the pressure lesion in patients with diabetes decreased after laser application, as well as increased VEGF and TGF-β levels; and the reduction of TNF-α levels, but did not alter IL6 levels, these data were obtained by biochemical analysis of ulcer edge tissue performed before and after laser photobiomodulation and subsequently submitted to gene expression assays for IL-6, TNF-α, VEGF and TGF-β by real-time quantitative polymerase chain reaction (qRT-PCR). Macroscopic results observed a 50% contraction in irradiated wound diameters after 7 days and also observed increased cell activity at the wound edge and base, faster granulation tissue formation, and accelerated wound closure in the irradiated group (Ruh *et al*., 2018).

The study conducted in Piauí - Brazil aimed to evaluate the effects of photobiomodulation therapy using laser in tissue repair in patients with diabetic wounds. Sixteen uncontrolled (decompensated) diabetic patients with lower limb wounds participated in the study and were divided into two groups: group 1 (control group) participants were instructed to use only physiological solution for daily ulcer asepsis and return after 30 days for the reevaluation process. In group 2, after cleaning the ulcer with a physiological solution, the patient was placed in a comfortable position and goggles for photobiomodulation therapy. Twelve procedures were performed, three of which were weekly, on alternate days. The laser used in this study used a wavelength of 632.8 nm, a peak power of 30 mW, an application time of 80 seconds. The application was punctual without contact (approximate distance of 1

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mm), with the pen being kept perpendicular to the wound, at equidistant points around it (Feitosa *et al*., 2015)

In both groups, the wound was measured in square centimeters (cm^2). Photographic records were made at the first consultation and the last, after 30 days of treatment. After a period of therapeutic intervention using laser photobiomodulation therapy, a reduction in wound size was noted, with a significant process of tissue repair, unlike in the control group, where a patient progressed to transfemoral amputation. Also noteworthy is the characterization of pain in patients undergoing intervention by photobiomodulation therapy, which had a significant improvement in pain after the procedures, with an average of 9 points, falling to 5 points, probably due to the analgesic effect of this therapy. In the control group, there were no changes in pain level, with presentation of pain very similar to the evaluation after 30 days of follow-up, with no significant improvement in this group. Therefore, the study noted the beneficial outcome of using photobiomodulation therapy through laser for healing as well as for pain relief (Feitosa *et al*., 2015).

The therapeutic method associated with the use of laser photobiomodulation therapy in *in vivo* studies were 3 types of drugs, curcumin, metformin and topical coenzyme Q10 and; mesenchymal stromal cells (EMF) derived from human bone marrow (Soleimani *et al*., 2018; Asghari *et al*., 2017; Pouriran *et al*., 2016)

Curcumin is one of the most prominent medicinal herbs, with many biological benefits such as antimicrobial, antioxidant and anti-inflammatory activities. Metformin is a biguanide, a first-line medication for the initial treatment of type 2 DM that works by suppressing glucose production by activating the activated protein kinase pathway. Coenzyme Q10 is commonly used to treat global mitochondrial dysfunction in diabetics and to improve glycemic control and blood pressure. It enhances mitochondrial activity, acts as a potent antioxidant and has antiulcer potential, so it can further accelerate the healing of diabetic wounds. Human bone marrow-derived mesenchymal stromal cells (CEM) have a significant effect on wound strength in diabetic rats (Soleimani *et al*., 2018; Asghari *et al*., 2017; Pouriran *et al*., 2016).

The first study was conducted with 30 rats and divided into 5 groups: G1 - control; G2 - placebo; G3 - Photobiomodulation; G4 - curcumin; G5 - Photobiomodulation + curcumin. FBM, curcumin, and the combination of both methods were found to significantly decrease bacterial colony-forming units compared with the control and placebo groups. FBM accelerated the wound healing process in the studied rats (Soleimani *et al*., 2018).

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In the second study, the authors' objective was to examine the combined influences of FBM and metformin on the microbial flora and biomechanical wound parameters in a non-genetic type II (streptozotocin-induced DM) model. Study results indicated that metformin and FBM increased the biomechanical healing properties (flexural stiffness, maximum force and high stress load) of open skin wounds in an experimental rat model with non-genetic type II DM and; whereas FBM decreased the counts of microbial flora colony-forming units of the wound bed 7 days after wound imposition compared with the placebo group (Asghari *et al*., 2017).

The third study conducted in the United States with 24 rats divided into 4 groups, G control: received simulated light + soybean oil (Placebo); PBM Group: received photobiomodulation + soybean oil; CoQ10 group: received simulated light + topical coenzyme Q10 (CoQ10); Photobiomodulation + CoQ10 group: received photobiomodulation + topical coenzyme Q10 (CoQ10). The results showed that photobiomodulation combined with CoQ10 additively accelerate wound healing in diabetic mice faster than photobiomodulation alone or using CoQ10 alone (MAO et al., 2016). In the sham-treated control group, the closed wound area was 19% on day 3, 30% on day 7, and 78% on day 13. In comparison, the associated treatment of photobiomodulation and topical CoQ10 significantly accelerated wound closure. 32% on day 3, 61% on day 7 and 97% on day 13, ie photobiomodulation + CoQ10 resulted in a 103% improvement in wound repair during the first week and more than 24% the following week. All wounds were completely closed within two weeks after the associated treatment (photobiomodulation + CoQ10). The beneficial effects on wound repair were probably attributed to increased production of Adenosine Triphosphate (ATP) by treatment with photobiomodulation and CoQ10 (Mao, Wu, Dong & Wu, 2016).

The fourth study investigated the combined effects of photobiomodulation and human bone marrow-derived mesenchymal stromal cells (EMF) on the biomechanical parameters (flexural stiffness, maximum force, and high-stress load) of wounds in an experimental model for diabetes mellitus (DM). Called EMF a small portion of mononuclear cells in the bone marrow, they are a source of cells that treat diabetes and its cardiovascular complications. EMFs are multipotent stem cells with immunomodulatory properties that can regulate various physiological responses, such as inflammation control, which is a potent therapeutic intervention for various autoimmune diseases, as well as sterile inflammatory processes such as diabetes. EMFs have been described as secretory of cardioprotective factors that may improve cardiac function. In addition, the therapeutic potential of EMF in restoring metabolic control in rats with diabetes has already been demonstrated (Volarevic, Arsenijevic, Lukic & Stojkovic, 2011; Stagg, 2007; Grishman, White & Savani, 2012; Dayan *et al.*, 2011).

The study above was conducted with 28 male rats divided into 4 groups. Group 1: control; Group 2: received human bone marrow-derived EMF (HBM-MSC-CM); Group 3: received laser therapy and Group 4: human bone marrow-derived EMF + laser photobiomodulation. The authors showed that, alone or in combination, laser photobiomodulation and marrow-derived EMF Human bone formation considerably increased the biomechanical parameters of the wounds (flexural stiffness, maximum strength, and high-stress load). However, laser photobiomodulation was statistically more effective compared to human bone marrow derived EMF (Pouriran *et al.*, 2016).

This concluded that the use of laser photobiomodulation in rats shows a significant increase in flexural stiffness compared to control wounds. Higher flexural stiffness has been demonstrated due to the following effects: increased fibrillary molecules per unit area increased fibril diameter or increased crosslinking of fibrillar molecules (Pouriran *et al.*, 2016).

Similarly, the use of laser photobiomodulation has been associated with two conventional therapies in clinical studies. The first used daily wet saline dressings or betadine dressings, antibiotic treatment, contact immobilization and splenic excision when necessary (Mathur *et al.*, 2017). The second conventional therapy used in association with the laser was the use of essential fatty acids (oil with Calendula officinalis) (de Carvalho *et al*., 2016).

The first study was conducted in Indore, India, with 30 patients with type 2 DM with Meggitt-Wagner grade I foot ulcers and negative culture results. The intervention group received laser + conventional therapy (debridement, splenic excision, and bandages with antiseptic solution) and the control group received conventional therapy only. The authors observed that subjects with wounds treated with laser photobiomodulation therapy contracted significantly more than wounds in the untreated group (37.2% for the laser group versus 15.12% for the control group). In addition to the reduction in wound area, most of the wounds in the laser group were devoid of pus and granulated. In contrast, the wound that received conventional treatment alone had more pus and less granulation (representative micrograph of the wound) and required more debridement and dressing changes. It was also observed that the participants of the group that used the laser did not feel discomfort with the procedure and were satisfied with the reduction of pain during the treatment period (Mathur *et al.*, 2017).

The second study was conducted in Piauí - Brazil, with 32 uncontrolled type II diabetic patients (decompensated). Participants were divided into group 1: control, group 2:

used laser photobiomodulation therapy, group 3: used essential fatty acids (oil with Calendula officinalis) and group 4: used laser photobiomodulation therapy associated with essential fatty acids (oil with Calendula officinalis). The authors showed that the use of laser photobiomodulation therapy alone or in combination with Calendula officinalis oil is effective in relieving pain due to its modulating action of inflammation and effective in reducing the total ulcer area by stimulating neovascularization. and acceleration of cell proliferation, thus contributing to the improvement of possible morbidity due to DM (de Carvalho *et al*., 2016).

One of the studies with light-emitting diodes, LED, was performed with 40 patients in Slovenia and evaluated the effect of LED predominantly by measuring the improvement of blood microcirculation using Doppler laser flowmetry and wound status according to score. Falanga wound bed, this score is obtained by percentage of granulation, presence or absence of fibrin and eschar. It is worth noting that sufficient blood supply to the wound area is another condition that must be fulfilled for a wound to begin to heal. Laser Doppler flowmetry provides a noninvasive method for assessing skin perfusion. Skin perfusion measurements using the laser Doppler technique depend on how light interacts with moving blood cells and tissue. Significant improvement in microcirculation was found in both the active LED-treated diabetic and non-diabetic patient groups compared to the placebo control groups after eight weeks of LED treatment. The healing process according to Falanga wound bed score was faster in diabetic and non-diabetic patients treated with active LED compared to control groups (Frangez, Cankar, Ban Frangez & Smrke, 2017).

National research aimed to examine the correlation between free radical formation and healing action of lower limb ulcers in a randomized controlled trial using a natural latex-derived patch on an LED-based circuit. The study wanted to demonstrate the advantage of using LED and latex biomembrane in ulcer repair. The healing method used in the study was based on a device called RAPHA which consists of light-emitting equipment that has a cluster of 30 high-brightness red LEDs to promote wound healing by stimulating the patient's tissues, regardless of whether the underlying cause of the ulcer. The LED photobiomodulation method associated with the latex biomaterial is noninvasive and non-destructive. Please note that the system assists the wound healing process by exposing the light generated by the LEDs to accelerate cell growth (López-Delis *et al*., 2018).

Regarding the study participants, 15 people were divided into three groups, G1 with five participants who used the RAPHA dressing by qualified nurses, G2 with five participants treated at home by nurses (silver alginate dressing) and G3 also included five participants who self-treated at home with the RAPHA dressing. To detect reactive oxygen species in the samples, the Electronic Paramagnetic Resonance was used. Samples were taken from the wound, venous blood and a collection of injured tissues taken from participants to assess the healing process (on the first day before treatment, on the second day after two weeks of treatment and at the end of treatment, approximately 30 days after initiation of treatment) (López-Delis *et al*., 2018).

The study showed that in groups G1 and G3 (patients treated with RAPHA), there was a reduction in the concentration of reactive oxygen species at the end of treatment (30th day), which corresponds to a decrease in inflammation. The decrease in inflammation is related to the roles of reactive oxygen species antioxidants in the repair of skin wounds, their possible involvement in chronic wounds and the potential value of biomarkers induced by these species in the prognosis of wound healing, ie, the results obtained. corroborate the hypothesis that reducing the amount of these molecules at the end of treatment is related to wound healing (López-Delis *et al*., 2018).

The study conducted in the United States aimed to investigate the cellular functions of organic LED and compare it with laser photobiomodulation in the repair of diabetic wounds. Importantly, organic light-emitting diodes are similar to LEDs in that they both produce non-coherent light. The advantages of organic diode include: less energy, uniform, and homogeneous illumination and lower production costs than LEDs. In addition, as they can be made on flexible substrates of highly variable shapes and sizes, organic diodes can be molded and customized to fit specific body areas and wounds of various shapes and sizes (Wu *et al.*, 2015).

Twenty-four male diabetic rats undergoing full-thickness skin wound surgery were used in the study. Two wounds were made on each rat, one on the left and one on the right, using 8 mm diameter sterile biopsy punctures. The right side wounds were treated with the organic LED or laser and the left side were the untreated control wounds. The organic LED used a power density of 10 mW/cm^2, an energy density of 5 J/cm^2, with an application time of 260s and a wavelength of 623 nm and a power density of 10 mW/cm^2. The laser was used on the same parameters as the organic diode, only the wavelength of 635 nm. The MTS assay [3-(4,5-dimethylthiazol-2-yl) -5- (3-carboxymethoxyphenyl) -2- (4-sulfophenyl) -2H-tetrazolium] was used to measure mitochondrial metabolism and a CyQuant based assay in DNA was used to measure cell proliferation (Wu *et al*., 2015).

The authors found that organic LED treatment increased ATP (Adenosine triphosphate) production, mitochondrial metabolism, and cell proliferation compared to untreated wounds. The percentage of wound closure was statistically higher in wounds treated with the organic diode (40.94 ± 3.49%) compared to control wounds (25.03 ± 5.29% on day 5 after injury. day after injury, both organic diode (45.91 ± 4.61%) and laser (50.50 ± 4.90%) treated wounds had significantly higher wound closure percentages than control wounds (29, 88 ± 5.08%) It is noteworthy that there was no significant difference between the laser and organic diode groups in the effectiveness of these devices in wound closure. Fibroblast factor-2) at 36 hours post-injury and increased macrophage activation during the early stages of wound healing (Wu *et al*., 2015).

5. Conclusion

The available scientific literature on photobiomodulation in wound repair associated with diabetes mellitus highlights the use of laser and LED. It was evidenced that the laser is more used in the wound repair, but is increasing the interest in using the led in the treatment of wounds. Still, the studies analyzed in this review present research with a high level of evidence and reliability using protocols that, although different from each other, show the efficacy of photobiomodulation in wound repair associated with diabetes mellitus.

The results obtained through the study will be used in the development of an experimental research, in which treatment combined with photobiomodulation therapy, will be used to treat wounds in diabetics.

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