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ORIGINAL ARTICLE

Effects of diode low-level laser therapy on healing of tooth extraction sockets: a histopathological study in diabetic rats

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Abstract

Diabetes mellitus is mostly interrelated to deficiency in wound healing. Low-level laser therapy has been shown to exert reliable effects on the acceleration of wound healing process. This study aimed to determine the potential influence of low-level laser therapy (LLLT) on the healing of extraction sockets in diabetic rats. A total of 24 healthy male Wistar rats were selected for this study. After diabetes induction, the maxillary first molars of all rats were extracted bilaterally. Then, the animals were subjected either to Ga-Al-As laser at 808 nm or to Al-Ga-In-P laser at 660 nm at the right extracted socket every day for the next 14 days. The left sockets served as controls. Rats were sacrificed on the 3rd, 5th, 7th, and 14th days after tooth extraction. The samples were examined by a pathologist. LLLT at 808 nm was able to significantly repress inflammation, improve osteoid formation, and promote vascularization in comparison to the non-treated sockets. LLLT at 660 nm significantly suppressed inflammation and developed vascularization in comparison to the non-treated sockets, but failed to improve osteoid formation in the treated sockets. This study suggests that LLLT could be considered as a reliable treatment for wound healing in diabetic experimental rats.

Keywords Low-level laser therapy · Diabetes mellitus · Tooth socket

Introduction

Diabetes mellitus (DM) is the most common metabolic disease of the adult population worldwide. As a significant global public health problem, this disease is known as a major source of morbidity and mortality in the world today. The World Health Organization (WHO) has predicted that the number of adults suffering from diabetes is going to increase to more than 300 million by 2025 [1]. DM is caused due to changes in the secretion and/or action of insulin, resulting in a hyperglycemic condition which may contribute greatly to endothelial dysfunction, impaired angiogenesis, failure in fibroblast immigration, and deficiency of wound healing [2].

DM complications in the oral area cause numerous issues including periodontal disease, dysfunction of oral mucosa, neurosensory disarrangement, and delayed healing of sockets following tooth extraction [3]. Due to this severe impairment, several studies have been conducted in an effort to tackle this issue. Some of the suggested treatments include electromagnetic field stimulation [4], low-intensity pulsed ultrasound [5], application of biological growth factors [6], and low-level laser therapy (LLLT) [7].

Low-level lasers, firstly discovered in 1967 by Endre Mester, are defined as non-invasive lasers in the range of red and near-infrared light [8]. LLLT, also known as photobiomodulation (PBM), exerts its effects through affecting various biological processes at the cellular level which stimulate and accelerate wound healing and tissue repair [9].

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Various reports suggest that LLLT acts by stimulation of immigration and proliferation of fibroblasts, keratinocytes, and endothelial cells alongside with collagen deposition and epithelialization. It has also been proposed that LLLT has an anti-inflammatory and angiogenic effect [10]. Clinical efficacy of LLLT on tissue healing has also been reported [11, 12]. These factors could potentially make LLLT a safe, reliable, and cost-effective therapeutic tool in assisting wound healing in DM and other chronic diseases [2]. However, several studies have reported no beneficial effect of LLLT on tissue healing [13]. These conflicting results are probably due to variations in parameters like power density, energy density, wavelength, number and frequency of treatment, duration of treatment, and other factors of experimental design. Indeed, there is a great controversy in the literature concerning the efficient parameters of LLLT in the acceleration of the healing process of extracted sockets. On the other hand, few studies have described the beneficial effect of LLLT on the healing process of alveolar bone after tooth extraction in diabetic status [14]. It is clear that there is so much need for further studies concerning the effective doses of LLLT in this field.

Thus, the primary aim of the present study was to investigate the potential effect of LLLT with different parameters on the healing process of extracted sockets in diabetic rats.

Methods and Materials

Animal experimental model and DM induction

All procedures and experimental protocols were in line with the Guide for the Care and Use of Laboratory Animals as published by the National Institutes of Health (NIH) and approved by the Animal Care and Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. A total of 24 male adult Wistar rats were selected based on the presence of healthy periodontium and teeth, and weighed prior to any intervention (230–320 g). They were housed at the animal research center of School of Dentistry, under standard conditions (26±2 °C, 60% humidity, 12-h light and 12-h dark photoperiod), and fed with pellet diet and tap water add libitum. Diabetes was induced with intraperitoneal injection of streptozotocin (STZ, 60 mg/kg in 0.5 mL of citrate buffer, Sigma, USA). Tail-blood glucose over 250 mg/dL, measured 48h after injection by a glucometer (Glucocard 01 mini, Japan), was considered a confirmation for successful diabetes induction. After confirmation of diabetes induction, the upper first molar of all animals was extracted under general anesthesia and induced by an intramuscular injection of ketamine HCL 10% (50mg/kg, Alfasan) combined with xylazine 2% (5mg/kg, Alfasan), followed by inhalation of isoflurane 5%. Right and left maxillary first molars in all animals were extracted on the same day.

Laser therapy

LLLT in this study was applied with low-level diode laser (Klas-DX, Konftel, Taiwan) to the alveolar sockets on the right side during the next 14 days)from the day of extraction(. Diabetic animals (DM; n = 24) were randomly divided into two groups (n = 12) based on the laser parameters irradiated to the alveolar sockets, as shown in Table 1. Thus, animals in group 1 (DM660) received LLLT with an In-Ga-Al-P laser at the wavelength of 660 nm (7.2 J/cm^2), while those in group 2 (DM808) received LLLT with a Ga-Al-As laser at the wavelength of 808 nm (7 J/cm^2).

Tissue harvesting

Rats in each subgroup were sacrificed on the 3rd, 5th, 7th, and 14th days (n = 3) after tooth extraction by injection of an overdose of ketamine–xylazine. Upper jaws of sacrificed animals were removed for clinical and histopathological analysis. Clinical evaluation was accomplished by measurement of wounds using a caliper. Afterwards, specimens were fixed in 10% buffered formalin for 5 days and decalcified using 10% ethylenediamine tetra acetic acid (EDTA, pH 7.2) for the next 4 weeks. Then, routine histopathological processing was carried out for all the decalcified samples. Tissues were cut serially into 4μ sections and stained with hematoxylin and eosin (H&E) for histopathological evaluation by a pathologist blinded to the groups [15].

Histopathological evaluation

Histopathological evaluation was carried out in H&E-stained sections of each group. To accomplish this, stained samples were photographed using an optical microscope (Olympus BX51, Japan) (×40 objective lens) and high-resolution camera. Then, the images were transferred to a computer [16]. Histopathological findings, including inflammation, fibrosis, and osteoid formation, as well as angiogenesis were evaluated and scored as described elsewhere [17]. Inflammation, fibrosis, and osteoid formation have been given a score of 0 (0%), 1 (%1–30), 2 (%30–60), or 3 (> %60) based on the related surface covering. Angiogenesis was evaluated based on the number of detectable vessels as follows: score 0 (0), 1 (1–10), 2 (11–29), and 3 (≥ 30 detectable vessels) [18]. Additionally, presence of RBCs and foreign body reaction were investigated and reported.

Statistical analysis

Statistical analysis was performed using SPSS 14. The data were described using descriptive statistics, and quantitative variables were compared across the groups using Mann-Whitney and Wilcoxon tests. Chi-square and McNemar tests were utilized for qualitative variables. The significant level was set to 0.05 for all tests.

Table 1 Properties of laser irradiation

Wavelength (nm)	808 nm	660 nm
Active medium	Ga-Al-As	In-Ga-Al-P
	"Gallium-Aluminum-Arsenide"	"Indium-Gallium-Aluminum-Phosphorus"
Energy density (j/cm^2)	7	7.2
Power (mW)	250	150
Power density (mW/cm^2)	127.32	76.40
Emission mode (continuous/pulse)	Continuous	Continuous
Time (s)	14	24
Beam spot size (cm^2)	0.5	0.5
Distance from the tissue (mm)	0	0

Results

Histopathological analysis

After 3 days, the non-lasered side showed heavy infiltration of inflammatory cells with hemorrhagic areas, slight cellular granulation tissue, and no evident sign of primary bone formation. The 808 nm– or 660 nm–lased sockets showed noticeably less infiltration of inflammatory cells with no substantial difference in the amount of granulation tissue or woven bone formation.

At 5 days, persistent inflammation and presence of granulation tissue were observed in the non-lasered sockets. However, no evidence of osteoid formation was noticeable in the non-lased or 660 nm–lased sockets. Only treatment with LLLT at 808 nm led to visible scanty new irregular bone trabeculae in the extraction sockets.

At 7 days, continuing inflammation with more amount of granulation tissue and scarce signs of osteoid formation was evident in the non-lased sockets. Lasered sockets with 660 or 808 nm showed more amount of fibrosis and new bone formation. In addition, lased sockets with 808 nm revealed decreased infiltration of inflammatory cells.

After 14 days, osteoid-like matrix lined with active osteoblasts was more observed on both lased and non-lased sockets; however, the lasered sockets demonstrated more amount of bone trabeculae that remain immature and irregular. Likewise, inflammation was lessened on both lased and non-lased sockets, with exhibiting more reduction on lased sockets (Fig. 1).

Impact of LLLT at 808 nm on the clinical size of wound as well as inflammation, fibrosis, osteoid formation, and vascularization of extraction sockets in diabetic rats

A-1) Clinical size of wound The mean clinical size of wounds (mm) of extraction sockets in diabetic rats treated with laser at 808 nm (group DM808) was 5, 5, 4.2, and 2.7 mm on days 3, 5, 7, and 14, respectively, while this parameter in the non-irradiated side was 5.4, 6, 5.2, and 3, in turn. The mean clinical size of wounds showed a significant decrease on day 14 in comparison to days 3, 5, and 7 in both the laser-treated and non-treated side ($p<0.05$). However, no significant difference in the mean clinical size of wounds was observed in the laser-treated side in comparison to the non-treated side on days 3, 5, 7, and 14 (Fig. 2a).

A-2) Inflammation The mean score of inflammation of extraction sockets in diabetic rats treated with laser at 808 nm (group DM808) was 1.7, 2.4, 1.5, and 1.6 on days 3, 5, 7, and 14, respectively, while this parameter in the non-irradiated side was 2.6, 3, 2.5, and 2.4, in turn. Although the trending score showed no significant difference in each individual side, there was a significant decrease in the mean score of inflammation of extraction sockets in the laser-treated side in comparison to the non-treated side on days 3, 5, 7, and 14 ($p<0.05$) (Fig. 2b).

A-3) Fibrosis The mean score of fibrosis of extraction sockets in diabetic rats treated with laser at 808 nm (group DM808) was 0.3, 0.7, 1, and 1 on days 3, 5, 7, and 14, respectively, whereas this parameter in the non-irradiated side was 0.3, 0.5, 0.7, and 1, in turn. The mean score of fibrosis showed a significant increase on days 7 and 14 in comparison to day 3 in the laser-treated side ($p<0.05$); likewise, it revealed a significant rise on day 14 in comparison to days 3 and 5 in the non-treated side ($p<0.05$). However, no significant difference in the mean score of fibrosis was observed in the laser-treated side in comparison to the non-treated side on days 3, 5, 7, and 14 (Fig. 2c).

A-4) Osteoid formation The mean score of osteoid formation of extraction sockets in diabetic rats treated with laser at 808 nm (group DM808) was 0, 0.3, 0.5, and 1.7 on days 3, 5, 7, and 14, respectively, while this parameter in the non-irradiated side was 0, 0, 0.5, and 0.4, in turn. The mean score of osteoid formation showed a significant rise on day 14 in comparison to days 3, 5, and 7 in the laser-treated side ($p<0.01$); while, it revealed a significant increase on days 7 and 14 in comparison to days 3 and 5 in the non-treated side

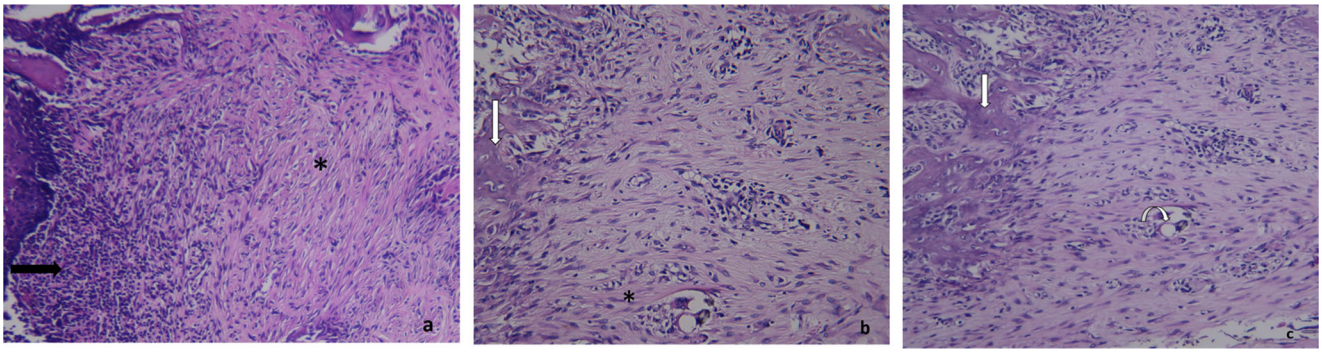

Fig. 1 Photomicrograph of tooth sockets after 14 days of extraction showing fibrous tissue (asterisk), infiltration of inflammatory cells (black arrow), newly formed bone (white arrow), and without laser treatment and blood vessel (curved white arrow) in non-lased (**a**) and 660 nm– (**b**) and 808 nm (**c**)–lased sockets; H&E ×100

(p<0.05). Significant difference in the mean score of osteoid formation was observed in the laser-treated side in comparison to the non-treated side on day 14 (p<0.01) (Fig. 2d).

A-5) Vascularization The mean score of vascularization of extraction sockets in diabetic rats treated with laser at 808 nm (group DM808) was 1.4, 1.7, 1, and 2.7 on days 3, 5, 7, and 14, respectively, whereas this parameter in the non-irradiated side was 0.4, 1, 0.5, and 1.6, in turn. The mean score of vascularization showed a significant rise on day 14 in comparison to days 3, 5, and 7 in both the laser-treated and non-treated side (p<0.05). Besides, the mean score of

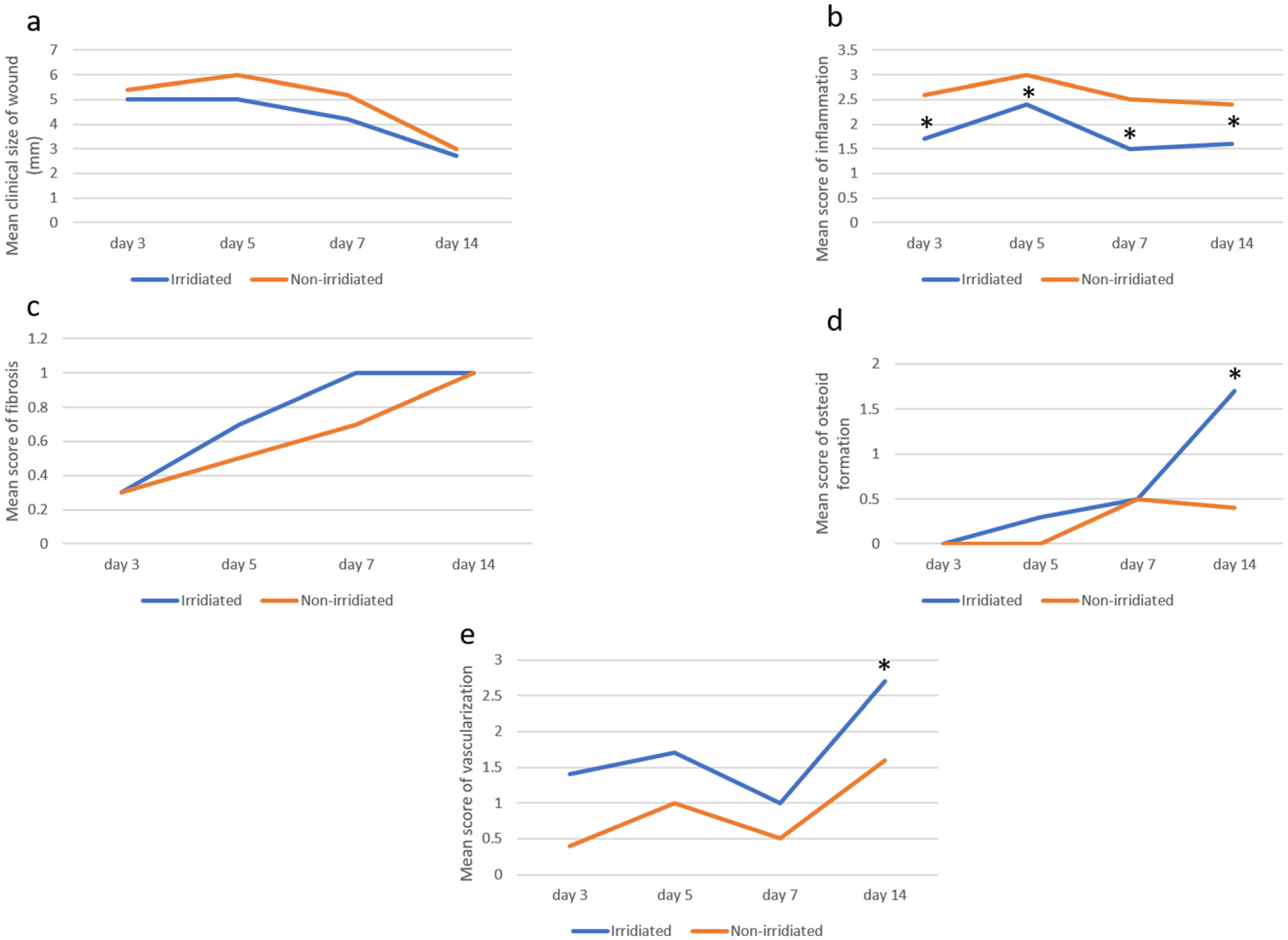

Fig. 2 Comparison of the mean clinical size of wounds (**a**), mean score of inflammation (**b**), mean score of fibrosis (**c**), mean score of osteoid formation (**d**), and mean score of vascularization (**e**) between the 808 nm laser-treated and non-treated extraction sockets of diabetic rats. *p<0.05 (significant difference of the laser-irradiated side as compared to the non-irradiated side)

vascularization showed a significant increase in the laser-treated side in comparison to the non-treated side on day 14 ($p<0.05$) (Fig. 2e).

Impact of LLLT at 660 nm on the clinical size of wound as well as inflammation, fibrosis, osteoid formation, and vascularization of extraction sockets in diabetic rats

B-1) Clinical size of wound The mean clinical size of wounds (mm) of extraction sockets in diabetic rats treated with laser at 660 nm (group DM660) was 5.5, 5.5, 5, and 4.2 mm on days 3, 5, 7, and 14, respectively, while this parameter in the non-irradiated side was 5.4, 5, 5, and 4.2, in turn. The mean clinical size of wounds showed a significant decrease on day 14 in comparison to day 3 in both the laser-treated and non-treated side ($p<0.05$). However, no significant difference in the mean clinical size of wounds was observed in the laser-treated side in comparison to the non-treated side on days 3, 5, 7, and 14 (Fig. 3a).

B-2) Inflammation The mean score of inflammation of extraction sockets in diabetic rats treated with laser at 660 nm (group DM660) was 1.3, 2, 2.5, and 1 on days 3, 5, 7, and 14, respectively, while this parameter in the non-irradiated side was 2.4, 2.6, 3, and 2, in turn. The mean score of inflammation showed a significant increase on day 7 in comparison to days 3 and 14 in both the laser-treated and non-treated side ($p<0.05$). There was a significant decrease in the mean score of inflammation of extraction sockets in the laser-treated side in comparison to the non-treated side on days 3 and 14 ($p<0.05$) (Fig. 3b).

B-3) Fibrosis The mean score of fibrosis of extraction sockets in diabetic rats treated with laser at 660 nm (group DM660) was 0.5, 0.1, 0.5, and 0.7 on days 3, 5, 7, and 14, respectively, whereas this parameter in the non-irradiated side was 0.1, 0.71, 0.5, and 0.5, in turn. The mean score of fibrosis showed a significant increase on days 7 and 14 in comparison to day 5 in the laser-treated side ($p<0.05$); likewise, it revealed a significant rise on days 7 and 14 in comparison to days 3 and 5 in the non-treated side ($p<0.05$). However, no significant

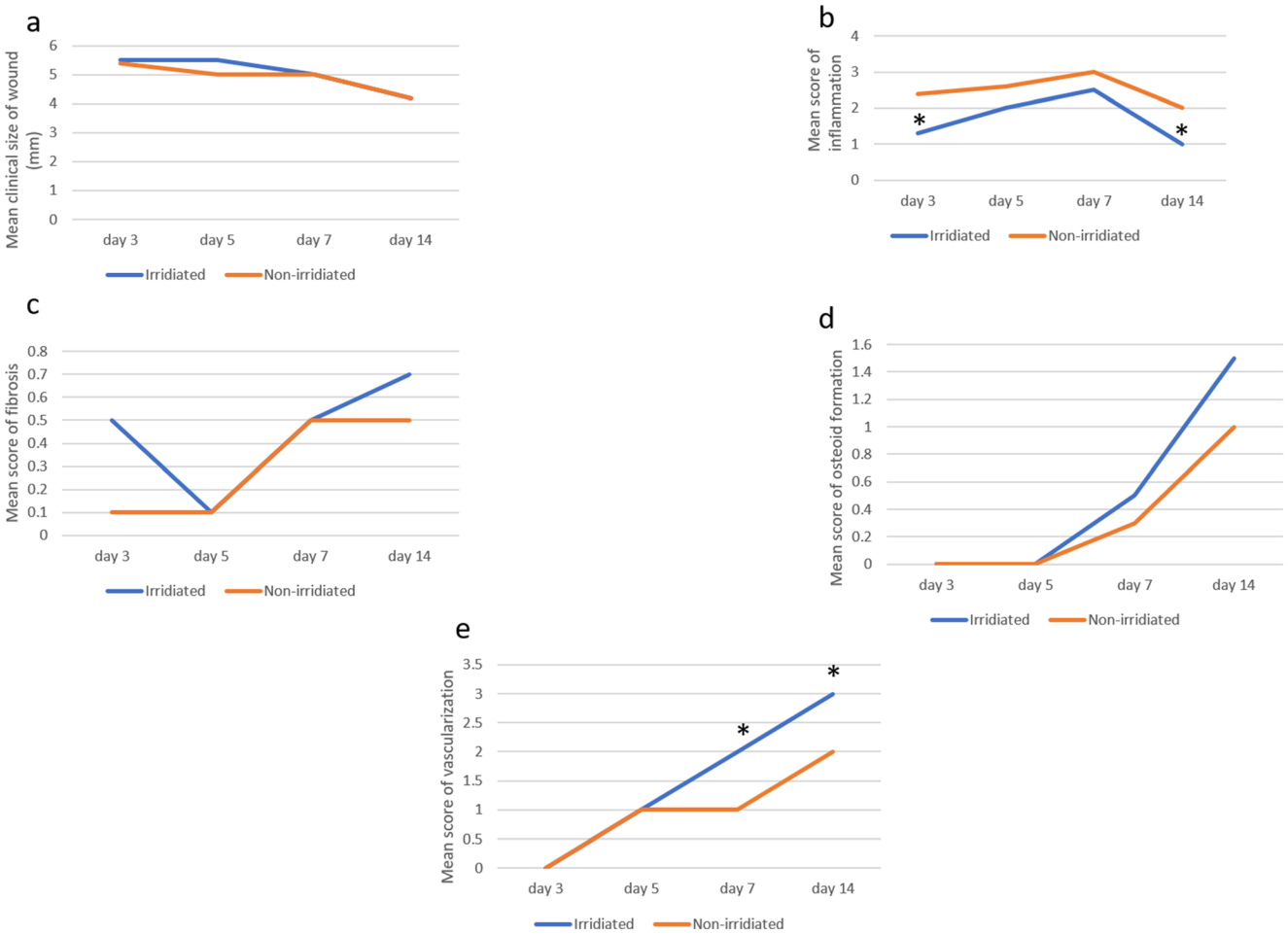

Fig. 3 Comparison of the mean clinical size of wounds (**a**), mean score of inflammation (**b**), mean score of fibrosis (**c**), mean score of osteoid formation (**d**), and mean score of vascularization (**e**) between the 660 nm laser-treated and non-treated extraction sockets of diabetic rats. *$p<0.05$ (significant difference of the laser-irradiated side as compared to the non-irradiated side)

difference in the mean score of fibrosis was observed in the laser-treated side in comparison to the non-treated side on days 3, 5, 7, and 14 (Fig. 3c).

B-4) Osteoid formation The mean score of osteoid formation of extraction sockets in diabetic rats treated with laser at 660 nm (group DM660) was 0, 0, 0.5, and 1.5 on days 3, 5, 7, and 14, respectively, while this parameter in the non-irradiated side was 0, 0, 0.3, and 1, in turn. The mean score of osteoid formation showed a significant rise on day 14 in comparison to days 3, 5, and 7 in both the laser-treated and non-treated side ($p<0.05$). However, no significant difference in the mean score of osteoid formation was observed in the laser-treated side in comparison to the non-treated side on days 3, 5, 7, and 14 (Fig. 3d).

B-5) Vascularization The mean score of vascularization of extraction sockets in diabetic rats treated with laser at 660 nm (group DM660) was 1, 1, 2, and 3 on days 3, 5, 7, and 14, respectively, whereas this parameter in the non-irradiated side was 0, 1, 1, and 2, in turn. The mean score of vascularization showed a significant rise on days 7 and 14 in comparison to days 3 and 5 in the laser-treated side ($p<0.05$), while it revealed a significant increase on day 14 in comparison to days 3, 5, and 7 ($p<0.05$). Besides, the mean score of vascularization showed a significant increase in the laser-treated side in comparison to the non-treated side on days 7 and 14 ($p<0.05$) (Fig. 3e).

Discussion

Wound healing, as a complex biological process, involves overlapping procedures categorized as inflammation, granulation tissue formation, angiogenesis, and tissue remodeling and regeneration. Thus, it was aimed in the present study to evaluate the impact of LLLT at 660 and 808 nm on inflammation, fibrosis, angiogenesis, and osteoid formation in the extracted sockets of experimental diabetic rats.

According to the findings of this study, a 14-day period of LLLT at 808 nm of extraction sockets in diabetic rats significantly improved osteoid formation and vascularization on day 14 in comparison to the non-treated sockets. Besides, LLLT at 808 nm significantly repressed inflammation on days 3, 5, 7, and 14 when compared to the non-treated sockets. However, LLLT at 808 nm made no significant difference in the mean clinical size or fibrosis of wounds.

In addition, a 14-day period of LLLT at 660 nm of extraction sockets in diabetic rats significantly developed vascularization on days 7 and 14 in comparison to the non-treated sockets. Furthermore, LLLT at 660 nm significantly suppressed inflammation on days 3 and 14 as compared to the non-treated sockets. However, LLLT at 660 nm failed to improve osteoid formation in the treated sockets. Also, LLLT at 660 nm made no significant difference in the mean clinical size or fibrosis of wounds.

In recent years, low-level lasers have widely been evaluated considering their efficacy in wound healing process in both medical and dental fields. Several studies have reported the beneficial effects of LLLT on new bone formation after radiation-related injury [19], osteoporosis resulted from ovariectomy [20], bone fractures [21], healing of tooth extraction sockets [22], implant osteointegration [23], and orthodontic movement [24]. Similarly, our results confirmed the positive bio-stimulatory effects of LLLT at 808 nm on new bone formation.

However, no therapeutic effect of LLLT at 660 nm on bone repair of extracted sockets was found in this study. Other studies reported beneficial influence of GaAlAs laser of 660 nm on the activity of bone cells in injured femurs [25]. Discrepancies might be due to different irradiation protocols or the experimental model of injury explored in this study.

In the present study, positive impact of LLLT at both 660 and 808 nm was observed on the angiogenesis of extracted sockets. Angiogenesis is a crucial process in tissue regeneration which involves vessel sprouting, endothelial cell proliferation, and tube formation. This step provides both oxygen and nutrients for the newly forming tissue which principally favors cell proliferation and migration as well as protein synthesis [26]. Previous studies have also confirmed assured power of LLLT on new vessel formation [27]. It has been well discussed that angiogenesis, essential for wound healing, gets severely impaired in diabetic status, which is largely responsible for compromised wound healing as a major diabetic complication [28]. Thus, the prompting influence of LLLT on new vessel formation, as indicated in this study, could be a novel adjunctive therapeutic approach in the process of wound healing in diabetic status.

Tooth extraction is one of the most common surgical procedures in the field of dentistry. Although healing of the remaining wound is usually followed in a standard manner, it could face major challenges in diabetic conditions [3]. Indeed, the subsequent deficiency in the wound healing process of extracted sockets could impose a burden for the diabetic patient and family as well as the dentist. LLLT has been proposed as a novel adjunctive therapeutic approach in various procedures of dentistry, such as the acceleration of wound healing, enhanced regeneration of bone, and modulation of inflammation [29]. Tissue healing via application of LLLT may be achieved through several mechanisms, mainly an increase in cellular metabolism; consequently, laser therapy has been observed to accelerate wound healing [30]. However, it should be noticed that the outcome of LLLT treatment varies with the treatment parameters including power, power density, wavelength, beam profile, energy density, frequency of treatment, and its duration. As indicated by histological results

of this study, both laser parameters were able to suppress inflammation and improve vascularization of extraction sockets; though, only LLLT at 808 nm succeeded to enhance osteoid formation. Indeed, sockets treated with diode laser at 808 nm showed heavy existence of osteoblasts at day 14 post-treatment, while this finding was not observed in 660 nm–treated sockets.

Wound healing, regardless of the type and cause of the injury, is known as a complicated biological process and composed of interrelating proceedings categorized as inflammation, granulation tissue formation, angiogenesis, and tissue remodeling and regeneration. These phases comprise a cascade of biological events that collectively lead to tissue healing and repair [31]. However, diabetic circumstances have been shown to alter the micro-environment, resulting in a noticeable impairment in the healing process of various injured tissues [28]. LLLT is considered an effective therapeutic method in the acceleration of wound healing as it favors the reduction of inflammatory phase as well as the lesion area, promotes angiogenesis, and helps in tissue regeneration. However, particular parameters should properly be respected including wavelength, power input, application time, and the interval between sessions [2]. In addition, LLLT is easily applicable and believed to be user-friendly with minimum possible complications for the patient [29]. The employment of LLLT as an adjunctive therapeutic tool in the process of wound healing was firstly studied by Mester et al. [32]. Low-level lasers work in the power range of 1–500 mW with the wavelength of red or near-infrared to visible light spectrum (400–980 nm) [8]. The basic mechanism of tissue repair is suggested on the principle of "photobiomodulation," which mainly entails its impact on altering the cellular behavior via absorbing the light photons by the photoreceptors inside the cell [33]. However, in spite of considerable research conducted in vitro and in vivo aiming at wound healing by LLLT, the use of LLLT has still not been widely accepted by the medical and dental communities. One of the main reasons is that different protocols are employed by researchers; so, a wide divergence between the used parameters is witnessed [34].

While numerous studies have been performed on the influence of LLLT on wound healing of extracted sockets in healthy experimental animal [35–38], few have set out to explore the outcome of LLLT in socket preservation in diabetic experimental animals. Park and Kang [14] proposed the beneficial effect of GaAlAs laser at 980 nm for the initial stages of alveolar bone healing of tooth extraction sockets in both diabetic and normal rats when applied every day at a dose of 13.95 J/cm^2 for 60 s.

Yet, it should strongly be noticed that making a direct comparison between similar studies could be complicated by some factors including the different experimental designs, laser parameters, and experimental animal models. With respect to previous researches, it appears reasonable to conclude that more animal as well as clinical studies are needed to confirm the worth of LLLT in the acceleration of wound healing in extracted sockets of diabetics, as well as to determine the optimal laser type and associated parameters.

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Declarations

Conflict of interest The authors declare no competing interests.

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