

# Evaluating the Effect of the Different Diabetic Control's Methods Including Tight Control on the Healing Response of Diabetic Foot Ulcer Treated with Low Level Laser Therapy (LLLT)

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## Abstract:

**Introduction:** Low-level laser therapy (LLLT) is shown effective in healing diabetic foot ulcer when combined with conventional therapy. Since; Diabetes mellitus is a leading cause of impaired wound healing. The aim of this study is to determine the effect of different diabetic control's methods on the healing response of diabetic foot ulcer in those patients treated with Low level laser therapy (LLLT), added to conventional therapy.

**Methods:** This study contains 74 diabetic foot-ulcers which most of them prone to resistance to conventional therapy. Different stages of diabetic foot ulcers and ways of controlling blood glucose level are included in this study. There were 3 response groups; Group 1-Insulin receiving patients, most of them had a very tight blood glyceamic level profile controlling. Group 2- Non-insulin receiving or drug dependent patients, had a periodical blood glyceamic level profile with flatuance. Group 3- Mixed methods. Most of the patients in this group had tight blood glyceamic level profile controlling. The way to control blood glucose level should be according to the internist's consult. The wounds irradiation are performed by the combination of infra-red and red, (860 nm and 650 nm) laser, with the total energy density of 3.6 J/cm<sup>2</sup> in addition of intravenous laser therapy (IVL) with 2.5 MW, 650 nm (red) laser used for 30 minutes. All wounds have been photographed from equal distance, before and after treatments, and all the wounds were staged by a surgeon who was neutral about the effects of the laser therapy. The surgeon's judgment was established only by the visual assessments of the wounds. All the mathematical and statistical analysis is based on the descriptive statistics using the software package SPSS<sub>16</sub>.

**Conclusion:** LLLT promote the tissue repair process of diabetic foot ulcer. Healing response of the patients was not dependent on methods of controlling blood glucose level. Previously it was reported that tight control of diabetes containing continuous subcutaneous insulin infusion and others on split mixed doses promotes healing of diabetic foot lesions. In this study; we found interruption of LLLT in the treatment of diabetic wound; can give a very acceptable result even in the absence of tight controlling of glucose level. When the quantity presentations value of the mean blood glucose level distribution was on the range of 144- 275 mg/dl. In this multi-disciplinary method we achieved a remarkably shorter mean healing time of two months, compared with other reported studies with healing time of three to six months.

**Keywords:** Wound Healing; Ulcer; laser therapy, Low level; Lasers; Endpoint Determination; Diabetic Foot

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## Introduction

Low-level laser therapy (LLLT) is shown effective in healing diabetic foot ulcer when combined with conventional therapy(1). Since; Diabetes mellitus is a leading cause of impaired wound healing. The aim of this study is to determine the effect of different diabetic control's methods including tight control on the healing response of diabetic foot ulcer in those patients treated with Low level laser therapy (LLLT), added to conventional therapy. Previously it was reported that tight control of diabetes containing continuous subcutaneous insulin infusion and others on split mixed doses promotes healing of diabetic foot lesions (2).

Low level laser therapy (LLLT) is gaining acceptance in clinical applications. For example, it is used as therapeutic modality for the repair of diabetic foot ulcer when conventional therapies are not effective (3,4).

According to the report of American Diabetes Association, 82,000 people lose a foot or leg due to diabetes, annually.

Low-energy photo-stimulation at certain wavelengths can enhance tissue repair by releasing growth factors from fibroblasts and can facilitate the healing process of diabetic wounds (3).

The molecular and cellular mechanisms of LLLT are as follow:

- 1) Target cells are blood leukocytes, fibroblasts, keratinocytes, endotheliocytes, etc.
- 2) Primary acceptors of radiation are porphyrins, which may cause radicals for secondary free radical reactions
- 3) The initiation of the secondary free radical reactions due to lipid peroxidation of cell membranes leads to an increase in ion permeability, including  $Ca^{2+}$ . The increase in intracellular  $Ca^{2+}$  concentration cause phagocytosis to increase production of reactive oxygen species (ROS)
- 4) ROS in the cytoplasm of some cells induces a free-radical activation of synthesis of proteins; the most significant is the de novo synthesis of inducible Nitric oxide (NO) –synthase (iNOS), super oxide dismutase, and various cytokines. NO has many functions in wound healing (5).

The foot ulcer in diabetic patients, as a pivotal

event, especially in its last stages demands urgent and aggressive management. Diabetic foot care in all stages needs multidisciplinary management to control mechanical, wound, microbiological, vascular, metabolic and educational aspects. Achieving good metabolic control of blood glucose, lipids and blood pressure is important in each stage (6). Aggressive management of diabetic foot ulceration will reduce the number of feet proceeding to infection and necrosis, and thus reduce the number of major amputations in diabetic patients (6).

## Methods

This study was carried out after approval of local ethics committee. The patients with different stages of diabetic foot ulcer, during the period of three years after signing appropriate written consent entered this study. LLLT and intravenous laser therapy (IVL) were used for 65 diabetic foot-ulcer patients who resisted to conventional treatment.

We divided the patients to the three main groups;

Group 1. Insulin receiving patients (those who receive insulin in order to control blood glucose level) most of them had a very tight blood glyceamic level profile controlling. These patients either were hospitalized or had daily glucose level checking.

Group 2. non-insulin receiving or drug dependent patients (those who receive chemical standard

Protocol, like; tab. Metformin or Gelbenclamide and etc. In order to control blood glucose level) had a periodical blood glyceamic level profile controlling.

Group 3. Mixed methods. (Those who receive insulin in combination with herbal and/or

Chemical standard protocol for the controlling blood glucose level) most of the patients in this group had tight blood glyceamic level profile controlling.

All the three mentioned ways are according the internist's prescriptions of the patients, mentioned in their files.

We arranged the stages of diabetic wound, into five stages using the Texas Diabetic Wound Classification:

Stage 1. The very superficially involvement of the skin and involvement of epidermis with redness.

Stage 2. The involvement of the full thickness of the skin and minor underlying tissue.

Stage 3. The deepest involvement of the full thickness of the skin, and major soft tissue involvement extending into the muscle or tendon.

Stage 4. Involvement of major soft tissue, muscle or tendon obviously and, or even bone.

Stage 5. presenting the necrotic tissue that can't stage the ulcer may contain complicated osteomyelitis.

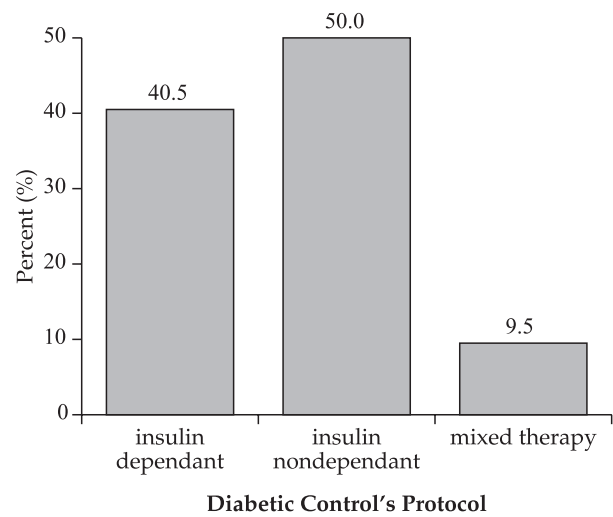
All of the patients received the required, conventional treatments of diabetic wound care, including dressing, antibiotics, controlling diabetes, cholesterol, and blood pressure along with aggressive drug treatment and wound debridement when needed. Before, after and during the laser therapy's procedure.

In those wounds that conventional therapy was not effective, separately, after passing the treatments deadline, in the case of delayed or none healing wounds, laser therapy added to the protocol. Then the results of the both methods compared together considering as two separate groups. Some patients had 2 or 3 ulcers, which included in ulcer count, which made a total number of 74 diabetic ulcers included in this study.

**Varieties of different parameters in his study are as the followings;**

- 1) The availability percentage of sex distribution in this study was; 70.27% (Fifty- two in numbers) were male patients and 29.73% (Twenty-two in numbers) females (1).
- 2) The availability of age distribution was: 25.68% (Nineteen in numbers) of < 50years old, 24.32%( Eighteen in numbers) of 50 - 60 years old, 27.03% (Twenty in numbers) of 60 - 70 years old and 22.97%( Seventeen in numbers) being >70 years old and the mean age was 59.69 Y with St Deviation = 1.46 (1).
- 3) The availability of diabetic control's protocol distribution was: 40.5% (Nineteen in numbers) of Insulin dependent, 50.0%(Eighteen in numbers) of Insulin-non dependent, 27.03% (Twenty in numbers) of mixed therapy.
- 4) The quantity presentations value of the mean blood glucose level distribution was divided into 3 main divisions:

The 1<sup>st</sup> division: those patients who had good blood control mean values (144-180 mg/dl) - 14.9% (Eleven in numbers)



**Diagram 1.** The diabetic control's protocol

The 2<sup>nd</sup> division: those patients who had poor blood control mean value or uncontrolled levels (205-275 mg/dl) - 62.2% (Forty-six in numbers)

The 3<sup>rd</sup> division: those patients who had border line values (180-205mg/dl) - 23.0% (seventeen in numbers)

3) The availability distribution of stages of diabetic wound: it was divided into five stages: (Diagram 1).

The 1<sup>st</sup> stage – 0 .0%. (Not available)

The 2<sup>nd</sup> stage - 21.6%. (Sixteen in numbers)

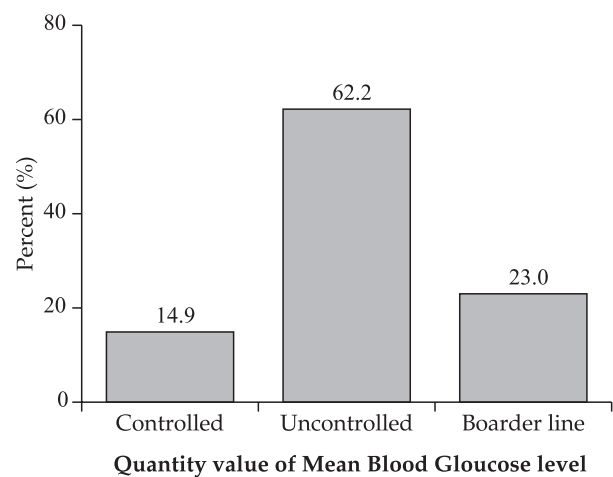
The 3<sup>rd</sup> stage - 35.1%. (Twenty-six in numbers)

The 4<sup>th</sup> stage - 32.4% (Twenty-four in numbers)

The 5<sup>th</sup> stage - 10.8%.( Eight in numbers)

The availability of the ulcers in 3rd stage was more than the other stages (1).

4) The result of wound culture with antibiogram



**Diagram 2.** Quantity value of mean blood Glucose level

and the required antibiotic therapy: Most of the ulcers (79.7%) (Fifty nine in numbers) had positive culture, while 6.8% (Five in numbers) of the ulcers had negative results, yet the remaining ( 13.5%)(Ten in numbers) had no documented result of their wounds culture in their file. This last group, based on their wound examination, didn't need antibiogram. 85.1% (Sixty-three in numbers) of patients were treated with regards to the result of cultures and examination with a suitable antibiotic regime and the remaining did not need the antibiotics in their treatment's schedule(1).

LLLT was applied using the following protocol:

- 1) Intravenous laser radiation (IVL) with 2.5 mW, 650 nm laser (GAALINP/ SIL85-6, IDFI-Behsaz Company, Iran) in order to radiate the blood stream from the large veins of upper limb, applied intravenously through venue of catheter for 30 minuets.
- 2) Wound irradiation by a combination of red and infra red laser, with the total energy density of 3.6 J/cm<sup>2</sup> in non contact irradiation technique. The ID of lasers was as follow:
  - I - GaAs diode laser (LO7 hand-held probe, Mustang 2000 Russia):  $\lambda = 860$  nm, radiation mode = pulse, peak power output = 100 W, surface area= 1 cm<sup>2</sup>, time = 30 S / cm<sup>2</sup>, frequency = 3000 Hz (the maximum produced frequency by the laser set), pulse duration = 200 nsec, energy density 1.8 J/ cm<sup>2</sup>.
  - II - GaAlInP diode laser (K30 hand-held probe,

AZOR, Technica, Russia):  $\lambda = 650$  nm, radiation mode = continues, Power = 30 mW, Surface area= 1 cm<sup>2</sup>, Time = 60 S/ cm<sup>2</sup>, Energy density = 1.8 J/ cm<sup>2</sup>.

- 3) The area of 1 centimeter from the ulcer margins were irradiated with IR laser using a hand-held probe LO7 ( $\lambda = 860$  nm, radiation mode = pulse, peak power output = 100 W, surface area= 1 cm<sup>2</sup>, time = 60 S, frequency = 3000 Hz, pulse duration = 200 nsec, energy density 3.6 J/ cm<sup>2</sup>) with irradiation technique of direct contact to cover around the wound.
- 4) Irradiation of lymphatic drainage and vascular vessels of wound area including around of external and internal malleolus, fossa poplliteal, and inguinal region with IR laser by hand-held probe LO7 ( $\lambda = 860$  nm, radiation mode = pulse, peak power output = 100 W, surface area= 1 cm<sup>2</sup>, frequency = 3000 Hz, pulse duration = 200 nsec, energy density 0.3 J/ cm<sup>2</sup>) using in contact scanning of the area. The scanning time was determined according to the regional size for each wound to receive, 0.3 J/ cm<sup>2</sup> in its surface area.

The therapeutic sessions were repeated 3-4 times per week (mean 18.45) for an average of 2 months/ on average for 2 months; depending on the patients' situation.

Based on the wound healing response, patients were divided into five categories, 1<sup>st</sup>) completely healed, 2<sup>nd</sup>) healed more than 50%, 3<sup>rd</sup>) healed less than 50%, 4<sup>th</sup>) not healed, 5<sup>th</sup>) patients who did not followed the treatment sessions for at least five sessions. All wounds have been photographed from equal distance, before and after treatments, and all the wounds were staged by a surgeon who was disinterested and neutral about the effects of the laser therapy. The judgments were based on the visual assessments of the photos. All the mathematical and statistical analyses were completed using descriptive statistics (SPSS version 16).

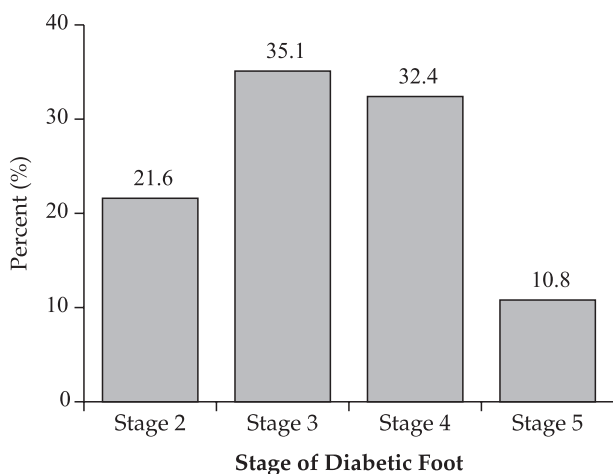


Diagram 3. The Stages of wound (1)

## Results

In the result of this study; Healing response of the patients was not dependent on the methods of controlling blood glucose level, statistically no any detectable and meaning full difference was found in the healing response of the patients receiving

different methods of controlling blood glucose. Which was contained; 1- insulin receiving, 2- non-insulin receiving, 3- mixed method, statistically all three groups of patients, achieved same response to the treatments in the different stages. Considering all had a very good response to the treatments comparatively as other methods.

The p-value in this study is; 0.584 ( $\alpha=0.05$ ), statistically shows, the methods of controlling blood glucose level has no detectable effect on the healing response.

Previously it was reported that tight control of diabetes containing continuous subcutaneous insulin infusion and others on split mixed doses promotes healing of diabetic foot lesions. In this study; all these three groups had shown equal response to the treatments. We suggest interruption of LLLT in the treatment of diabetic wound; can give a very acceptable result even in the absence of tight controlling of glucose level. When the quantity presentations value of the mean blood glucose level distribution was on the range of 144- 275 mg/dl.

The way to control blood glucose level should be according to the internist's consult. In this multi-disciplinary method we achieved a remarkably shorter mean healing time of two months, compared with other reported studies with healing time of three to six months (1).

The total variety response to healing were; 62.2%

(Forty-six in numbers) of the ulcers completely healed, 12.2% (Nine in numbers) healed more than 50%, 8.1% (Six in number) healed less than 50%, 5.4% (four in numbers) were not healed, 12.2% (Nine in numbers) did not continue the treatment. In this study, if we omit those patients who did not complete the therapeutic sessions (at least 5 sessions), we can say almost all the patients achieved some degree of healing, and 74.4% of patients got more than 50% to complete healing (1).

The followings are the healing durations and the percentages of healing in each stage of the diabetic wounds:

Stage 2: 86.8% of diabetic wounds in this stage completely healed during 2 months

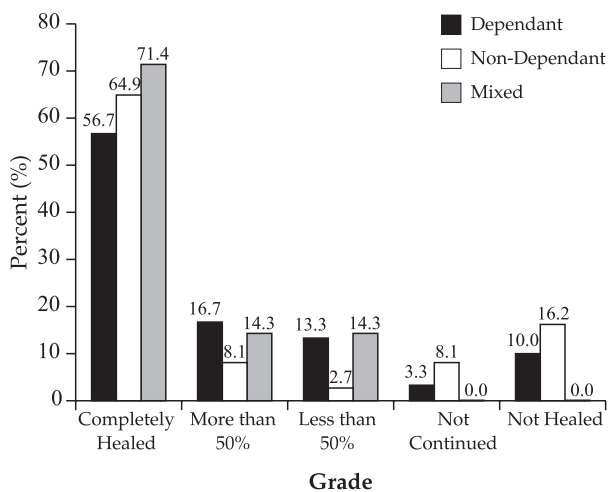
Stage3: 61.5% of diabetic wounds in this stage completely healed while 7.7% showed more than 50% healing during 2 months.

Stage 4: 58.3% of diabetic wounds in this stage completely healed while 25% showed more than 50% healing during 2 months.

Stage 5: 33.3%, of diabetic wounds in this stage completely healed and 25% showed more than 50% healing within 2-4 months (1). According to the statistic measurements, Healing response of the patients was not depend on the methods of controlling blood glucose level, it means; statistically no any detectable difference found in the healing response of the patients receiving different methods of controlling blood glucose.

Crosstabulation

		grade					Total	
		completely healed	more than 50%	less than 50%	not healed	not continue		
insulin	Dependant (very tight blood glyceamic level profile control)	Count	17	5	4	1	3	30
		Expected Count	18.6	3.6	2.4	1.6	3.6	30.0
		% within insulin	56.7%	16.7%	13.3%	3.3%	10.0%	100.0%
		% of Total	23.0%	6.8%	5.4%	1.4%	4.1%	40.5%
	Non-dependant	Count	24	3	1	3	6	37
		Expected Count	23.0	4.5	3.0	2.0	4.5	37.0
		% within insulin	64.9%	8.1%	2.7%	8.1%	16.2%	100.0%
		% of Total	32.4%	4.1%	1.4%	4.1%	8.1%	50.0%
	Mixed therapy (tight blood glyceamic level profile control)	Count	5	1	1	0	0	7
		Expected Count	4.4	.9	.6	.4	.9	7.0
		% within insulin	71.4%	14.3%	14.3%	.0%	.0%	100.0%
		% of Total	6.8%	1.4%	1.4%	.0%	.0%	9.5%
Total	Count	46	9	6	4	9	74	
	Expected Count	46.0	9.0	6.0	4.0	9.0	74.0	
	% within insulin	62.2%	12.2%	8.1%	5.4%	12.2%	100.0%	
	% of Total	62.2%	12.2%	8.1%	5.4%	12.2%	100.0%	



**Diagram 4.** The total response to healing in the different diabetic control's methods in the patients treated with Low level laser therapy (LLLT) in combination with intravenous laser therapy (IVL), added to conventional therapy.

## Discussion

Diabetic foot problem due primarily to neuropathy and microcirculatory damage imposes considerable morbidity and costs on individuals and societies (7-10).

Diabetic foot care in all stages needs multidisciplinary management to control mechanical, wound, microbiological, vascular, metabolic and educational aspects. Achieving good metabolic control of blood glucose, lipids and blood pressure is important in each stage, as is education to teach proper foot care appropriate for each stage (6).

Ardon Rabinson and Converse E. Pierce reported that tight control of diabetes promotes healing of diabetic foot lesions. Fifteen diabetic patients, with neuropathic foot ulcers refractory to conventional treatment, were found to be poorly balanced and were put on meticulous regimens; some on continuous subcutaneous insulin infusion and others on split mixed doses. In the result of this study they suggest that tight control of diabetes promotes healing of diabetic foot lesions (2).

Schindl et al. reported the first case of diabetic foot patient treated with low-intensity laser therapy in 1992 and proposed that this therapeutic method might constitute a useful side effect-free alternative treatment modality for the induction of wound healing of neuropathic ulcers in diabetic patients (1).

Byrnes KR et al. during a study showed that

LLLT at an energy density of 4 J/cm<sup>2</sup> was effective in improving the healing of full-thickness skin wounds (stage III) in an animal model of type II diabetes; and the quantitative analysis of basic fibroblast growth factor expression at 36 h post-injury revealed a threefold increase in the diabetic and non-diabetic Sand Rats after LLLT (12).

LLLT was used concurrently with topical hyperbaric oxygen in an Israeli study of 100 consecutive diabetic foot ulcer patients who had not responded to prior therapies. 81 percent of them were healed in an average of three months (According to the March 2001 issue of Yale Journal of Biology and Medicine)(13).

Landau reported the treatment of 50 patients with chronic diabetic foot ulcers were treated with topical hyperbaric oxygen alone or in combination with LLLT and 42 patients showed complete healing (14).

Low-level laser irradiation has been reported to enhance ATPase activity, long-term erythrocytes membrane proteins as well as lipid bilayer structural changes, and resulting change in membrane ion pumps activities (15), respiratory burst of neutrophils through activation of protein tyrosine kinas and phospholipase C (16). Also, improvement of skin circulation in patients with diabetic microangiopathy has been reported (17). In addition, according to some clinical researches, laser stimulation at certain wavelengths can also enhance tissue repair by releasing growth factors from fibroblasts and can facilitate the healing process of diabetic wounds<sup>3</sup>.

Moreover, low-level laser irradiation has been shown to accelerate collateral circulation, enhance microcirculation (18) as well as relaxation of vascular smooth muscle (19).

LLLT can improve nerve activity and it is reported to be used in the cases of Sacral and trochanteric pressure sores in patients with plegias successfully. Foot ulcerations in patients with diabetic neuropathy are similar, because these wounds occur in tissues that do not have normal innervations. While it is recognized that insensitive tissue increases the likelihood of ulceration outbreak and recurrence (20).

Intravenous laser therapy (IVL) or photohaemotherapy is a method of low level laser therapy that was pioneered in Russia and refers to blood irradiation through an intravenous needle

or transcutaneously, venous radiation. The most common used wavelengths include 890 nm, 630 nm, 650 nm, and recently 450 nm. According to the Russian studies IVL increases oxygen content and reduces the partial pressure of carbon dioxide. It eliminates tissue hypoxia, stimulates oxygenation, normalizes tissue metabolism, and activates the non-specific mechanisms of anti - infectious immunity.

IVL reduces content of C - reactive protein, raises activity of complement, increases the plasma level of immunoglobulins (IgA, IgM, IgG), decreases thrombocyte aggregation ability, and activates fibrinolysis which enhances peripheral circulation (21).

Lebed'kov EV et al. found that IVL has impact on the blood lipid and phospholipid components as well as membrane erythrocyte in patients with diabetes mellitus and pyo-necrotic injuries of lower extremities. Additionally, the results prove that the IVL favorably affects the blood components in a complex treatment of diabetes mellitus (22).

Dr. P. Ramadawon used IVL in combination with LLLT and acupuncture laser therapy to control blood sugar in diabetes (23).

Our work was a multi-method low intensity laser therapy which obtained a very satisfying result comparatively as previously shown through other therapeutic methods. It contained both intravenously and locally low level laser irradiations.

According to the Wagner categories, median healing time increased from 51 (2M) days in class 1 to 174(9 M) days in class 4.(24) In this method we have achieved a very acceptable goal in order to treat diabetic ulcers, even in highly damaged tissues, in a shorter time (on average of 2 months) as compare to the other reported study [the combination of LLLT and topical hyperbaric oxygen that achieved healing in an average of 3 months) conducted by Landau Z, 2001](13), and it seems that IVL and LLLT together can reduce the treatment time with satisfying healing and its response could be get even in non tight control of blood glucose.

## Conclusion

In conclusion; LLLT promote the tissue repair process of diabetic foot ulcer. Healing response of the patients was not dependent on methods

of controlling blood glucose level. It means; statistically no any valuable difference found in the healing response of the patients receiving different methods of controlling blood glucose. In the literature review it was reported that tight control of diabetes containing continuous subcutaneous insulin infusion and others on split mixed doses promotes healing of diabetic foot lesions(2). In this study we added LLLT, in all three groups, that contained; Group 1-Insulin receiving patients, most of them had a very tight blood glyceamic level profile controlling.,

Group 2- non-insulin receiving or drug dependent patients, had a periodical blood glyceamic level profile with flatuance.

Group 3- Mixed methods. Most of the patients in this group had tight blood glyceamic level profile controlling. The way to control blood glucose level were according to the internist's advise of the patients.

As a result; all these three groups had shown equal response to the treatments. We found interruption of LLLT in the treatment of diabetic wound, can give a very acceptable result even in the absence of tight controlling of glucose level. When the quantity presentations value of the mean blood glucose level distribution was on the range of 144- 275 mg/dl.

In this multi disciplinary method we obtained a remarkably shorter mean healing time of two months, compared with other reported studies of three to six months. [Excluding the exceptional cases seen; in stage 5, which more than 80% of the diabetic wounds achieved more than 50% of complete healing during 2months.and more after 2months (for a total period of 4 months), The remaining reached to 58% of complete healing. Means 37% of the cases did not prone any response to healing and the remaining left the therapy before 5<sup>th</sup> session](1).

We hope to open a new angel of vision for our medical members in order to reduce the rate of limb amputation, and the number of patients who may suffer, in addition, we hope to make a way for achieving more reasonable treatments in diabetic foot patients, in a very close future.

## Acknowledgment

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and we offer our gratitude to IDFI- B. Institute for the instrumental supports in completing this study.

### Dedication

We would like to dedicate this effort to Dr. assist.prof.Abdolrhman Rostamian (Department of Rumatology, Imam Khomeini Complex Hospital, University of Medical Science, Tehran, Iran)

For his great helps and supports to the colleagues and students.

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