

# Intravenous Laser Wavelength Irradiation Effect on Interleukins: IL-1 $\alpha$ , IL-1 $\beta$ , IL6 in Diabetic Rats

Amjadi. A<sup>1</sup>, Mirmiranpor. H<sup>2</sup>, Khandani. S<sup>3</sup>, Sobhani. S.O<sup>4</sup>, Shafae. Y<sup>5</sup>

*Abmad Amjadi<sup>1</sup>, Ph.D. (Corresponding Author) Laser and Medical Physics Lab, Department of Physics, Sharif University of Technology, Tehran, Iran, E-mail: amjadi@sharif.edu, Tel: +98-2166164521 Fax: +98-2166022711*

*Hossein Mirmiranpour<sup>2</sup>, M.D. Endocrinology and Metabolism Research Center (EMRC), Valiasr Hospital, School of Medicine, Tehran University of Medical Science, Tehran, Iran, E-mail: b\_mirmiranpoor@yahoo.com, Tel: +98-9123388654*

*Salile Kbandani<sup>3</sup>, Laser and Medical Physics Lab, Department of Physics, Sharif University of Technology, Tehran, Iran, E-mail: salile.kb100@gmail.com, Tel.: +98-9155828735*

*Seyed Omid Sobhani<sup>4</sup>, Laser and Medical Physics Lab, Department of Physics, Sharif University of Technology, Tehran, Iran, E-mail: omid.sobhani@gmail.com, Tel.: +32-494903687,*

*Yasaman Shafae<sup>5</sup>, Laser and Medical Physics Lab, Department of Physics, Sharif University of Technology, Tehran, Iran, E-mail: Yasaman\_shafae@yahoo.com, Tel.: +98-9101030472*

**Background and aims:** The main purpose of this investigation in Low-Level Laser Therapy (LLLT) on diabetic rats is laser wavelength effect on interleukins: IL-1 $\alpha$ , IL-1 $\beta$ , IL6.

**Materials (Subjects) and Methods:** At first, diabetes was induced in Wistar rats by streptozotocin (STZ) injection. Then, by intravenous laser therapy, the rats were irradiated by four continuous wave lasers: IR ( $\lambda = 808$  nm), Red ( $\lambda = 638$  nm), Green ( $\lambda = 532$  nm) and Blue ( $\lambda = 450$  nm) to compare the related laser wavelength effect on different interleukins. The inflammatory parameters were measured 2,6 and 24 hours after laser therapy from blood samples and plotted for different laser wavelengths.

**Results:** The results show a decrease in all the above parameters by different laser irradiation in comparison to non-irradiated diabetic control ones. More importantly with constant laser energy as the laser wavelength decreases, it affects more efficiently on lowering the above parameters.

**Conclusions:** we can conclude from our data on diabetic rats that in intravenous LLLT, with constant laser energy, shorter wavelengths like Blue ( $\lambda = 450$  nm) is more effective than longer wavelengths such as Red ( $\lambda = 638$  nm) and IR ( $\lambda = 808$  nm) lasers to lower the level of interleukins toward non-diabetic ones.

**Key words:** Inflammation • Low Level Laser Therapy • IL-1 $\alpha$  • IL-1 $\beta$  • IL6 • Diabetes

## Introduction

Leucocytes migration from the vasculature into damaged or infected tissue is a part of the defense mechanism which causes the tissue inflammation. In diseases such as

diabetes, the leucocyte migration is much more than what it is needed to be. Higher levels of Cytokines are inflammatory disease indicators. Interleukins which are a member of Cytokines family, are one of the key substances that play a crucial role in inflammatory processes by controlling leucocyte migration and activity<sup>1, 2, 3, 4, 5, 6</sup>. Any kind of interruption in the process of nutrition of the pancreatic islets of Langerhans leads to a decrease in the secretion of insulin and the setting diabetes in motion.<sup>7</sup>

### \*Addressee for Correspondence:

Enter the **full postal address** of the author to whom all correspondence is to be addressed, and paper proofs sent for checking.

Include Telephone and FAX numbers (if appropriate), starting with the international code (e.g., +81-3-5269-1403)

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For many years, there has been an increasing number of laboratory and epidemiologic evidence indicating that insulin resistance and type 2 diabetes mellitus (DM) are conditions of low grade inflammation. It's now believed that there is a causal link between this inflammation and pathogenesis of these disorders.<sup>8)</sup>

Inflammation is a physiological response to different stimuli such as infection, tissue damage, metabolic disorder, etc. This response could have many different forms.<sup>8)</sup> An acute inflammatory response is usually a very fast and intense stage with a very short period. This stage is followed by a rapid change in the concentration of some plasma proteins called "APP (Acute Phase Proteins)". These proteins are secreted from the liver. IL1 and IL6 play a crucial role in the APP's secretion. Inflammation is usually accompanied by swelling, heat, pain, and redness in tissue. This process is accompanied by extra production of Reactive Oxygen Species (ROS) including oxidants, and a reduction in the activity of antioxidant enzymes<sup>9)</sup>.

Pro-inflammatory Cytokines including the interleukins including IL-1 $\alpha$  and IL-1 $\beta$ <sup>10)</sup> are crucial mediators of inflammation, immunity and cell recruitment and proliferation. It has been reported that one of the principal parameters responsible for inducing inflammation is the existence of inflammatory cells at the injured site, caused by interactions between the inflamed tissue and circulating leukocytes.<sup>11)</sup>

IL-1 $\beta$  is a pro-inflammatory cytokine and plays a key role in acute and chronic inflammatory and autoimmune diseases. IL-1 $\beta$  is related to functions in the normal organism, such as in the regulation of feeding, sleep, and temperature, therefore it's very important when conditions like type 2 diabetes mellitus, rheumatoid arthritis (RA), multiple sclerosis, and Alzheimer's disease alter the production of IL-1 $\beta$  in the body<sup>12, 13, 14)</sup>.

IL-1 $\alpha$  is also a pro-inflammatory cytokine and can help to initiate the inflammation process, by inducing Tumor Necrosis Factor  $\alpha$ , which is another well-known inflammatory parameter that can activate some other interleukins<sup>15, 16)</sup>. The IL-1 $\alpha$  expression can occur as a result of different physiological stimuli, oxidative stress, lipid overload, hormonal stimulation and exposure to cytokines like IL-1 $\beta$  and IL-1 $\alpha$  itself. The diversity of stimuli that activate IL-1 $\alpha$  expression causes IL-1 $\alpha$  to have an initiative role in the inflammation process. Over expression of pro-IL-1 $\alpha$  in autoimmune diseases usually increases IL6 secretion<sup>17)</sup>.

IL6 is a multi-functional mediator, in the meaning that it can act as both pro-inflammatory and anti-inflammatory mediator (by interpreting TNF- $\alpha$  functioning), therefore it attracts a lot of attention toward itself. Usually, IL6 is secreted in the time after exercise when insulin secretion has increased. It's also related to obesity and insulin resistance caused by lipid overload and IL6 level is es-

pecially high in people with obesity or type 2 diabetes mellitus. IL6 is effective in both innate (by helping producing APPs in the liver) and adaptive immune system (by increasing B cell growth)<sup>18, 19)</sup>. IL6 expression also can be encouraged by oxidized low-density lipoprotein (ox-LDL)<sup>20)</sup>.

Low-level laser therapy (LLLT) has been used for treating tissue damage and conditions related to inflammatory processes since the 1960s<sup>21)</sup>, some years after progression of the first laser, evidence about laser irradiation resulting in both stimulation and inhibition in biological processes, was observed.<sup>22)</sup> This approach has been known as a safe, noninvasive way of applying therapeutic photonic energy to the tissue.<sup>23)</sup>

Low-level laser therapy (LLLT) has been very successful for treating conditions involving inflammation such as muscle regeneration and wound healing<sup>24, 25, 26, 27, 28, 29, 30, 31, 32)</sup>, attenuating chronic and acute pain associated with inflammatory diseases<sup>15, 33, 34)</sup>.

LLLT can positively influence biologic tissues by improving micro-circulation, nerve conduction, and cell proliferation. Other positive effects may include stimulation of the host immune system, increased enzyme activity and DNA synthesis, and enhancement of cell membrane structure.<sup>35)</sup>

There are several phases for inflammation developing including the release of biochemical mediators which are secreted through membranes of the inflamed cells. It has been suggested that the laser directly has an effect on blocking these mediators. A decrease in the number of clinical inflammation signs and lower values of acute phase proteins has been observed as a confirmation of the anti-inflammatory effect of laser.<sup>36)</sup> Oxidative stress causing the inflammation can be reduced by applying LLLT.<sup>37)</sup>

Promotion in tissue regeneration, inflammation reduction and pain relief has been hypothesized as the LLLT effects. It is known that there is a biphasic dose response pattern in LLLT functioning, which follows the Arndt Schulz Law. Different bio stimulatory effects can take place using doses within a dose range, also known as therapeutic window. By using doses above this therapeutic window, inhibitory effects are observed, and in the same way, by using doses below the therapeutic window, no effects are observed. For applying optimized LLLT to different pathologies and conditions, the establishment of optimal doses and therapeutic windows is very important.<sup>38)</sup> Effects of LLLT on inflammatory mediators and on neutrophils and macrophages in acute joint inflammation were investigated on Wistar rats by Alves et al<sup>35)</sup>. In that research, animals were subjected to joint inflammation (papain solution, 4%) and immediately after that was submitted for the administration of 808nm laser therapy. Their results indicated that 50 mW, 80 seconds irradiation time was more efficient than 100 mW, 40 seconds irradiation

tion time in reducing cellular inflammation and decreasing the expression of IL-1 and IL6. They also concluded that 100 mW, 40 seconds irradiation reduces TNF- $\alpha$  more efficiently than 50 mW, 80 seconds treatment.

Among the pro-inflammatory mediators present in lung inflammation, IL-1 $\beta$  plays a very interesting role by participating in both early and later inflammatory response, by initiating and perpetuating the inflammation. Effects of LLLT on pulmonary microvascular leakage and IL-1 $\beta$  level in lungs from rats subjected to LPS-induced inflammation were investigated by Aimbire et al<sup>19</sup>. Results indicated that LLLT caused a very noticeable decrease in the IL-1 $\beta$  level, even though its level had become very high in the result of LPS induction<sup>39, 40</sup>.

In our previous studies, we reported the effect of different wavelengths LLLT on the activity of glycated catalase in-vitro<sup>41</sup>. In another study, we focused on the effect of different wavelengths of laser irradiation on the activity of antioxidant parameters in diabetic wistar rats and reported the activity elevation level of glycated catalase and antioxidants<sup>43</sup>.

In this article, we are following the same concept and investigate the effects of different wavelength laser irradiation on level reduction of inflammatory factors (IL1- $\alpha$ , IL1- $\beta$ , and IL6) in diabetic wistar rats.

## Materials and Methods

### Materials:

Quantity assay kits of IL1 $\alpha$  (850.005.048), IL1 $\beta$  (850.006.048) and IL6 (860.020.048, 860.020.096, 860.020.192) were purchased from Mercodia Co (Sweden), DIACLONE Co (France), DIACLONE Co (France) and DIACLONE Co (France), respectively. Streptozotocin (STZ) (S0130) was acquired from Sigma-Aldrich Co (USA).

### Animals:

Adult male Wistar rats (aged 8 weeks) with the average body weight of  $240 \pm 20$  g (purchased from Pasteur Institute of Iran) were held in a climate controlled vivarium (a temperature of  $23 \pm 3^\circ$  C and a relative humidity range,  $50 \pm 10\%$ , and 12h light: 12h dark cycle). The animals were provided with water and standard food ad libitum. Twenty-four rats that showed appropriate growth after 1 week of acclimation under these conditions, were selected for more studies. Selected rats were randomly divided into 6 equal groups.

The first group (Non-diabetic control) included normal rats without any interference; the second group was diabetic control that had been given an injection of STZ to induce diabetes and was not affected by irradiation; the third, fourth, fifth and sixth groups were treated by IR, red, green and blue irradiation, respectively.

### Ethical aspects:

The animal ethics review committee has approved the study protocol, in accordance with the guidelines for the care and use of laboratory animals prepared by Tehran University. Informed consent of this investigation has been ordered by the Medical Physics and Laser Lab of Physics Department at the Sharif University of Technology.

### STZ-induced diabetes:

All groups (except non-diabetic control group) received an injection of STZ. They received an intra-venous injection of streptozotocin (50 mg/kg of body weight in Na-citrate buffer, PH 4.5) to induce diabetes. Rats' blood glucose levels were measured by an Accu-check blood glucose meter every week, rats with blood glucose levels equal or more than 200 mg/dl for 2 weeks uninterruptedly were deliberated diabetic. Diabetic rats in third to sixth groups were exposed to LLLT.

### Laser Therapy:

Lasers were supplied by International Faran Tech Company in Tehran, Iran. Medical lasers are regularly calibrated by Atomic Energy Organization of Iran using CW power meter model FieldMaxII, Part number: 1098580, from Coherent Inc. located in Santa Clara, CA 95054.

We used multi-mode fiber optics with core radius = 0.1 mm for delivering treatment intravenously via the animal's caudal vein. Four diode lasers with power output 0.01 mW at the end of the fiber optics and wavelengths: 808 nm (IR), 638 nm (Red), 532 nm (Green) and 450 nm (Blue) were used as the laser source.

### Irradiation:

For intravenous LLLT, multi-mode fiber optics were used. Lasers power was 0.01 W at the end of fiber optics. Rats in each of four groups were irradiated intravenously for 120, 240, 360 and 480 seconds. Fiber of laser was brought in the animal blood circulation through the animal's caudal vein during irradiation. During the irradiation no scattered beam was observed around the caudal vein. Therefore, we concluded that all the laser power was absorbed through the multiple scattering process in blood.

Sample Collections: Rats' blood samples were obtained four times:

1. Before irradiation
2. 2 hours after irradiation
3. 6 hours after irradiation
4. 24 hours after irradiation

15-min centrifugation of blood at  $5000 \times g$  has been used in order to prevent serum-clot.

### Evaluation of inflammatory factors:

In this study, we measured levels of IL-1 $\alpha$ , IL-1 $\beta$ , and IL6.

Interleukin1 (IL1) is pro-inflammatory cytokine, IL-1 $\alpha$  and IL-1 $\beta$  are two groups of IL1. These two groups have inflammatory properties<sup>42, 44</sup>. IL6 has both anti-inflammatory and pro-inflammatory properties, therefore plays a significant role in the studies<sup>16</sup>. The sera levels of IL1 $\alpha$ , IL1 $\beta$  and IL6 were assessed by ELISA method and immunoenzymometric assay (DIACLONE kit, France). All measurements were done using a Mindray ELISA reader instrument (MR-96A model, Germany).

**Statistical Analysis:**

All measurements were conducted in triplicate. The data analysis was applied using Microsoft Excel for Mac software version 15.30. Data are interpreted as mean  $\pm$  SD. By using analysis of variance (ANOVA), the significant differences between groups were assessed. A comparison between the non-irradiated control group and all samples was conducted and  $p < 0.05$  was considered statistically significant.

**Results**

The results of our investigation are summarized in **Figures 1 to 3**. The effect of different levels of irradiation on inflammation mediator IL-1 $\alpha$  level is illustrated in figure 1. It shows the IL-1 $\alpha$  within 6 and 24 hours after different irradiation configurations. The gray solid boxes express the level of IL-1 $\alpha$  for the diabetic control group and repeated for different irradiation times in the horizontal axis in order to make a better comparison. As it can be observed in this figure, the level of IL-1 $\alpha$  lowered with increasing the irradiation time, which is proportional to irradiation energy. At the same time, the level of IL-1 $\alpha$  lowered when the wavelength of the lasers decrease. As it is illustrated in **figure 1**, for each irradiation time group, IR irradiation has the smallest effect on the IL-1 $\alpha$  level and the blue laser has the greatest effect on lower-

ing its level.

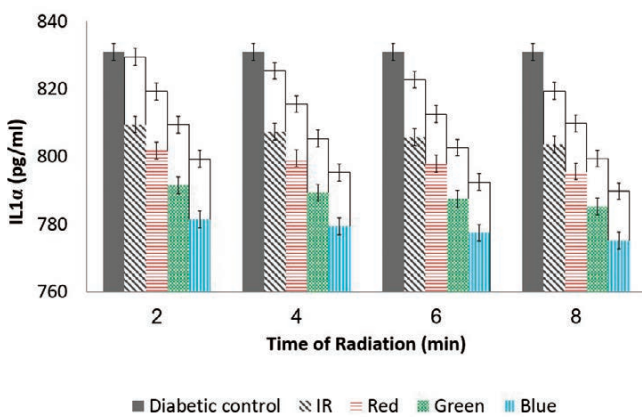
**Figure 2** represents the effect of different radiations configurations on the level of IL-1 $\beta$  measured within 6 and 24 hours after irradiation. In this figure, the same as **figure 1**, gray solid boxes express the level of IL-1 $\beta$  for the diabetic control group. As can be observed in this figure, the level of IL-1 $\beta$  is lowered by the increase of radiation time. Furthermore, the level of IL-1 $\beta$  is lowered by the decrease of wavelength. As it is exhibited in **figure 2**, the smallest effect on IL-1 $\beta$  level occurs when using IR radiation and the greatest effect on IL-1 $\beta$  level occurs when using Blue radiation. **Figures 3** expresses the level of IL6 under different radiation configurations, respectively. These measurements also occur within 6 and 24 hours after irradiation. As illustrated in this figure, the level of IL6 is lowered with increased irradiation time. Also, IL6 level is lowered by decreasing laser wavelength.

**Table 1**, represents the level of different studied interleukins after 24 hours of 6 min of irradiation. In this table, the second numbers in each cell show the percentage of lowering compared to diabetic control. As can be seen for each wavelength, IL-1 $\beta$  is the factor that has been most affected by LLLT. As it can be observed in **table 3** and **figure 4**, for each irradiation configuration, the most sensitive studied interleukin is IL-1 $\beta$  and the least sensitive is IL-1 $\alpha$ .

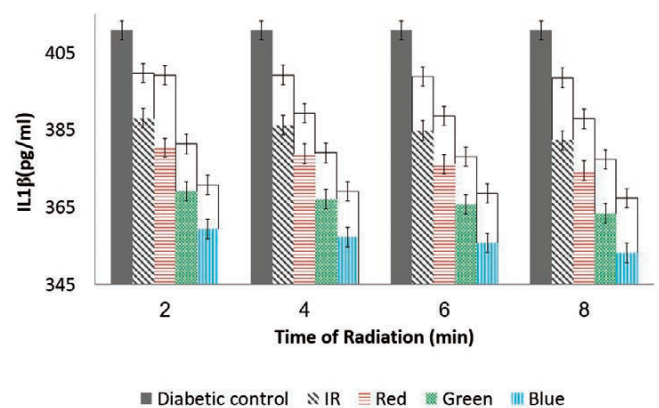
**Discussion**

Diabetes mellitus is a metabolic disorder that is characterized by higher levels of glucose in the blood (hyperglycemia) and lack of production or action of insulin produced by the pancreas or elevated level of insulin resistance in the body.<sup>45</sup>

It has been shown that type 2 diabetes mellitus (T2DM) can contribute to poorly functioning insulin signaling and selective annihilation of  $\beta$ -cells that produce



**Figure 1**



**Figure 2**



insulin. Interleukins play a very critical role in this process.<sup>46)</sup>

In this this article, we have focused on the laser wavelength effect mostly used in intravascular low-level laser therapy to lower the level of inflammatory cytokines IL-1 $\alpha$ , IL-1 $\beta$ , IL6.

Our in-vivo data pointed out a decrease in the level of the above parameters after laser therapy for all wavelength lasers, moreover, this effect is extended or magnified by choosing shorter wavelength laser.

In this research, laser irradiation energy dosage is a very critical parameter. Laser energy can be defined in parallel by two equations: Laser energy = Laser Power \* Time of irradiation, Laser energy = photon's energy \* number of photons.

Where the amount of photon's energy is proportional to the inverse of laser wavelength. Meaning that at constant laser energy, once the photon's energy is higher such as in Blue laser, the number of photons is lower in comparison to the Red or IR laser.

If we treat the laser effects as a function of laser energy, by plotting it we get a Gaussian shape curve, which has a maximum at certain laser energy. The proper energy of laser irradiation could be obtained from the diagram of laser effect as a function of laser energy. For example, as it is shown in **Fig. 1** IL-1 $\alpha$  level continuously decreases as the radiation time increases from 2 min to 8 min, it can be concluded that the laser power is not over-dosage therefore there is no present damage to the subjects. At the same time, by increasing the time of radiation, the difference on the IL-1 $\alpha$  level is getting smaller. It demonstrates that we are almost at the top of the Gaussian curve with maximum laser effect and we may get a negative effect or damage effect from laser irradiation, if we increase the time of laser irradiation. From our data, the laser effect appears more efficiently after 24 hours of laser therapy than 6 hours after. Immediately af-

ter laser irradiation, no effect was achieved and also 2 hours after laser therapy the effect was not much to be noted in this article.

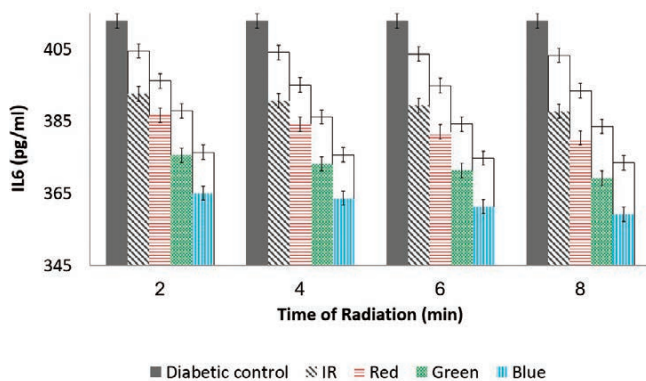
**Conclusions**

In all of our reported data, we have a decrease in interleukins level by increasing the time of radiation. In conclusion, our experimental data indicate that the maximum effect in reducing the level of studied factors extracted from the blood sample of the diabetics rats, can be achieved by using the blue laser with wavelength 450 nm. On the other hand, the reduction of the level of studied factors decreases continuously when increasing the laser wavelength toward red and IR.

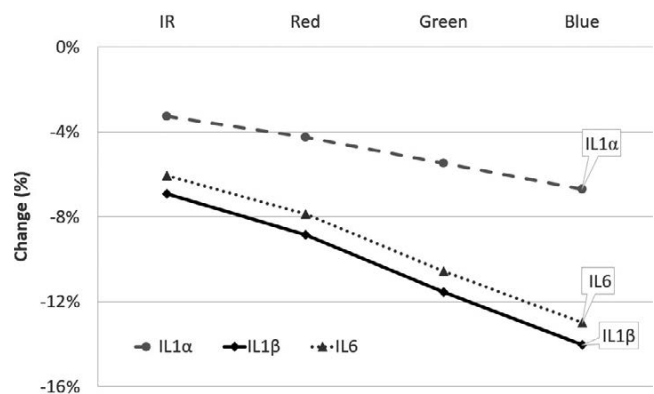
These results are utterly important because, we have less number of photons, at constant laser energy for blue laser. In other words, the energy of each photon is more important than the number of photons. From this state-

**Table 1:** Inflammatory factors and their percent decrease after 24 hours of irradiation, time of irradiation is 6 min. The second number in each cell represents the percentage of decrease compared to diabetic control.

	IL-1 $\alpha$	IL-1 $\beta$	IL6
IR	805.74 -3.02%	384.9 -6.33%	389.4 -5.68%
Red	797.82 -3.97%	376.2 -8.45%	382.1 -7.45%
Green	787.35 -5.23%	365.8 -10.98%	371.4 -10.04%
Blue	777.45 -6.42%	355.8 -13.41%	361.4 -12.47%
Non-diabetic	75.6	56.3	53.7
Diabetic control	830.8	410.9	412.9



**Figure 3**



**Figure 4**

ment, we can conclude that in the glycation process more covalent bonds are involved which higher photon energy is needed for bonds to be recovered.

There is a direct correlation between the recent process and the production of inflammatory factors, because

of which, it is expected that the mentioned energy would be effective to reduce the studied factors. However, one may relate the responsible mechanism to electron changes between higher photon energy and molecular structure of glycated bio-molecule.

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