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Wavelength Effect in Laser Therapy of Diabetic Rats on Oxidants: AGEs, AOPP, ox-LDL Levels

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Abstract: In Low-Level Laser Therapy (LLLT) choosing the proper laser wavelength is extremely important. In this article, we have investigated the effects of four different laser wavelengths on oxidant parameters (AGE, AOPP, and ox-LDL) levels in diabetic Wistar rats experimentally. At first, 24 rats were divided into six equal groups. Except for the none diabetic control group, the other five groups received streptozotocin (STZ) injection to induce diabetes. Four groups of diabetic rats were then irradiated by four different laser wavelengths IR (808nm), Red (638nm), Green (532nm) and Blue (450nm). The last group which did not receive any irradiation is named non-irradiated diabetic control group. Laser therapies were performed Intravenously through an animal's caudal vein by a fiber Optics. Finally, the levels of oxidant parameters in rat's blood samples of each group were discussed. Results show a decrease in oxidants levels in all four irradiated groups of rats relative to the non-irradiated diabetic control group. More importantly, shorter wavelengths affect more efficient than longer wavelengths on reducing the oxidants levels with constant Laser energy. As a result, we conclude that laser with shorter wavelength e.g. Blue is more effective than longer wavelengths e.g. IR or Red, in reducing the oxidant parameters (AGE, AOPP, and ox-LDL) levels in Intravenous LLLT.

Keywords: Laser Therapy, Diabetes, Oxidants, AGEs, AOPP, Ox-LDL

1. Introduction

Low-level laser therapy (LLLT) also recognized as laser photo-therapy [1], has been known as a dose rate related treatment without any promptly noticeable temperature rise in the irradiated tissue. [2] Low-level laser therapy (LLLT) has been evolved in medicine for more than 40 years. [3, 41] The mechanism of LLLT is proposed to be based on the absorption of photons by cytochrome c oxidase, the terminal enzyme in the mitochondrial respiratory chain that catalyzes the reduction process of oxygen used in energy metabolism. [4]

Metabolic diseases such as diabetes are one of the most concerning health problems [18].

Regarding the worldwide complications caused by diabetes, the WHO Global Burden of Disease estimated that around 177 million people in the world were dealing with diabetes in the year 2000. It is also estimated that around two-thirds of these people are in developing countries. [5, 40, 43]

The estimations for the future show no comfort at all. If current trends continue, the above statements may easily become more than double by the year 2025. It is also known that already nearly a quarter or even a third of acute sector health expenditures has to be dedicated to diabetes and the long-term complications caused by it, in some communities. It is estimated that presently around 194 million people worldwide, or 5.1 (%) among the adult population, are dealing with diabetes and that this will jump to 333 million, or 6.3 (%), by 2025. [5] And it has been estimated that by 2030, there will be 370 million people that are affected by diabetes,

worldwide.[6] Especially since, 80% of the total number of patients are from poor and middle-income countries. [40]

The most prevalent type of diabetes is type 2 diabetes mellitus, which can be resulted from resistance to insulin action and a compensatory insulin secretory response [7]. Type 2 diabetes embodies about 85 (%) to 95 (%) of all diabetes in developed countries and attributes to an even higher percentage in developing countries. Whereas previously type 2 diabetes was observed only in individuals in the older age groups, there is now an ever-growing number of reports of this disease in children, in some cases as young as eight, all around the world. Nowadays there is a developing concern that type 2 diabetes in children has the potential to become a global public health issue causing serious outcomes [5].

The most significant complications caused by diabetes, in a public health perspective is regarding human suffering and disability, such as blindness [8, 9], amputation [10], coronary artery, and peripheral vascular disease, stroke [11], diabetic neuropathy [12], and renal failure [13, 14], which are responsible for magnificent reduced life expectancy, social and financial burdens. [5] It has also been suggested that diabetes mellitus can be responsible for both macro and microvascular modifications, as well as neurological diseases [15, 42, 43]. For example, studies have shown convincing evidence that type 2 diabetes mellitus has an increased risk of cognitive impairment and dementia and in general, the prevalence of dementia in diabetic patients is raised by 50%-100% compared to non-diabetic people. [44]

It is expected from present estimations that in 2025 total direct healthcare expenditure on diabetes worldwide will be between 213 billion and 396 billion international dollars (around 7- 13 (%) of the total world healthcare budget in the year 2025). Almost in every developed society, type 2 diabetes is highly noticeable among all other leading causes of blindness. It is also one of the prominent causes of death in most developed countries, because of the way it affects cardiovascular disease (around 70-80 (%) of people dealing with diabetes, die of cardiovascular disease.).

All in all, diabetes is certain to be one of the most challenging health problems in the 21st century [5]. For example, in the United States, diabetes is ranked as the 7th main cause of death.[16] In India, which is considered the world's capital of diabetes, with a predicted diabetic population approaching the alarming range of 70 million people by 2025 and 80 million by 2030 [17].

The mechanism by which diabetes causes these complications is still not fully understood, but involves the direct toxic effects of high glucose levels, along with the impact of elevated blood pressure, abnormal lipid levels [5].

Diabetes mellitus is a convoluted disease with both metabolic and vascular elements outlined by hyperglycemia due to dysfunctions in insulin secretion or insulin action [19].

Increased production of high levels of oxygen free radicals has been linked to glucose oxidation and non-enzymatic glycation of proteins which can lead to inducing some obstacles caused by diabetes, such as stroke, neuropathy, retinopathy, and nephropathy [20, 21]. LLLT can trigger or suppress disordered biological functions and normalize them. LLLT has been known to accelerate wound healing, collagen production, and modulation of the immune system, also it can affect impaired functions of diabetic patients [18].

The inequality in the level of ROS production and the antioxidant defense is called "Oxidative Stress" [22]. Oxidative stress plays a very important role in diabetic pathogenesis and progress of its late complications [23-25]. ROS are known to play a key role in oxidative damage of DNA, proteins, lipids, and cell membrane structure [24, 26].

Ox-LDL is a key parameter in atherosclerosis because of its stimulating effect on inflammation around the arterial wall [27, 28, 29]. Ox-LDL may contain a specific oxidation product, such as lipoxygenase treated LDL. The lipoprotein subjected to such treatment contains varying amounts of phospholipid and cholesterol ester hydroperoxides. Ox-LDL may also contain limited amounts of a variety of degraded oxidized lipid products [28]. Different forms of oxidized LDL can stimulate the transformation of macrophages into foam cells. They are also capable of inducing the expression of cell adhesion molecules in endothelial cells, which leads to abnormal endothelial cell monocyte interactions. Therefore, it is suggested that the accelerated development of macro vascular complications in diabetes could be because of elevated levels of modified lipoproteins [30].

AGEs (Advanced Glycation End-Products) are a complex and heterogeneous group of compounds that are one of the key factors in diabetes-related complications [31]. The effect of a large amount of glucose on bio-molecules like protein leads to the formation of advanced glycation end products. During hyperglycemia, AGEs can be produced by oxidative stress reactions. AGEs play a main role in diabetic vascular complication pathogenesis, and its formation increases in the blood of diabetic patients [32, 33]. Furthermore, AGEs are involved in various pathological conditions such as Alzheimer's disease and end-stage renal disease (ESRD) [31]. AGEs have also been determined as a novel biomarker for patients with peripheral artery disease (PAD) [34].

The activity of chlorinated oxidants during oxidative stress makes dityrosine-containing cross-linked protein products which are determined as Advanced Oxidation Protein Products (AOPP) [35]. AOPP represents a helpful Oxidative Protein Damage (OPD) marker in diabetics [22]. Moreover, AOPP has been considered as inflammation mediators that their elevated level is noticeable in diabetes [35, 36].

In our previous studies, we focused on the effect of different wavelengths on the activity of glycated catalase in-vitro [37]. In another study, we investigate the effect of different wavelengths of laser irradiation on the activity of antioxidant parameters in diabetic Wistar rats [38].

In this article, we are following the same concept and investigate the effects of different wavelengths laser irradiation on oxidants (AGEs, AOPP, and ox-LDL) levels in diabetic Wistar rats.

The aim of present medical approaches toward diabetes is to keep the amounts of glucose and lipids in normal levels and

control these factors as closely as possible to prevent complications.[43] Diabetes is currently treated by pharmaceutical drugs which cause many unwanted side effects.

Considering that the therapeutic approach of using a low-level laser is verified to be harmless to organisms, having laser therapy beside Pharmaceutical drugs to reduce the levels of oxidants parameters may result in a reduction in the consumption of these drugs and their existing side effects, which is the main aim of this study.

2. Method and Materials

2.1. Materials

Quantity assay kits of ox-LDL (10-1143-01) were acquired from Mercodia Co (Sweden). Streptozotocin (STZ) (S0130) was purchased from Sigma-Aldrich Co (USA). And for acquiring AGE and AOPP no kits were used, and the method for obtaining these oxidants is fully explained in the following text. Accu-check blood glucose meter kit was purchased from Roche Diagnostics Co (Switzerland).

2.2. Animals

The initial total number of rats was 50. The age of each rat was eight-week-old. The body weight of each rat was 240±20g and they were purchased from Pasteur Institute of Iran. Animals were held in a climate-controlled vivarium (a temperature of 23±3°C and a relative humidity range, 50±10%, and 12h light: 12h dark cycle). Diets and water were supplied adlibitum. After being kept 1 week in this accommodation, 24 rats that showed appropriate growth were picked for more studies. Selected rats were randomly distributed into 6 equal groups of 4 animals each.

The first group including 4 rats (Non-diabetic control) included normal rats that didn't receive interference, all other groups had been given an injection of STZ to induce diabetes; the second group, including 4 rats, was diabetic control and was not affected by irradiation; the other four groups, including 4 rats in each group received four different wavelength irradiation with different time of irradiation.

2.3. STZ-induced Diabetes

Except for the non-diabetic control group, all other groups of rats received an injection of STZ. They were administrated by intraperitoneal 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, if blood glucose level was equal or more than 200 mg/dl for 2 weeks uninterruptedly, rats were deliberated diabetic. Diabetic rats in third to sixth groups were subjected to the administration of laser irradiation.

2.4. Laser Therapy

The study was performed using four diode lasers: IR (λ=808nm), Red (λ=638nm), Green (λ=532 nm), and Blue (λ=450 nm).

One out of six groups of studied rats is related to the non-diabetic control group (healthy rats without any interference). The second group is the diabetic control group, which received no irradiation. The other four groups of rats are receiving different wavelength laser irradiation.

Each of the last four groups consists of four rats that are receiving different times of irradiation (2, 4, 6, 8 min).

2.5. Irradiation

Multi-mode fiber optics for intravenous laser irradiation was used. The core radius of fiber optics was 0.1 mm, and the average laser power was 0.01 mW at the end of the fiber. Animals were held by appropriate fixator.

Lasers were used to irradiate intravenously each of four groups for 2, 4, 6, and 8 minutes. The lead of the laser apparatus was brought in the animal blood circulation through the animal's caudal vein, parallel to the caudal vein, to avoid vein rupture and being able to place the lead into the vein more easily during irradiation.

2.6. Sample Collection

In each venipuncture, the amount of blood obtained from each rat was equal to 800λ. Then by centrifuge process, 200 λ serum was obtained from it.

Blood samples of rats were obtained from their caudal vein. Related serum samples of each group were prepared to detect the biochemical parameters. Recent preparation was accomplished during 15-min centrifugation of blood at 5000 × g, clot separation, and storage at -70°C for further studies.

Rats 'blood samples were taken during four periods:

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

To prevent serum-clot, 15-min centrifugation of blood at 5000× g has been used.

2.7. Evaluation of Oxidant Factors

2.7.1. AGEs

AGEs were assessed by the spectrophotometric method of Kalousova et al [39]. Rats' sera were diluted by a factor of 50 in PBS. Fluorescence intensity at 350nm excitation and 440nm emission was recorded and is expressed as the percentage of fluorescent emission. The volume used to measure AGEs was obtained from the mentioned 50 λ serum.

2.7.2. AOPP

AOPP concentration was determined with spectrophotometric methods (FLUOstar OPTIMA, BMG, Germany) as described by Kalousova et al [39]. In this method, 200 λof serum is diluted by a factor of 5, in phosphate-buffered saline (PBS). Besides, 200 λ of chloramine T (0e100 mmol/l) for calibration and 200 λ of PBS as blank id also added to different microplates. Finally, 10ml of acetic acid and 20ml of 1.16 M Potassium Iodide (KI) is added to preparations. Measurements are done at the absorbance of 340 nm and are expressed in mmol/L.

2.7.3. Ox-LDL

The quantity level of ox-LDL in rat's serum was determined by the ELISA method and the Mercodia kit (Sweden). Mindray ELISA reader apparatus (MR-96A model, Germany) was used to measure related amounts.

3. Statistical Analysis

All measurements were made in triplicate and the average with a standard deviation was used to plot the data. The data were analyzed using Microsoft Excel software version 15.30 for MacOS. Results were expressed as *mean* ± *SD*. We conducted a comparison between all samples and the non-irradiated control group and the accepted statistical significance difference was p-value <0.05. Analysis of variance (ANOVA) was used to evaluate the statistical differences both inter and intragroup.

4. Results

The unit of the oxidants was determined according to fluorescence light. This light was supposed (arbitrary) as 100% for the most fluorescence light during the examination. So, other measurements of the oxidants were performed based on that.

The effect of different irradiation durations on the AGE level is depicted in figure 1. It shows the level of AGE in 6 and 24 hours after different irradiation configurations. The gray solid boxes represent the level of AGE for the diabetic control group and repeated in the horizontal axis to make a better comparison. From figure 1 it appears, that the level of AGE decreased with increasing the irradiation time. At the same time, the level of AGE decreased when the wavelength of the lasers is reduced. As it is shown in figure 1, for each irradiation time group, IR irradiation has the minimum effect on reducing the AGE level and the Blue laser has the greatest effect on it.

Figure 2 represents the effect of different radiations configurations on the level of AOPP measured 6 and 24 hours after irradiation. In this figure, the same as figure 1, gray solid boxes show the level of AOPP for the diabetic control group. As can be seen in this figure, the level of AOPP decreased by the increase of radiation time. Furthermore, the level of AOPP decreases by decreasing wavelength. As it is illustrated in figure 2, IR radiation with the longest wavelength has the smallest effect on the AOPP level and Blue radiation with the shortest wavelength has the greatest effect on the AOPP level.

Figure 3 represents the level of ox-LDL under different radiation configurations, respectively. These measurements also take place within 6 and 24 hours after irradiation. From figure 3 it is seen, that the level of ox-LDL decreased with increased irradiation time. Also, the ox-LDL level is reduced with decreased wavelength.

Error bars in Figures 1, 2, 3 represent standard deviations of the data.

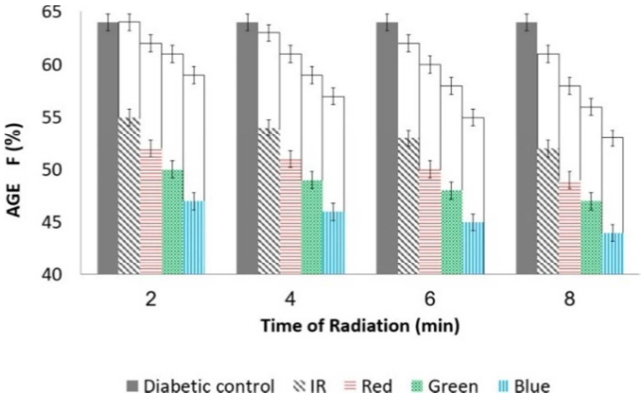

Figure 1. *Level of AGE 6 hours (white boxes) and 24 hours (colored boxes) after irradiation. In this study, an arbitrary unit for AGEs level for non-diabetic control was 23.9% F. In each column three samples of blood were taken from each rat.*

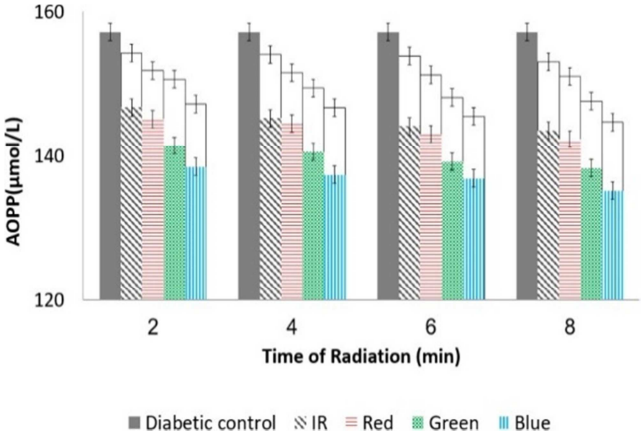

Figure 2. *Level of AOPP 6 hours (white boxes) and 24 hours (colored boxes) after irradiation. In this study, an arbitrary unit for AOPP level for non-diabetic control was 93.3 µmol/L. In each column, three samples of blood were taken from each rat.*

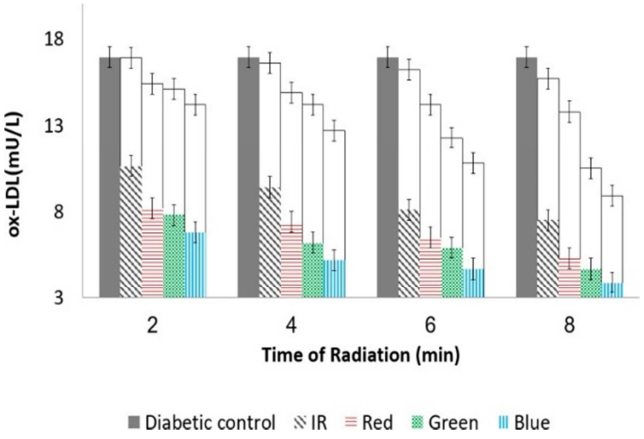

Figure 3. *Level of ox-LDL 6 hours (white boxes) and 24 hours (colored boxes) after irradiation. In this study, an arbitrary unit for ox-LDL level for non-diabetic control was 6.3 mU/L. In each column, three samples of blood were taken from each rat.*

Table 1. *Amount of oxidants parameters after irradiation.*

	AGE	AOPP	Ox-LDL
IR	53±0.84 (-17.18%)	144.2±1.12 (-8.27%)	8.1±0.31 (-52.17%)
Red	50±0.86 (-21.87%)	143.1±1.09 (-8.97%)	6.5±0.29 (-61.62%)
Green	48±0.91 (-25%)	139.2±1.04 (-11.45%)	5.9±0.21 (-65.16%)
Blue	45±1.5 (-29.68%)	(-11.45%)	4.7±0.19 (-72.25%)
Non-diabetic	23.9±1.5	93.28±1.18	4.4±0.13
Diabetic control	64±0.81	157.21±0.95	16.9±0.33

+ Oxidants and their decrease percentage after 24 hours from irradiation, the duration of irradiation is 6 minutes. The second number in each cell represents the percentage of decrease compared to diabetic control.

Table 1, represents the level of different studied oxidant factors after 24 hours of 6 min of irradiation. In this table, the second numbers in each cell represent the percentage of lowering the level of oxidants compared to diabetic control. From table 1 it is clear that for each wavelength, the maximum effect on reducing oxidant parameters is on ox-LDL. As it is shown in table 1 and figure 4, for each irradiation configuration, the most sensitive oxidant is ox-LDL and the least sensitive is AOPP.

No significant changes were observed on oxidants level from blood samples that were taken 2 hours after radiation, these data are not indicated in figures 1 to 3.

5. Discussion

In low-level laser therapy, the plot of laser effect vs laser energy has a Gaussian shape. Such that at very low laser

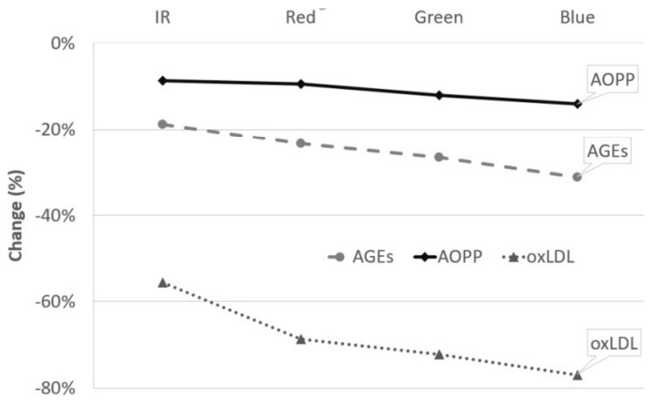

Figure 4. *Change of different oxidants (relative to diabetic control) 24 hours after irradiation for 8 minutes.*

energy no significant effect could be detected. While at very high energy dosage a negative or destructive effect is the

outcome. The best effect is achieved if the laser energy is adjusted somewhere in between.

To select the proper energy dosage for irradiation we choose a wide range of laser power and time of irradiation to make sure it is not under or over-irradiated. If we are on the positive slope of the Gaussian shape curve by increasing the laser energy, its effect is increased. Then we know that we are choosing proper energy dosage.

In this article, we have focused on the laser wavelength effect mostly used in intravascular low-level laser therapy to reduce the oxidant parameters: AGE, AOPP, and ox-LDL.

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

In this research, laser irradiation energy dosage is extremely important. Laser energy is defined in parallel by two equations: Laser energy=Laser Power × Time of irradiation, Laser energy=photon's energy × number of photons.

Where photon's energy is proportional to the inverse of laser wavelength. 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 longer wavelengths.

If we plot the laser effect as a function of laser energy, it is similar to the Gaussian shape curve which has a maximum at certain laser energy. The appropriate energy of laser irradiation could be obtained from the plot of laser effect as a function of laser energy. For example, on Figure 1 AGE level continuously decreases as the radiation time increases from 2 min to 8 min, from figure 1 We can conclude that the laser power is not over-dosage therefore there is no damage to the subjects. At the same time, the difference in the AGE level is getting smaller as the time of radiation is increasing. It shows that we are almost at the top of the Gaussian curve with maximum laser effect and if we increase the time of laser irradiation we may get a negative effect or damage effect from laser irradiation.

The results for different wavelengths are quite important because at constant laser energy for blue laser we have fewer photons than the number we have for red and IR laser. In other words, the photon energy is more important than the number of photons. This could lead us to the conclusion in the glycation process more covalent bonds with higher energy bonds are involved which need higher photon energy to be recovered. However, the responsible mechanism may be related to electron changes between higher photon energy and molecular structure of glycated bio-molecule. We have reported a similar conclusion in an in-vitro study that the activity of pure catalase is elevated more efficiently by shorter wavelengths (λ=450 nm) than longer wavelengths (λ=808nm) [24]. Also, we have observed in intravenous laser irradiation that the most effective wavelength in increasing the activity of LCAT, PON1, and Catalase is in shorter wavelengths such as blue laser ranges [37].

As can be seen in Figures 1 to 3, by increasing the time of radiation, it is indicated that we are getting close to the

maximum of its effect. Therefore, we can conclude that we have chosen the proper laser power and time of radiation. On the other hand, from figure 4 we conclude that laser therapy has the most effect on lowering the ox-LDL level by about 70% and the least effect on lowering AOPP level by about 10% relative to the diabetic control group.

From our data, the laser effect appears more strongly after 24 hours of laser therapy compared to 6 hours after. Immediately after laser irradiation, no effect was obtained and also 2 hours after laser therapy the effect was not much to be reported in this article.

Table 1 shows that oxidant parameters including AGEs, AOPP and ox-LDL due to third (affected by IR irradiation), fourth (affected by red irradiation) and sixth (affected by blue irradiation) groups have been decreased after irradiation and it is neared to the measurements of the non-diabetic group. However, the approach of related changes of blue irradiation to the non- diabetic group was more than the other ones.

We supposed the non-diabetic group as a normal or natural group. Then, we observed that the measure of the 6th group (Blue group) had been neared to non-diabetic or normal group more than other groups. This means that the result of Blue irradiation was closer to the natural level than other groups.

6. Conclusions

In all of our reported data, a decrease in the oxidant level is shown by increasing the time of laser irradiation, so we conclude that irradiation has a positive effect while it has not overdosed.

Moreover, with constant laser irradiation energy, blue laser has the most effect on the reduction of oxidants level and IR laser has the least effect.

Among studied oxidant parameters, the ox-LDL level is reduced the most by LLLT, in diseases such as diabetes or hyperlipidemia that the level of ox-LDL is high, intravenous blue laser therapy can be an excellent treatment.

In conclusion, our experimental data shows that the blue laser with wavelength 450nm has the maximum effect on reducing the level of oxidant factors (AGE, AOPP, and ox-LDL).

This study shows that LLLT can reduce the levels of the oxidants parameters in diabetic rats. This is evidence of the potential of LLLT in reducing the use of pharmaceutical drugs and their side effects and may lead to laser therapy becoming more prominent for treating diabetes.

In some articles, IR and red Lasers are introduced as good candidates for LLLT.

In these cases, the therapy is performed through the skin. For example, for radiating rats' liver. Their results are because of the good penetration depth of longer wavelengths in biological tissue. While in our case Laser Irradiation is performed Intravenously, therefore penetration depth doesn't come into account.

Ethical Approval

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.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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References

[1] S. A. Al-Maweri, B. Kalakonda, N. A. AlAizari, W. A. Al-Soneidar, S. Ashraf, S. Abdulrab, E. S. Al-Mawri, Efficacy of low-level laser therapy in management of recurrent herpes labialis: a systematic review, Lasers in medical science 33 (7) (2018) 1423–1430.

[2] P. R. King, Low level laser therapy: A review, Lasers in Medical Science 4 (3) (1989) 141.

[3] Z. Sharifian, M. Bayat, M. Alidoust, R. M. Farahani, M. Bayat, F. Rezaie, H. Bayat, Histological and gene expression analysis of the effects of pulsed low-level laser therapy on wound healing of streptozotocin-induced diabetic rats, Lasers in medical science 29 (3) (2014) 1227–1235.

[4] S. B. Alinca, E. Saglam, N. O. Kandas, O. Okcu, N. Yilmaz, B. Goncu, M. A. Dogan, Comparison of the efficacy of low-level laser therapy and photodynamic therapy on oral mucositis in rats, Lasers in medical science (2019) 1–9.

[5] D. Atlas, International diabetes federation, IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation.

[6] S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes care 27 (5) (2004) 1047–1053.

[7] E. Ko¸cak, M. Sa˘glam, S. A. Kayı¸s, N. Du¨ndar, L. Kebap¸cılar, B. G. Loos, S. S. Hakkı, Nonsurgical periodon- tal therapy with/without diode laser modulates metabolic control of type 2 diabetics with periodontitis: a randomized clinical trial, Lasers in medical science 31 (2) (2016) 343–353.

[8] H. A. Kahn, R. Hiller, Blindness caused by diabetic retinopathy, American journal of ophthalmology 78 (1) (1974) 58–67.

[9] C. for Disease Control, P. (CDC, et al., Blindness caused by diabetes–massachusetts, 1987-1994., MMWR. Morbidity and mortality weekly report 45 (43) (1996) 937.

[10] L. A. Lavery, D. C. Lavery, T. L. Quebedeax-Farnham, Increased foot pressures after great toe amputation in diabetes, Diabetes Care 18 (11) (1995) 1460–1462.

[11] D. Ziegler, Type 2 diabetes as an inflammatory cardiovascular disorder, Current molecular medicine 5 (3) (2005) 309–322.

[12] P. J. Dyck, J. Karnes, P. O'Brien, P. Thomas, A. Asbury, A. Winegrad, D. Porte, Diabetic neuropathy.

[13] J. L. Gross, M. J. De Azevedo, S. P. Silveiro, L. H. Canani, M. L. Caramori, T. Zelmanovitz, Diabetic nephropathy: diagnosis, prevention, and treatment, Diabetes care 28 (1) (2005) 164–176.

[14] M. E. Molitch, R. A. DeFronzo, M. J. Franz, W. F. Keane, et al., Nephropathy in diabetes, Diabetes care 27 (2004) S79.

[15] S. B. Rabelo, A. B. Villaverde, R. A. Nicolau, M. A. C. Salgado, M. D. S. Melo, M. T. T. Pacheco, Comparison between wound healing in induced diabetic and nondiabetic rats after low-level laser therapy, Photomedicine and Laser Therapy 24 (4) (2006) 474–479.

[16] C. for Disease Control, Prevention, et al., National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the united states, 2011, Atlanta, GA: US department of health and human services, centers for disease control and prevention 201 (1) (2011) 2568–2569.

[17] P. Chatterjee, A. K. Srivastava, D. A. Kumar, A. Chakrawarty, M. A. Khan, A. K. Ambashtha, V. Kumar, L. De Taboada, A. B. Dey, Effect of deep tissue laser therapy treatment on peripheral neuropathic pain in older adults with type 2 diabetes: a pilot randomized clinical trial, BMC geriatrics 19 (1) (2019) 218.

[18] N. Kazemikhoo, A. Sarafnejad, F. Ansari, P. Mehdipour, Modifying effect of intravenous laser therapy on the protein expression of arginase and epidermal growth factor receptor in type 2 diabetic patients, Lasers in medical science 31 (8) (2016) 1537–1545.

[19] R. Obradovi´c, L. Kesi´c, D. Mihailovi´c, S. Anti´c, G. Jovanovi´c, A. Petrovi´c, S. Pe˘sevska, A histological evaluation of a low-level laser therapy as an adjunct to periodontal therapy in patients with diabetes mellitus, Lasers in medical science 28 (1) (2013) 19–24.

[20] U. Asmat, K. Abad, K. Ismail, Diabetes mellitus and oxidative stressa concise review, Saudi Pharmaceutical Journal 24 (5) (2016) 547–553.

[21] A. Maritim, a. Sanders, J. Watkins Iii, Diabetes, oxidative stress, and antioxidants: a review, Journal of biochemical and molecular toxicology 17 (1) (2003) 24–38.

[22] A. Piwowar, M. Knapik-Kordecka, M. Warwas, Aopp and its relations with selected markers of oxidative/antioxidative system in type 2 diabetes mellitus, Diabetes research and clinical practice 77 (2) (2007) 188–192.

[23] D. Bonnefont-Rousselot, Glucose and reactive oxygen species, Current Opinion in Clinical Nutrition & Metabolic Care 5 (5) (2002) 561–568.

[24] J. Kuyvenhoven, A. Meinders, Oxidative stress and diabetes mellitus: pathogenesis of long-term complications, European Journal of Internal Medicine 10 (1) (1999) 9–19.

[25] P. Mart´ın-Galla´n, A. Carrascosa, M. Gussiny´e, C. Dom´ınguez, Biomarkers of diabetes-associated oxidative stress and antioxidant status in young diabetic patients with or without subclinical complications, Free Radical Biology and Medicine 34 (12) (2003) 1563–1574.

[26] P. Dandona, K. Thusu, S. Cook, B. Snyder, J. Makowski, D. Armstrong, T. Nicotera, Oxidative damage to dna in diabetes mellitus, The Lancet 347 (8999) (1996) 444–445.

[27] Z. Zheng, Y. Zeng, X. Zhu, Y. Tan, Y. Li, Q. Li, G. Yi, Apom-s1p modulates ox-ldl-induced inflammation through the pi3k/akt signaling pathway in huvecs, Inflammation (2018) 1–12.

[28] S. Parthasarathy, A. Raghavamenon, M. O. Garelnabi, N. Santanam, Oxidized low-density lipoprotein, in: Free Radicals and Antioxidant Protocols, Springer, 2010, pp. 403–417.

[29] S.-F. Li, Y.-W. Hu, J.-Y. Zhao, X. Ma, S.-G. Wu, J.-B. Lu, Y.-R. Hu, Y.-C. Wang, J.-J. Gao, Y.-H. Sha, et al., Ox-ldl upregulates crp expression through the igf2 pathway in thp-1 macrophages, Inflammation 38 (2) (2015) 576–583.

[30] M. F. Lopes-Virella, G. Virella, T. J. Orchard, S. Koskinen, R. W. Evans, D. J. Becker, K. Y.-Z. Forrest, Antibodies to oxidized ldl and ldl-containing immune complexes as risk factors for coronary artery disease in diabetes mellitus, Clinical Immunology 90 (2) (1999) 165–172.

[31] R. Singh, A. Barden, T. Mori, L. Beilin, Advanced glycation end-products: a review, Diabetologia 44 (2) (2001) 129–146.

[32] V. Jaku˘s, N. Rietbrock, Advanced glycation end-products and the progress of diabetic vascular complications, Physiological research 53 (2) (2004) 131–142.

[33] M. Chang, B. Zhang, Y. Tian, M. Hu, G. Zhang, Z. Di, X. Wang, Z. Liu, N. Gu, Y. Liu, Ages decreased sirt3 expression and sirt3 activation protected ages-induced epcs dysfunction and strengthened anti-oxidant capacity, Inflammation 40 (2) (2017) 473–485.

[34] L. C. de Vos, J. D. Lefrandt, R. P. Dullaart, C. J. Zeebregts, A. J. Smit, Advanced glycation end products: An emerging biomarker for adverse outcome in patients with peripheral artery disease, Atherosclerosis 254 (2016) 291–299.

[35] A. Piwowar, Advanced oxidation protein products. part i. mechanism of the formation, characteristics and property, Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego 28 (164) (2010) 166–169.

[36] G. V. Bochi, V. D. Torbitz, L. P. Cargnin, J. A. M. de Carvalho, P. Gomes, R. N. Moresco, An alternative pathway through the fenton reaction for the formation of advanced oxidation protein products, a new class of inflammatory mediators, Inflammation 37 (2) (2014) 512–521.

[37] H. Mirmiranpour, F. S. Nosrati, S. O. Sobhani, S. Nazifi Takantape, A. Amjadi, Effect of low level laser irradiation on the function of glycated catalase, Journal of Lasers in Medical Sciences 9 (3) (2018) 212–218.

[38] A. Amjadi, H. Mirmiranpour, S. O. Sobhani, N. Moazami Goudarzi, Intravenous laser wavelength radiation effect on lcat, pon1, catalase, and frap in diabetic rats, Lasers Med Sci (2019) https://doi.org/10.1007/s10103-019-02805-5

[39] M. Kalousova, J. Skrha, T. Zima, et al., Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus, Physiological research 51 (6) (2002) 597–604.

[40] Purifine, Aké-Tano Sassor Odile, et al. "Macroangiopathy and Associated Factors in Outpatients with Type 2 Diabetes Attending the Antidiabetic Center of Abidjan in Ivory Coast." *Science Journal of Public Health* 5.4 (2017): 347.

[41] Ma, Wuren, et al. "Complicated Effect of He-Ne Laser Therapy on Pro-/Anti-Inflammatory Cytokines from Serum in Rats." *Animal and Veterinary Sciences* 6.5 (2018): 88.

[42] Moroianu, Lavinia Alexandra, et al. "Depression in Patients with Diabetes."

[43] Papadopoulou, L., and F. Papoulia. "Depression and quality of life in patients with diabetes." *American Journal of Nursing Science* 4.2 (2015): 88.

[44] Myint, Aye Aye, Kyaw Soe Win, and Zaw Aung. "Alzheimer's disease and type 2 diabetes mellitus: Risk factors and effectiveness of antidiabetic agents in treatment of Alzheimer's disease." *SJCM* 2.3 (2013): 114.