



Effects of quercetin and low-level laser on oxidative and inflammatory factors among patients with type 2 diabetes mellitus and mild cognitive impairment

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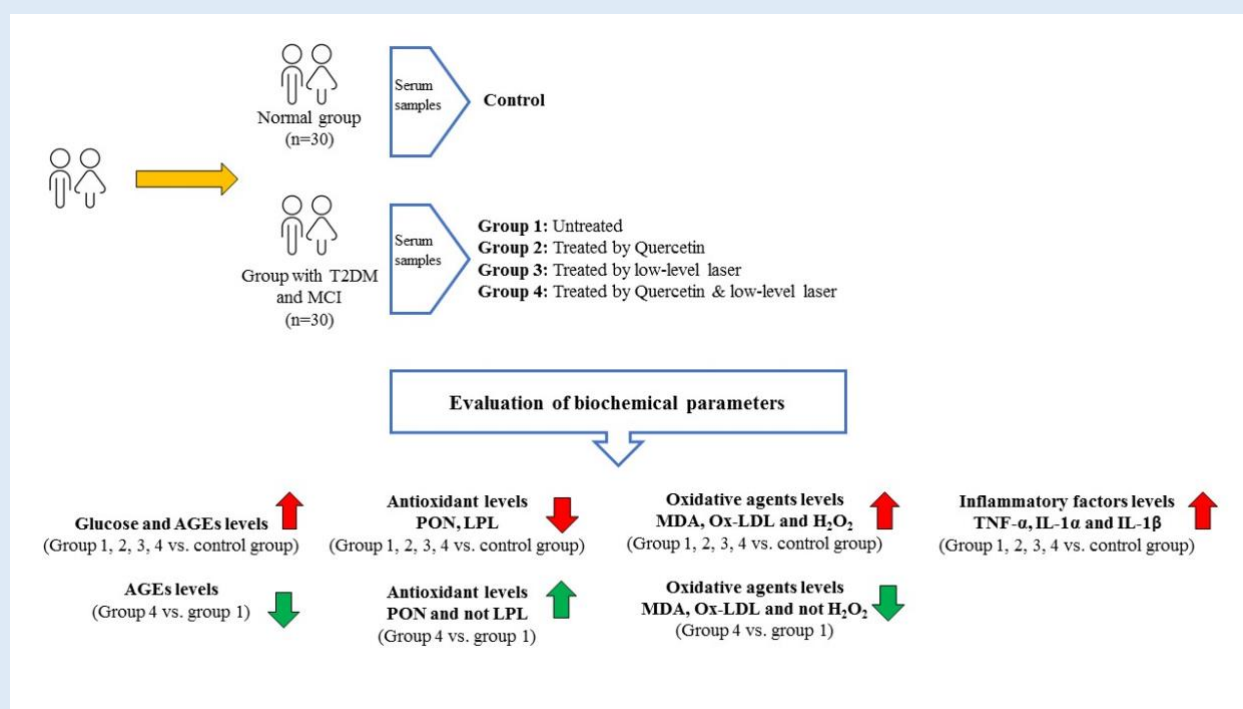
ABSTRACT

Background: Unmanaged type 2 diabetes mellitus has dangerous consequences, such as neuropathy. Oxidative stress and inflammatory factors play an important role in the development of diabetic neuropathy. Diabetics are prone to mild cognitive impairment, which is a neurological disease. The aim of this study was to investigate the effects of quercetin as a functional food and oxidative agents and inflammatory factors of low-level laser.

Methods: In this study, 60 elderly volunteers were selected: 30 normal as a control group and 30 with type 2 diabetes mellitus and mild cognitive impairment. The average age was 75 years old. Groups of diabetic patients were examined for changes in glucose levels, oxidants, antioxidants and inflammatory factors before and after treatment with quercetin and low-level laser therapy—green laser diode with a wavelength of 532 nm at 100 mw and compared with the control group. Changes in the levels of biochemical parameters were performed according to the instructions of the relevant kits.

Results: The results of the obtained data analysis showed that there was a significant difference (P value < 0.05) in the levels of glucose, hydrogen peroxide, advanced glycation end-products, malondialdehyde, oxidized-low density lipoprotein, paraoxonase, lipoprotein lipase, and inflammatory factors including TNF- α , interleukin-1 alpha and interleukin-1 beta between diabetic samples before and after treatment with quercetin and laser from control subject samples. There was no significant difference (P value > 0.05) in inflammatory factors between quercetin-treated, laser-treated and both quercetin and laser treated groups. The synergistic effect of quercetin and laser between the quercetin and laser treated group and the untreated group on changes in the levels of biochemical parameters was observed significantly only in advanced glycation end-products, malondialdehyde, oxidized-low density lipoprotein, and paraoxonase.

Conclusion: The results showed that quercetin, laser, and their synergistic effect can play a role in reducing some oxidant factors.



Keywords: Quercetin, Low-level laser, Inflammatory factors, Oxidative factors, Diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is one of the most important chronic metabolic disorders that is increasing rapidly in human societies in recent decades [1]. Today, this disease related to carbohydrate metabolism is divided into two main groups: type 1 diabetes mellitus (T1DM) and type 2

diabetes mellitus (T2DM). T1DM is a complex autoimmune disease caused by the rapid and permanent degradation of insulin of beta cells in the pancreas [2-3]. T2DM is characterized by a relative lack of insulin caused by dysfunction of beta cells in the pancreas and insulin resistance in target organs [4]. The prevalence of T2DM

is much higher than T1DM and it is projected to increase to 700 million by 2045 [5]. Problems such as neuropathy can occur if DM is not controlled and managed. One of the neurological consequences of uncontrolled DM, especially in the elderly, is mild cognitive impairment (MCI) that may lead to Alzheimer's disease [6]. It has been shown that oxidative stress, reactive oxygen species [7], and various inflammatory cytokines are involved in the pathogenesis of type 1 and type 2 diabetes and its consequences, such as neuropathy, due to uncontrolled diabetes [8, 9]. Tumor necrosis factor- α (TNF- α) is one of the most important pro-inflammatory mediators that is involved in insulin resistance and T2DM pathogenesis [10]. In uncontrolled DM, the formation of advanced glycation end products (AGEs) and oxidative stress are interrelated. Increased AGEs may lead to oxidative stress and vice versa; ROS may facilitate the formation of AGEs [11]. Another destructive effect of ROS is the activation of stable aldehydes, such as malondialdehyde (MDA) active aldehydes, which damage cell membranes [12-13]. MDA is a biomarker of lipid damage mediated by free radicals and oxidative stress [14].

Antioxidants can reduce or inhibit molecular oxidation. Proper diet as a source of antioxidants is especially important in maintaining good health. Today, experimental studies have shown that plants with antioxidant activity are effective in treating and preventing the complications of diabetes [15]. One of these antioxidants is quercetin (Figure 1). Quercetin is an important flavonol among flavonoids. Its name has been used since 1857 [16]. Quercetin is found in fruits, vegetables, nuts, seeds and wines [17]. In general, flavonoid antioxidants such as quercetin reduce the damaging effects of free radicals. In this way, they are involved in the prevention and control of diseases such as DM, high blood pressure and neurological diseases [17].

Studies have reported that quercetin may play a role in controlling and improving DM and its consequences [18-20] by reducing oxidative stress, as evidenced by lower MDA levels [21].

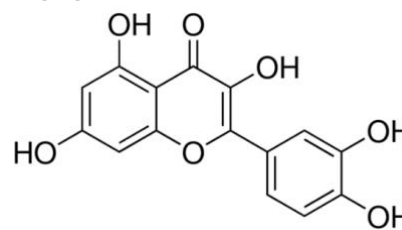


Figure 1. Chemical structure of quercetin

Today, low-level laser therapy (LLLT) is being widely used in medical studies. This treatment can reduce the inflammatory process by acting on inflammatory markers, tumor necrosis factor alpha (TNF- α) and interleukin-1 beta (IL-1 β) [22]. The role of antioxidant enzymes in counteracting oxidative damage in DM is very important. Paraoxonase (PON) is an important plasma antioxidant enzyme that protects lipoproteins from oxidative damage. Low levels of serum paraoxonase are associated with an increased risk of cardiovascular consequences of T2DM [23-24]. Lipoprotein lipase (LPL) is involved in lipid metabolism. Decreased activity of this enzyme is associated with DM [25]. Studies have also reported that LLLT can reduce oxidative stress by modulating ROS [26] and increasing the activity of antioxidant enzymes such as PON [27]. In this study, we aimed to investigate the synergistic effects of quercetin and LLLT on oxidative stress and inflammatory factors in patients with T2DM and MCI.

MATERIALS AND METHODS

Materials: Quercetin was purchased from sigma (PHR 1488). The enzyme-linked immunosorbent assay (ELISA) kit to assay human glucose levels (with an intra- and inter-assay CV < 8% and < 10%, respectively) was purchased from MyBioSource Inc. (San Diego, USA). The hydrogen peroxide (H₂O₂) assay kit was purchased from ZellBio (ZellBio GmbH, Ulm, Germany) for the measurement of H₂O₂ levels. The colorimetric method

was used to study changes in paraoxonase (PON), lipoprotein lipase (LPL), and MDA levels. The MDA assay kit was procured from Cayman chemical company (Cayman Chemical, 1180 East Ellsworth Road, Ann Arbor, Michigan 48108 USA).

Additionally, AGEs parameters were evaluated by the method of Kalousova et al [28]. The concentration of oxidized-low density lipoprotein (Ox-LDL) was determined by the kit purchased from Mercodia Company (Uppsala, Sweden). Ox-LDL levels were measured by ELISA method. In the current study, the concentration of inflammatory factors, such as interleukin-1 alpha (IL-1 α), IL-1 β , and TNF- α , was studied using the ELISA method. Test kits for IL-1 α and IL-1 β were purchased from Diaclone (25020 Besancon cedex, France). The TNF- α analytical kit was procured from R&D Systems, Inc. (614 McKinley Place NE Minneapolis, MN 55413).

Methods

Participants: In this study, 30 healthy people as a control group and 30 patients with T2DM and MCI were selected from among the persons referred to Vali-Asr medical laboratory in Tehran, Iran. Concurring to the World Health Organization (WHO) criteria, individuals with fasting plasma glucose \geq 126 mg/dL or glycated hemoglobin (HbA1c) \geq 6.5% were considered as diagnosed T2DM. Individuals with T2DM co-morbid with cardiovascular illness were prohibited from consideration. Informed consent was obtained from all patients.

The sample of diabetic patients was divided into four groups.

Group 1: Samples of diabetics before treatment with quercetin or laser (Diabetic).

Group 2: Samples of diabetics after treatment with quercetin (Diabetic + Quercetin).

Group 3: Samples from diabetic patients after laser treatment. The laser was irradiated on the serum samples of these people. (Diabetic + Laser).

Group 4: Diabetic patients treated with both quercetin and laser irradiation (Diabetic + Quercetin + Laser).

After determining the control and diabetic groups and dividing the samples of the diabetic groups into four groups, blood samples were taken from all control and diabetic groups. The biochemical variables depicted above were measured in control and diabetics before untreated with quercetin and laser irradiation (as group 1). The serum sample separated from diabetic subjects was irradiated with laser before using quercetin and then the mentioned biochemical parameters in their serum sample were examined (as group 3). At that point, the same patients were treated with quercetin (at a dose of 75 mg per day) for two weeks [29]. After two weeks, a blood test was taken from them. Once more, biochemical variables were measured before laser irradiation (as group 2) and after laser irradiation (as group 4). During treatment with quercetin, the patient group received their main drugs, including memantine.

General Features and Sampling: The age, sex, weight, height, and body mass index (BMI) of all study patients were recorded. Blood samples were taken from all patients after 12 hours of nighttime fasting. After collecting the blood sample, they were centrifuged (250 g for 10 min); following this, the serum was separated from the centrifuged samples. Isolated serum samples were used to assess the biochemical endpoints and antioxidant enzymes described earlier.

Laser Irradiation: The samples were irradiated with a low-level green laser pointer diode with a wavelength of 532 nm at 100 mw in continuous mode with divergence $<$ 1.5 mRad, beam mode (TEM₀₀), aperture beam diameter \sim 1.5, crystal type Nd:VYO4:KTP and power supply 1 \times 3V CR2 alkaline batteries. The laser power density was 509.55 mW/cm² at a distance of 6.5 cm between the laser device and the serum in the tube; the diameter of the laser spot was fixed to 0.5 cm. As in our previous study, the irradiation was applied for 8 seconds.

Green diode pumped solid state (DPSS) Laser Pointer (model RLP-532, 1040 Vienna, Austria) was used for LLLT [30].

Statistical Analysis: Statistical analysis was done by SPSS (version 23, IBM, USA) software for Windows. All results were expressed as mean \pm standard deviation (SD). Independent-sample T-test was used to compare the mean of general characteristics of the participants. Statistical significance was analyzed by one-way ANOVA to compare the mean of the obtained data. After the one-way ANOVA test, Tukey post hoc was used. The Kolmogorov-Smirnov test was used to analyze the normal

distribution of data. P-values $<$ 0.05 were considered significant.

RESULTS

General Features: The age of contributing volunteers was between 65 and 80 years old. In control group, 50% were male (n = 15) and 50% were female (n = 15). In the group of people with T2DM (diabetic group), 50% were female (n = 15) and 50% were male (n = 15). The results for the general features of control and diabetic groups are given in Table 1. As shown in Table 1, the height, weight, and BMI of control individuals were compared with those of diabetics. There was no statistically significant difference in the comparison of general features between control and diabetic groups.

Table 1. Anthropometric data

Feature	Control Sample (n=30)	Diabetic Sample (n=30)	P value
Height (Cm)	165.8 \pm 6.4	167.9 \pm 6.2	0.20
Weight (Kg)	85.2 \pm 5.4	85.8 \pm 4.7	0.69
BMI (Kg/m ²)	31.1 \pm 3.2	30.6 \pm 2.9	0.46

Data are given as mean \pm SD. p $<$ 0.05 is significant.

Biochemical Parameters: We also evaluated some important biomedical parameters in serum samples from the control group and diabetics group. These biochemical variables included blood glucose, antioxidant enzymes (PON, and LPL), an oxidizing agent (H₂O₂), and inflammatory agents (IL-1 α , IL-1 β , and TNF- α). Changes in the concentration of biochemical variables were investigated in the serum samples of the control group and the serum samples of subjects with type 2 DM in groups 1, 2, 3, and 4. An assessment of the results of inflammatory factors (IL-1 α , IL-1 β , and TNF- α) between the control group and the four diabetic groups is presented in Figure 2 and Figure 3. A comparison of the consequences of other biochemical variables such as glucose, H₂O₂, antioxidant parameters (LPL, and PON), and AGE, MDA, and ox-LDL. is shown in Table 2. There was a statistically significant difference (P value $<$ 0.05) in the results of groups 1 to 4 compared to the control

group. As shown in Figures 1 and 2, the results of the level of inflammatory factor in diabetic patients treated with quercetin (as a functional food) as well as treated serum samples of these patients with laser did not show a significant difference compared to the untreated diabetic group.

Biochemical parameter levels were assessed between the groups of patients with type 2 DM under untreated conditions, treatment with quercetin, treatment with laser irradiation and treatment with quercetin and laser irradiation. To evaluate the effect of laser versus the effect of quercetin, as well as the effect of both laser and quercetin on the biochemical parameters, a comparison of the results was done between the groups. Multiple comparisons were made by Tukey HSD Post Hoc test (Table 3). Statistically, there was no significant difference in reduction of inflammatory factors in comparison between the groups

(Figure 2 and Figure 3). A significant difference was detected in the comparison of AGEs, MDA, and Ox-LDL in

the group treated with both quercetin and laser irradiation, compared to the untreated diabetic group.

Table 2. Comparison between the levels of biochemical parameters of the control group (non-diabetics) with the four groups of diabetics.

Groups	Control	Group 1	Group 2	Group 3	Group 4	P value
Biochemical parameters						
PON (U/ml)	180.2±6.9	103.2±4.9	106.4±7.9	107.8±5.4	108.2±4.9	< 0.001
LPL (pg/ml)	1386.5±45.9	867.5±45.9	869.5±45.9	871.9±41.1	872.9±43.6	< 0.001
Glc (µg/ml)	219.5±20.2	387.9±22.5	385.4±19.8	384.4±19.9	382.9±22.5	< 0.001
H ₂ O ₂ (µM/ml)	242.6±18.6	350.3±25.5	340.3±25.5	337.9±15.1	335.3±25.5	< 0.001
AGEs (AU)	39.1±5.1	83.1±5.9	73.0±5.9	72.4±6.7	70.6±5.9	< 0.001
MDA (µM/ml)	2.2±0.1	3.0±0.2	2.9±0.2	2.8±0.2	2.8±0.2	< 0.001
Ox-LDL (mU/l)	10.6±0.8	18.5±1.2	14.3±0.8	13.9±0.6	12.8±0.9	< 0.001

Data are given as mean ± SD. Control: non-diabetic, not treated. Group 1: Diabetic Untreated. Group 2: Diabetic + Quercetin. Group 3: Diabetic + Laser. Group 4: Diabetic + Quercetin + Laser. PON, paraoxonase; LPL, lipoprotein lipase; IL-1α, Interleukin 1 alpha; IL-1β, Interleukin 1 beta; and TNF-α, tumor necrosis factor alpha; Glc, glucose; AGEs, advanced glycation end products; MDA, malondialdehyde; Ox-LDL, oxidized low-density lipoprotein.

Table 3. Multiple comparisons between the levels of biochemical parameters between the diabetic groups

Biochemical parameters		PON (U/ml)	LPL (pg/ml)	Glc (µg/ml)	H ₂ O ₂ (µM/ml)	AGEs (AU)	MDA (µM/ml)	Ox-LDL (mU/l)
Group 1	Group 2	0.06	0.86	0.65	0.17	< 0.0001	0.002	< 0.0001
	Group 3	< 0.0001	0.71	0.58	0.02	< 0.0001	< 0.0001	< 0.0001
	Group 4	0.001	0.66	0.38	0.03	< 0.0001	< 0.0001	< 0.0001
Group 2	Group 1	0.06	0.86	0.65	0.17	< 0.0001	0.002	< 0.0001
	Group 3	0.40	0.85	0.84	0.64	0.68	0.75	0.07
	Group 4	0.33	0.76	0.63	0.39	0.09	0.35	< 0.0001
Group 3	Group 1	< 0.0001	0.71	0.58	0.02	< 0.0001	< 0.0001	< 0.0001
	Group 2	0.40	0.85	0.84	0.64	0.68	0.75	0.07
	Group 4	0.74	0.92	0.80	0.65	0.33	0.55	< 0.0001
Group 4	Group 1	0.001	0.66	0.38	0.03	< 0.0001	< 0.0001	< 0.0001
	Group 2	0.33	0.76	0.63	0.39	0.09	0.35	< 0.0001
	Group 3	0.74	0.92	0.80	0.65	0.33	0.55	< 0.0001
					P value			

P value < 0.05 is significant. Group1: Diabetic Untreated. Group 2: Diabetic + Quercetin. Group 3: Diabetic + Laser. Group 4: Diabetic + Quercetin + Laser. PON, paraoxonase; LPL, lipoprotein lipase; Glc, glucose; AGEs, advanced glycation end products; MDA, malondialdehyde; Ox-LDL, oxidized low-density lipoprotein.

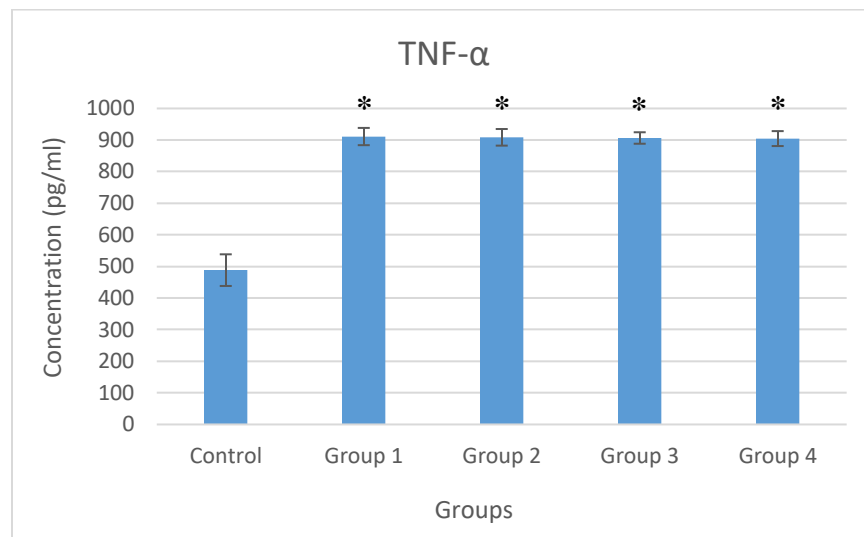


Figure 2. Changes in TNF- α levels in the control group and diabetic samples in different conditions. * $p < 0.05$ vs. Control. Group 1: Diabetic Untreated. Group 2: Diabetic + Quercetin. Group 3: Diabetic + Laser. Group 4: Diabetic + Quercetin + Laser.

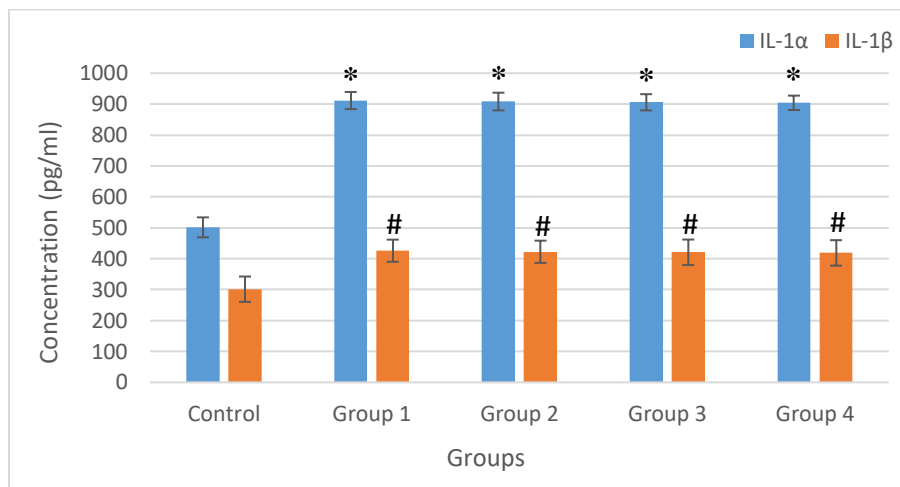


Figure 3. Changes in IL-1 α and IL-1 β levels in the control and diabetic groups (in different conditions). * and # $p < 0.05$ vs. Control. Group 1: Diabetic Untreated. Group 2: Diabetic + Quercetin. Group 3: Diabetic + Laser. Group 4: Diabetic + Quercetin + Laser.

DISCUSSION

In this study, we evaluated the effect of functional food and physical method on diabetes. For this purpose, we used quercetin and a low-level laser on samples of diabetics. According to the results of Table 2 and Figures 2 and 3, a significant difference was observed between the measured parameters between the diabetic group and the control group. This significant difference was also observed in the treated diabetic groups compared to the control group. The results showed that treatment of the samples with quercetin or laser irradiation can decrease oxidative stress and inflammation parameters. Also, the

obtained data revealed that the use of quercetin or laser irradiation leads to a synergistic effect.

There are several studies which show laser irradiation can modify protein structures and change their activities. Simoes et al. evaluated protein concentration and enzymatic activities by irradiating parotid and submandibular glands using an infrared diode laser [31]. They reported that peroxidase and catalase activities of rat submandibular and parotid glands irradiated with 4 J/cm² and 8 J/cm² was increased. However, the activity of lactate dehydrogenase (LDH) and amylase were decreased. In another study, Silva and

Potrich irradiated amylase with GaAlAs laser at different doses. They stated that enzymes have an optimal laser range (dose) at which their activity is maximized, while with increase or decrease of laser dose, activity decreases. Also, they expressed the effect of pH and temperature induced by laser irradiation must be considered for the proper choosing of the optimum dosage on modulation of enzymatic activity [32]. Overall, the increase of PON and LPL activities may be due to modification of their structure with laser irradiation.

Moreover, the use of laser irradiation on diabetic samples resulted in a decrease in H_2O_2 content and oxidation by-products including MDA and ox-LDL. Based on our previous studies, the laser treatment could modify glycosylated protein enzymes (such as superoxide dismutase, catalase and glutathione peroxidase), recover their enzymatic activity, and thereby, improve the antioxidant defense system [33]. Also, there are different studies that confirm the decrease of oxidative stress through the improvement of antioxidant activities by irradiation of different type-lasers [34-35]. Another possible mechanism can be the photo modulation of mitochondrial activity and ROS production [36]. Amaroli et al. evaluated the interaction of a 980 nm diode laser light and mitochondrial activity. They reported an inhibitory effect at low power, no effect at intermediate power, an increase of ATP production at high power, and recovery of the ATP synthesis to the control level at higher power [37].

Based on the results, the inflammatory parameters decrease after laser therapy. Rezaeinezhad et al. in several studies demonstrated that inflammation can be reduced following a decrease in oxidative stress [38-39].

Quercetin, as a plant ingredient, is possibly the flavonoid with the strongest antioxidant and anti-inflammatory activities [20, 40-44]. So, the decrease of oxidative stress and inflammation as the results of using quercetin is a logical result. In this study, we evaluated the effect of laser and quercetin on diabetics' samples.

The results showed that they can have synergistic effects such that inflammation and oxidative stress in the group which received both laser and quercetin therapies are more decreased than other groups which receive laser and quercetin separately. Ahmed et al. studied the effect of quercetin and low-level laser therapy on wound healing in diabetic rats [45]. They found that the use of laser and quercetin therapy led to a larger production of insulin and a larger decrease in the secretion of pro-inflammatory cytokines than in rats that received only laser irradiation or only quercetin treatment. These observations are in line with our results. In a study by Bhuiyan et al., [46] the effect of quercetin on AGEs formation was studied. They reported that quercetin could play a role in reducing the formation of AGEs as well as ROS by chelating metal ions. In this case, our results agree with the study of Bhuiyan et al. Studies have shown that quercetin can inhibit the formation of ox-LDL through a variety of pathways as well as by regulating the expression of various genes [47-48]. In our study, a significant decrease in ox-LDL levels was observed in the treated groups with quercetin and LLL, but the effect of quercetin in reducing the levels of inflammatory factors was not significant. Zhao et al. [49] showed that quercetin significantly reduced the expression of TNF- α and IL-1 β . They also stated that quercetin do not decrease blood glucose levels in a diabetic rat model.

CONCLUSION

According to our results, laser therapy is effective to decrease oxidative stress induced by diabetes. Also, quercetin as an antioxidant and anti-inflammatory agent likely had a significant role in decreasing biomarkers of oxidative stress. Moreover, the results showed that the use of laser and quercetin simultaneously could have synergistic effects.

List of Abbreviations: DM: diabetes mellitus, T1DM: type 1 diabetes mellitus, T2DM, type 2 diabetes mellitus, MCI: mild cognitive impairment, AGEs: advanced glycation end-products, MDA: malondialdehyde, LLLT: low-level laser therapy, ELISA: enzyme-linked immunosorbent assay, H₂O₂: hydrogen peroxide, Ox-LDL: oxidized-low density lipoprotein, IL-1 α : interleukin-1 alpha, IL-1 β : interleukin-1 beta, TNF- α : tumor necrosis factor alpha, PON: paraoxonase, LPL: lipoprotein lipase, WHO: world health organization, HbA1c: glycated hemoglobin, BMI: body mass index, DPSS: diode pumped solid state, LDH: lactate dehydrogenase, ATP: adenosine triphosphate.

Author's contributions: DM was involved in the planning of the study and the article final editing. MRA participated in the writing. SA and AR assisted in low-level laser therapy and doing experimental work. FJ and SP contributed to data collection and analysis of the results. ASM participated in the abstract writing. HM recruited the patients and supervised the project. All authors read and approved the final version before its submission.

Conflict of interest: The authors declare that there is no conflict of interest.

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