REVIEW ARTICLE

Low-level Laser Therapy and Changes in Salivary Proinflammatory Cytokines: A Systematic Review

Fatemeh Baljani[1], DMD Student; Habib Khoshvaghti[2], PhD Student; Fatemeh Tavakoli[3], Graduate Student; Vahid Fakhrzadeh[4], DMD ; Hosein Eslami[5], DMD

[1]Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Histology and Embryology, Medical Faculty, Zonguldak Bülent Ecevit University, Zonguldak, Turkey
[3]Oral and Maxillofacial Disease Department, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Prosthodontics, School of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Oral and Maxillofacial Medicine Department, School of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence:
Hosein Eslami, MD;
Oral and Maxillofacial Medicine Department, School of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
Tel: +98 41 33355965
Email: eslamihosein56@yahoo.com
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Abstract

Background: The effect of laser on reducing inflammation has always been considered. The aim of this study was to evaluate the clinical studies on the effect of using low-power lasers on the production and activity of proinflammatory cytokines such as IL-1, IL-6, and TNF-α.

Methods: This study is a systematic review of Google Scholar, PubMed, and SCOPUS database articles which was conducted from 1990 to 2021. All information was categorized in a table.

Results: In the review conducted in the mentioned databases and according to the considered time period, 239 articles related to the searched terms were found through the abstract. After removing duplicate titles and articles, 31 articles were selected and a more detailed review by the evaluation team yielded 16 articles. The full texts of these 16 articles were reviewed. For the final selection, 13 articles met the inclusion criteria and included the objectives of the present study.

Conclusion: Understanding the true mechanisms of low-level laser therapy (possible photochemical, photomechanical, and photobiological changes) and examining the relationship between cellular effects and changes in cytokines and clinical phenomena require numerous controlled clinical trials to develop an effective treatment protocol.

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Keywords: Low-level laser therapy, IL-6, IL-1, TNF-α

Introduction

Low-level laser therapy (LLLT) is applied as a technique in dentistry by many dentists. Stimulating the healing process and relieving pain are among its most popular applications.[1] Many studies have revealed no significant difference between anti-inflammatory effects of LLLT and nonsteroidal anti-inflammatory drugs (NSAIDs); however, anti-inflammatory impacts of LLLT were slightly less than those of glucocorticoid steroids.[2, 3] Immune cells are widely active throughout the body. These cells and their products are present at the site of infection when it occurs in a specific part of the body. Inflammation refers to the process, during which these results are obtained. Inflammation in the acute phase is characterized by increased blood flow and vascular permeability along with accumulation of fluids, leukocytes, and inflammatory mediators such as cytokines.[4]

Cytokines are soluble hormone-like proteins that enable communication between the cells and extracellular space. Although cytokines are produced by many cell populations, their main producers are T helper cells (Th) and macrophages.[5] They are released by one cell and act on another cell, thereby altering the function of their target cells.[6, 7] In general, there is a dynamic and variable balance between proinflammatory cytokines and anti-inflammatory compounds of the immune system in two ways.[8] Any change in this balance can put negative effects on the individual, so that if the balance shifts to pro-inflammatory cytokines, it can lead to

autoinflammatory diseases and tissue injury; however, if the balance shifts to anti-inflammatory compounds and cytokines, it puts the person at risk of systemic contamination.[9-11]

Many studies conducted on the effect of laser therapy on reducing inflammation have reported the reduction of inflammatory cells and, subsequently, inflammatory phase duration.[7, 12, 13] Bayat et al. found that laser therapy with gallium aluminum arsenide (GaAlAs) laser reduced the number of monocytes as well as inflammation in the early stages of repair.[14]

In one study, 30 patients were randomly divided into two groups of control and LLLT. The results showed LLLT was effective in reducing the severity of chemotherapy-induced oral mucositis (OM), decreasing inflammation, and accelerating repair. Also, IL-6 concentration was lower in the laser group than the control.[15] In another study, 40 individuals were voluntarily selected for diagnosis and treatment of BMS. After 4 weeks of LLLT, TNF-α and IL-6 levels were measured by ELISA. The results indicated a significant reduction in salivary proinflammatory cytokines.[16]

Although various studies have been conducted on using LLLT for wound healing and its anti-inflammatory effect, dispersion of information makes users confused. Therefore, the present study aimed to provide an overview of the effect of using laser on changes in proinflammatory cytokines and review the clinical studies on the impact of applying low-level lasers on the production and activity of proinflammatory cytokines such as IL-1, IL-6, and TNF-α.

Methods

To have a comprehensive review, we investigated the studies on the effect of LLLT and changes in salivary proinflammatory cytokines. Figure 1 displays PRISMA flow diagram. The relevant papers published from 1990 to 2021 in Google Scholar, PubMed, Scopus, Cochrane Library, PsycINFO, CINAHL, Medline, ProQuest, Web of Science, and other reputable databases were searched. Also, Magiran, IranDoc, SID, and IranMedex databases

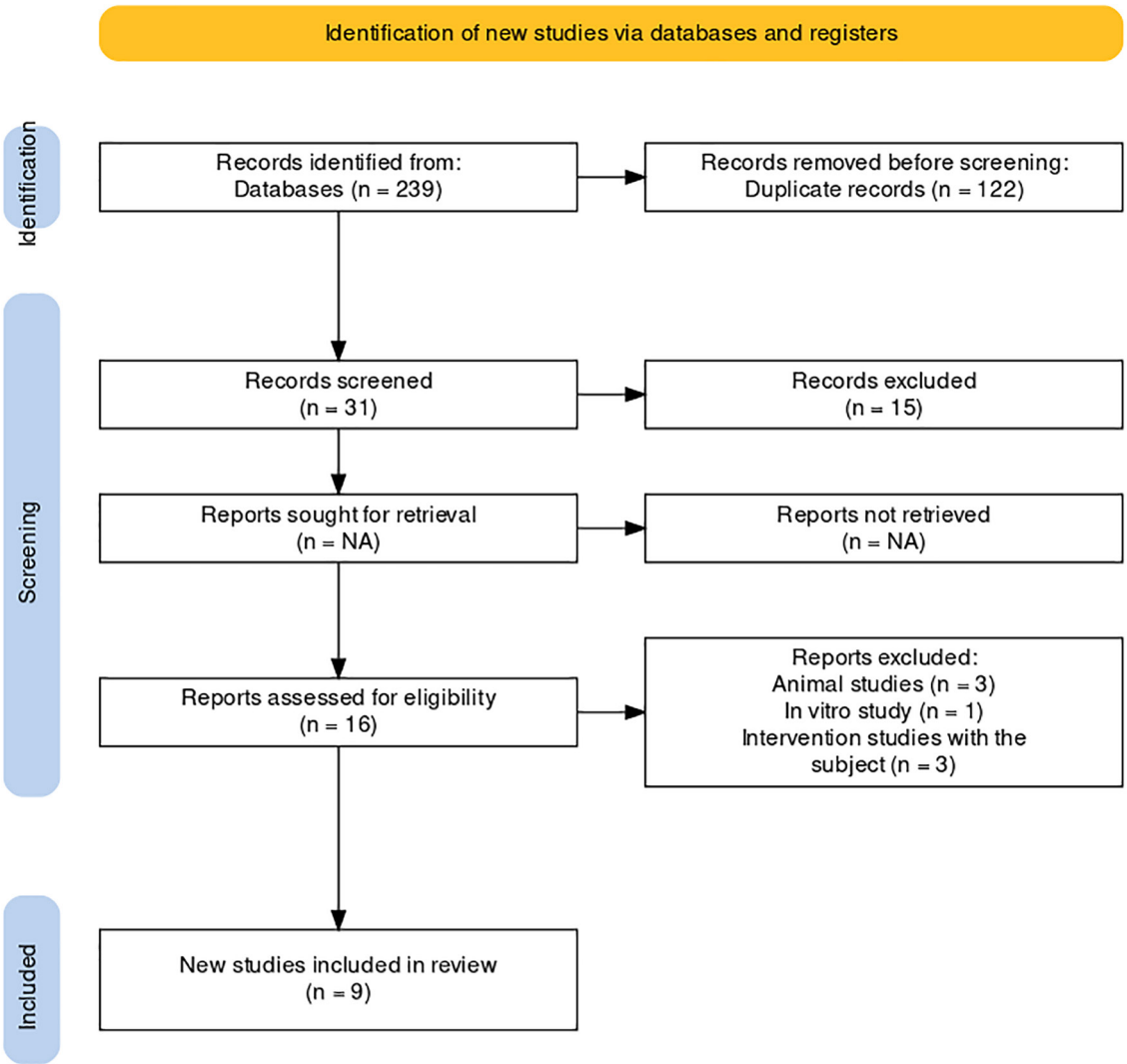

Figure 1: PRISMA flow process

were searched for retrieving the Persian papers. Papers were selected by reviewing their titles, abstracts, and bibliographies. The keywords employed to search for papers were selected by PICO method.
P: Burning mouth syndrome, lichen planus, mucositis
I: Low-level laser
C: Before
O: Changes in cytokines) TNF-a, IL-6, and IL-1ß (

The keywords used to search for the relevant papers were tumor necrosis factor-α, interleukin (IL)-6, interleukin (IL)-1, saliva, cytokine, interleukin, low-level laser, laser therapy, anti-inflammatory treatments, wound healing, burning mouth syndrome (BMS), lichen planus, and mucositis.

Inclusion criteria were papers published from 1990 to 2021, original English and Persian papers with explicit methodology relevant to the research subject, and in vitro and in vivo clinical trials. Exclusion criteria were review articles, case reports, letters, questionnaires, and papers with poor quality.

Titles of all papers were first examined and those that were not consistent with the objectives of our study were excluded. Then, abstracts and full texts of papers were reviewed, respectively, in order to exclude those studies that did not meet the exclusion criteria and had poor relevance to the objectives of the study. Then, the selected studies were evaluated by two independent evaluators using the STROBE and the JBI (Joanna Briggs Institute) checklist for bias risk, and the differences between the two evaluators were referred to a third party. The selected papers were assessed by two individuals in terms of the risk of bias using STROBE checklist. In the case of disagreement between the two assessors, it was referred to the third party. After selecting the eligible papers, the required data were extracted and summarized using the designed extraction table in Excel software. EndNote X8 reference management software was applied to organize the titles and abstracts as well as identify duplicates. Finally, 13 relevant papers were included in the study.

Results

After searching for papers published in the specified time period in the mentioned databases, we found 239 relevant papers using the keywords. The titles and abstracts of papers were reviewed, and 31 papers were selected. Then, the number of papers was reduced to 16 after being reviewed more precisely by the assessment team. Finally, 13 papers that met the inclusion criteria and were in line with the research objectives were included. To the best of our knowledge, no systematic review has ever been conducted in relation to the objectives of the present study.

The Joanna Bridges Institute (JBI) and the STROBE checklist were used for randomized and controlled trials, case-control studies, and quasi-experimental studies to assess the risk of bias. In total, there were 7 clinical trials, 4 case-control studies, and 2 quasi-experimental studies. Almost all items were present in clinical trials, and they were assessed as having low risk of bias.

Items 1, 6, 7, and 9 were not present in case-control studies. In quasi-experimental studies, there was no control group, and all the items were present except for items 4 and 6 in the JBI checklist. These studies had high risk of bias (Table 1 and 2).

Table 1: Qualitative data obtained from reviewing papers on the effect of LLLT on salivary proinflammatory cytokines

Author	Year	Title	Population	Type of study/ Treatment Method	Outcome criteria
Oton-Leite et al.[14]	2015	Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patient	Patients with head and neck cancer	Clinical (orthopedic surgery)/ 1-Control 2.LLLT laser	1.The severity of the oral mucosa 2.Proinflammatory and anti-inflammatory cytokines (TNF-α, IL-6, IL-1β, IL-10, TGF-β), 3. Growth factors (EGF, FGF, VEGF) 4-Metalloproteinases (MMP2 / TIMP2, MMP9 / TIMP2
Martins et al.[16]	2021	The Effect of Photo biomodulation on Nitrite and Inflammatory Activity in Radiotherapy-Induced Oral Mucositis: A Randomized Clinical Trial.	Patients undergoing radiotherapy	Randomized Controlled Trial/ (double-blinded) 1-Control (POCP) 2-(POCP+PBMT)	1. The severity of the oral mucosa Pro-inflammatory and anti-inflammatory cytokines (IL-6, IL-8, IL-10, IL-12p70, IL-1β and TNF-α)
GiathGazal et al.[17]	2020	Management of an emergency tooth extraction in diabetic patients on the dental chair	36 Study	Review tooth extraction in diabetic patients	FBS180mg/dl And the most acceptable level of blood glucose 240mg/dl as a cut point in diabetic patients for tooth extraction

Salvador et al.[18]	2017	Effect of photobiomodulation therapy on reducing the chemo-induced oral mucositis severity and on salivary levels of CXCL8/ interleukin 8, nitrite, and myeloperoxidase in patients undergoing hematopoietic stem cell transplantation: a randomized clinical trial	Patients with hematopoietic stem cell transplantation (HSCT)	Randomized Controlled Trial/ 1-Control 2-PBMT	1. The severity of the oral mucosa 2. CXCL8 / IL-8 salivary levels 3-Nitrite (NO) 4-myeloperoxidase (MPO)
Basso et al.[19]	2016	Proliferation, migration, and expression of oral-mucosal- healing-related genes by oral fibroblasts receiving low-level laser therapy after inflammatory cytokines challenge.	Human gingival fibroblasts	Invitro/ LLLT	TNF-α ،IL-1β ، IL-6 and IL-8 cytokines
Rezk-Allah et al.[20]	2019	Effect of Low-Level Laser Therapy in Treatment of Chemotherapy Induced Oral Mucositis	Patients undergoing chemotherapy	Randomized Controlled Trial (double-blinded)/ LLLT	TNF-α IL-6
Campos L et al.[21]	2016	Comparative study among three different phototherapy protocols to treat chemotherapy-induced oral mucositis in hamsters.		In vivo/ Control Chemotherapy (CT) CT+LED CT+HPL CT+LLLT	The severity of the oral mucosa TNF-α
Silva et al.[22]	2015	Effect of low-level laser therapy on inflammatory mediator release during chemotherapy-induced oral mucositis: a randomized preliminary study.	Patients with hematopoietic stem cell transplantation (HSCT)	Randomized preliminary study/ 1-Control 2.LLLT laser	Severity of chemotherapy-induced oral mucositis
Pezelj-Ribarić et al.[15]	2013	Proinflammatory cytokine levels in saliva in patients with burning mouth syndrome before and after treatment with low-level laser therapy	Patients (BMS)	Randomized Clinical Trial/ 1-control 2- LLLT laser	TNF-α and IL-6
Barbosa et al.[23]	2018	Evaluation of laser therapy and alpha-lipoic acid for the treatment of burning mouth syndrome: a randomized clinical trial	1-Syndrome (BMS) 2. Secondary oral irritation (SOB)	Randomized clinical trial/ BMS LLLT BMS+ALA SOB+LLLT SOB+ALA	Salivary TNF-α
Fukuoka et al.[24]	2020	Early effect of laser irradiation in signaling pathways of diabetic rat submandibular salivary glands	Diabetic rats	In vivo Study/ LPLI	TNF-α
Simunović-Soskić et al.[25]	2010	Salivary levels of TNF-alpha and IL-6 in patients with denture stomatitis before and after laser phototherapy	Patients with denture stomatitis (DS)	Randomized Controlled Trial/ 1-Control 2. LPT laser	TNF-α IL-6
Li et al.[26]	2018	Effects of low-level laser combined with basic periodontal therapy on cytokines and LPS, leptin in gingival crevicular fluid of diabetes mellitus complicated with chronic periodontitis patients	Diabetic patients with chronic periodontitis	Randomized Controlled Trial/ 1- Control (periodontal basic treatment) 2-test (LLLT + basic periodontal treatment)	TNF-α IL-1 hs-CRP LPS leptin
Safavi et al.[27]	2008	Effects of low-level He-Ne laser irradiation on the gene expression of IL-1beta, TNF-alpha, IFN-gamma, TGF-beta, bFGF, and PDGF in rat's gingiva	Rat gums	In vivo Study/ A (24): He-Ne laser (2 times in 24 hours) A (48): He-Ne laser (3 times in 48 hours) B (48): Control B (48): Control	IL-1β, TNF-α, IFN-γ, TGF-β, bFGF, PDG

LLLT: Low-level laser therapy; IL: Interleukin; TNF: Tumor necrosis factor; TGF: Transforming growth factor; EGF: Epidermal growth factor; FGF: Fibroblast growth factors; VEGF: Vascular endothelial growth factors; MMP: Matrix metalloproteinases; TIMP: Tissue inhibitors of metalloproteinases; FBS: Fasting blood sugar; POCP: Photochemical Ozone Creation Potential; PBMT: Photobiomodulation Therapy; CXCL: Chemokine (C-X-C motif) ligand; HSCT: Hematopoietic stem cell transplantation; NO: Nitrite; MPO: Myeloperoxidase; CT: Chemotherapy; LED: Light-emitting diode; HPL: High pressure laminate; BMS: Burning mouth syndrome; SOB: Secondary oral irritation; ALA: Alpha lipoic acid; DS: Denture stomatitis; Hs-CRP: High-sensitivity C-reactive protein; LPS: Lipopolysaccharide; bFGF: Basic Fibroblast Growth Factor

Table 2: Results of reviewing papers on salivary proinflammatory cytokines

		Results
1	Oton-Leite et al. (2015)[14]	Laser radiation reduced the severity of oral mucositis (OM). The IL-6 level in the laser group was significantly lower than the control in the 35th session. There was a decrease in TNF-α level in the laser group compared to the control group; however, this difference was not statistically significant.
2	Martins et al. (2021)[16]	The severity of OM was lower in the PBMT group. PBMT stabilized the nitrite concentration level during radiotherapy, increased IL-10, IL-12p70, and TNF-α, and decreased IL-1β.
3	Salvador et al. (2017)[18]	PBM reduced OM severity among patients with hematopoietic stem cell transplantation (HSCT). Also, PBM decreased the salivary levels of CXCL8/IL-8 and nitrite among patients.
4	Basso et al. (2016)[19]	LLLT could counteract the negative effects of high concentrations of inflammatory cytokines, particularly IL-6 and IL-8, on gingival fibroblast functions that were directly associated with wound healing.
5	Rezk-Allah et al. (2019)[20]	Using GaAs LLLT for treating chemotherapy-induced OM improved mucositis. However, the mechanism of action was not completely associated with changes in cytokines. The results showed TNF-α level decreased among patients with breast cancer. Also, IL-6 level declined among patients with head and neck cancer and lymphoma.
6	Campos et al. (2016)[12]	LLLT and LED were the best choices for reducing OM severity, accelerating tissue repair, and decreasing the inflammatory process (TNF-α). HPL showed no impact on the final improvement of OM.
7	Silva et al. (2015)[22]	LLLT had no effect on pro- or anti-inflammatory cytokines including TNF-α, IL-6, IL-1β, IL-10, and TGF-β among HSCT patients.
8	Pezelj-Ribarić et al. (2013)[15]	LLLT decreased the salivary levels of TNF-α and IL-6 among patients with BMS after 4 weeks.
9	Barbosa et al. (2018)[23]	LLLT and ALA increased the salivary flow in BMS patients but had no effect on SOB as well as TNF-α levels in patients with BMS and SOB.
10	Fukuoka (2020)[24]	LPLI treatment significantly reduced the expression of tumor necrosis factor alpha (TNF-α). In other words, LPLI hampered chronic inflammation and contributed to homeostasis in submandibular salivary glands of diabetic rats.
11	Simunović-Soskić et al. (2010)[25]	LPT significantly reduced TNF-α and IL-6 levels among patients with denture stomatitis (DS) after 4 weeks.
12	Li et al. (2018)[26]	Low-level laser combined with basic periodontal treatment could effectively reduce TNF-α and IL-6 levels.
13	Safavi et al. (2008)[27]	Low-level He-Ne laser irradiation inhibited IL-1β and IFN-γ gene expression, while it significantly increased PDGF and TGF-β gene expression and had no effect on TNF-α and bFGF gene expression.

OM: Oral mucositis; PBMT: Photobiomodulation Therapy; HSCT; Hematopoietic stem cell transplantation; CXCL: Chemokine (C-X-C motif) ligand; LLLT: Low-level laser therapy; TNF: Tumor necrosis factor; LED: Light-emitting diode; ALA: Alpha lipoic acid; BMS: Burning mouth syndrome; SOB: Secondary oral irritation; He-Ne: Helium–neon; IFN: Interferon; PDGF: Platelet-derived growth factor; TGF: Transforming growth factor; bFGF: Basic Fibroblast Growth Factor

Discussion

Cytokines are among the most important factors for cell proliferation, migration, and chemotaxis as well as angiogenesis in the wound healing process.[9] This study aimed to review the effect of LLLT on changes in salivary proinflammatory cytokines of TNF-α, IL-6, and IL-1.

Low-level lasers have the property of causing photochemical reactions and improving cellular metabolism. These lasers react with the tissue and stimulate or inhibit the cell without generating heat.[13, 14] However, studies on the effectiveness of LLLT in facilitating inflammation repair in both animal and human models have indicated different and sometimes conflicting results.[28] Lack of coordination between laser systems and selected parameters could complicate the comparison of results.[29]

Several parameters are evaluated in LLLT. Device power is the main characteristic factor, ranging from 10^{-3} to 10^{-1} W. Other important factors are wavelength in the range of 300-10600 nm, pulse width from 0 (continuous wave) to 5000 Hz, pulse interval of 1-500 ms, total irradiation duration of 10-3000 sec, power density (power divided by radiation area) in the range of 10^{-2}-10 W/cm^2, and dose that can vary between 10^{-2} and 10^2 J/cm^2. Therefore, different parameters used in studies can limit the possibility of making a significant comparison between the results.[30, 31] The effect of laser on reducing inflammation in different types of diseases has always received great attention. The impact of low-level laser radiation on preventing and treating chemotherapy- and radiotherapy-induced OM is among its wide applications. Clinical trials and animal studies have examined the effect of low-level laser on the severity of OM and salivary inflammatory mediators.[14, 16, 20-22]

One study showed that photobiomodulation therapy (PBMT) decreased the severity of OM, increased TNF-α level, and reduced IL-1β.[16] Another study found that laser irradiation reduced the severity of OM and salivary IL-6. However, no significant impact was observed on the reduction of TNF-α level compared to the control group.[14] A study on hamsters that underwent chemotherapy found that LLLT and LED were the best choices for reducing the severity of OM, accelerating tissue repair, and reducing the inflammatory process (TNF-α).[21] Using GaAs LLLT improved mucositis. However, the mechanism of action was not completely associated with changes in cytokines. The results showed TNF-α level decreased among patients with breast cancer. Also, IL-6 level

declined among patients with head and neck cancer and lymphoma.[20]

Laser-tissue interaction is among the most important topics in the field of treatment and many studies have tried to identify the nature of this interaction. The most important mechanisms of low-level laser include shortening tissue inflammation phase, accelerating the onset of cell proliferation, having antibacterial effect, increasing tissue blood flow, changing cell membrane potential, and having impact on cell mitochondrial function, which can ultimately accelerate the healing process.[32] Salivary cytokines of TNF-α, IL-6, and IL-1 are proinflammatory cytokines with multiple functions that play an effective role in reducing inflammation.[33]

An in vitro study on human gingival fibroblasts found that LLLT could counteract the negative effects of high concentrations of inflammatory cytokines, particularly IL-6 and IL-8, on gingival fibroblast functions that were directly associated with wound healing.[19] IL-6 regulated immune responses and acute phase reactions and played a crucial role in host defense mechanism and inflammatory and immune responses.[34]

Studies have reported conflicting results regarding the effect of low-level laser on treating patients undergoing HSCT. For example, a study showed that PBMT reduced the salivary levels of CXCL8/IL-8 and nitrite among patients.[18] However, another study showed LLLT had no significant impact on pro- or anti-inflammatory cytokines including TNF-α, IL-6, IL-1β, IL-10, and TGF-β among HSCT patients.[22]

Although there are many discrepancies in the results of OM treatment with low-level laser and inflammatory cytokines before and after laser therapy among patients, it should not be neglected that safety of low-level laser was approved by the U.S. Food and Drug Administration (USFDA), and no side effect has been reported for using laser.[35]

LLLT can increase the cellular activity and collagen synthesis and alleviate the inflammatory process. The known mechanism in this field includes increased cell division and altered nerve conduction through the release of endorphins and enkephalin. It seems that the effect of laser begins during the cell proliferation phase, which is accompanied by the increased mitochondrial respiration through cytochrome oxidase stimulation, increased number of fibroblasts and, subsequently, increased collagen synthesis and production of growth factors, lymphocytes, extracellular matrix, and macrophage activation. The ideal wavelength of low-level laser for wound healing is between 680 and 880 nm.[36-38]

Some studies have examined changes in salivary proinflammatory cytokines among patients with BMS by LLLT. LLLT reduced the salivary levels of TNF-α and IL-6 among patients with BMS after 4 weeks.[15] However, LLLT had no effect on TNF-α levels among patients with BMS and secondary oral burning (SOB).[23]

Although some studies have reported changes in interleukins during the BMS treatment, indicating the role of these proinflammatory cytokines in BMS,[8] extensive and controlled studies should be performed on the effect of laser therapy on cytokines due to the chronic nature of this disease, presence of confounding variables such as psychological problems, and lack of sufficient evidence in the standard course of treatment.[39]

The initial effect of laser radiation on signaling pathways of submandibular salivary glands in diabetic rats and found that LPLI had a significant effect on expression of tumor necrosis factor alpha (TNF-α).[40] LPLI hampered chronic inflammation and contributed to homeostasis in submandibular salivary glands of diabetic rats. The main physiological function of TNF-α was to stimulate and send the neutrophils and monocytes to infection sites and activate these cells to eradicate the microbes.[41]

A study investigated the effect of low-level laser irradiation on rats' gingiva and found that He-Ne laser irradiation inhibited IL-1β and IFN-γ gene expression and had no effect on TNF-α and bFGF gene expression.[27] IL-1β is associated with inflamed tissue damage. In the oral cavity, IL-1b is produced by local cells of the connective tissue such as fibroblasts and endothelial cells, or released from the leukocytes such as mononuclear cells, macrophages, and polymorphonuclear cells.[42]

A study on patients with DS showed that LPT significantly reduced TNF-α and IL-6 levels after 4 weeks.[25] An investigation demonstrated that the effect of LLLT combined with basic periodontal treatment on cytokines in the gingival sulcus fluid of patients with diabetes mellitus complicated with chronic periodontitis (DMCP) and indicated LLLT combined with basic periodontal treatment could effectively reduce the TNF-α and IL-6 levels.[26]

Laser can selectively affect inflammatory mediators by penetration into body fluids and tissues. Although LLLT seems to have photochemical or photomechanical impacts rather than thermal, none of the papers have convincingly described the mechanism of action of LLLT. Moreover, factors such as the type of laser, wavelength, and selected dose can affect the results. Most of the studies had limited number of samples and short follow-up duration. None of the investigations compared treatment with placebo and all were performed in the open-label uncontrolled manner. Therefore, interpreting the results should be done with caution after reviewing the quality of methodologies.

In general, more research should be performed to identify the true mechanism of LLLT, for example probable photochemical, photomechanical, and photobiological changes, and investigate the correlation between cellular effects, changes in cytokines, and clinical phenomena. Furthermore, these studies should consider a control group with an appropriate sample size and logically select laser systems in accordance with the parameters.

The results showed that many controlled clinical trials should be conducted to determine the mechanism of action of laser therapy in reducing inflammation through decreasing inflammatory cytokines induced by laser radiation-tissue interaction, develop an effective therapeutic protocol, and apply this modality in the clinical field.

Conclusion

Understanding the true mechanisms of LLLT (possible photochemical, photomechanical, and photobiological changes) and examining the relationship between cellular effects and changes in cytokines and clinical phenomena require numerous controlled clinical trials to develop an effective treatment protocol.

Conflict of Interest: None declared.

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