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Effect of 980nm Low-Level Laser Therapy on Matrix Metalloproteinase-1 Levels in Gingival Crevicular Fluid During Fixed Orthodontic Treatment

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Abstract

Introduction: Given the unique biostimulatory effects of low-level lasers, particularly on collagen production and fibroblast activity, this study aimed to measure the changes in MMP-1 levels in response to low-level laser therapy (LLLT) in individuals undergoing orthodontic treatment. The increase in MMP-1 may signal beneficial tissue adaptation to orthodontic force.

Methods: This double-blind, randomized clinical trial included 22 individuals referred to the orthodontic department of Yazd Faculty of Dentistry who required fixed orthodontic treatment. The left and right mandibular anterior teeth of patients meeting the inclusion criteria were randomly assigned to the intervention and control sides. A low-level diode laser (980 nm, 100 mW output power) was applied to two teeth in the intervention group for two consecutive days. Gingival crevicular fluid (GCF) samples were collected from both sides at 24 hours (T1) and 164 hours (T2) post-irradiation. MMP-1 levels were measured using ELISA. Data were analyzed using SPSS software with independent and paired t-tests, with a significance level set at 0.05.

Results: At T1, the mean MMP-1 level in the intervention group was 6.77 ± 0.54 ng/mL, which was significantly higher than the control group's level of 6.15 ± 0.40 ng/mL ($P < 0.001$). At T2, the mean MMP-1 level in the intervention group (6.20 ± 0.62 ng/mL) was not significantly different from that in the control group (6.21 ± 0.55 ng/mL) ($P = 0.960$). The average MMP-1 level in the control group did not differ significantly between T1 and T2 ($P = 0.546$). However, the mean MMP-1 level in the intervention group at T1 was significantly higher than at T2 ($P < 0.001$).

Conclusion: MMP-1 levels in GCF increase temporarily after low-level laser irradiation with orthodontic force, indicating a potentially beneficial effect on tissue remodeling. Levels return to baseline by 164 hours, suggesting a controlled, short-term response.

Keywords: Matrix metalloproteinase-1; Gingival crevicular fluid,; Low-level laser therapy.

Introduction

The prolonged duration of orthodontic treatment, typically lasting 12 to 24 months, is a significant concern for patients and clinicians.[1] The typical 24-month period of orthodontic treatment seems too long for patients who are looking for orthodontic treatment today, especially for young people, and may even result in treatment discontinuation.[2] Moreover, extending the duration of treatment can result in complications, including root resorption, caries, enamel decalcification, and periodontal problems.[3] Therefore, reducing treatment time is a major concern for patients and clinicians.

In recent years, there have been several reports of options for accelerating orthodontic treatment, with the most notable ones being corticotomy (and piezosurgery), microperforation, low-level laser therapy (LLLT), and vibration therapy. The desire for non-invasive methods such as LLLT, the lack of solid evidence on the effect of LLLT on accelerating tooth movement, as well as the lack of an effective treatment protocol (laser wavelength, output power, laser mode, radiation time, radiation sessions, etc) have caused the need for more studies in this field.[3]

Low-level lasers cause minimal thermal effects on tissues. Instead, they stimulate tissues through a process called photobiostimulation, resulting in mild and gradual tissue responses.[4] Biostimulation operates on the premise that exposure to specific wavelengths can induce changes in cellular behavior. As a result, this leads to increased cell metabolism and proliferation. The output power of Low-level lasers is usually less than 250 mW. Without generating significant heat, low-level lasers can still be effectively stimulated with a power density of less than 670 mW/cm^2.[5]

The specific biochemical process that accounts for the effects of LLLT is still unclear. One of the suggested mechanisms is that low-level photon radiation causes the production of small amounts of reactive oxygen species (ROS) and adenosine triphosphate (ATP) as soon as

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the photon is absorbed in the mitochondria. RANK, RANK-L and IGF-1 receptors and interleukin (IL-1β) levels increase. By promoting the proliferation and differentiation of various cell types, including osteoclasts, osteoblasts, fibroblasts, and periodontal ligament (PDL) cells, this anabolic effect speeds up tooth movement and enhances bone remodeling, collagen synthesis, and the formation of new blood vessels.[6,7]

Matrix metalloproteinases (MMPs) are enzymes that rely on Zn^{2+} and Ca^{2+} ions and have the capability to break down nearly all extracellular matrix (ECM) components, making them crucial in various biological and pathological processes.[8] In humans, the MMP family comprises 23 enzymes, which are divided into six distinct groups according to their substrate specificity and structural homology: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs), and other MMPs. MMP-1 belongs to the group of collagenases.[9,10] Gingival crevicular fluid (GCF) serves as a key medium for analyzing biochemical markers, with remodeling changes in the alveolar bone and PDL triggering the production of cell mediators and enzymes that act as biomarkers in orthodontic treatment.[11]

Laboratory studies have indicated that mechanical stress leads to the upregulation of MMP-1 and MMP-2 mRNA and protein in human gingival and periodontal fibroblasts.[12,13] In dogs, an increase in MMP-1 levels was also observed in the gingiva during tooth movement.[14] Additionally, research by Bolcato-Bellemin et al revealed that MMP-1, -8, and -13 are expressed in PDL, with their expression levels temporarily rising during orthodontic tooth movement (OTM).[15]

Cantarella et al conducted a study analyzing GCF samples from 11 healthy orthodontic patients. Their findings revealed that compression force led to a significant rise in MMP-1 protein levels within the first hour, which persisted until the third hour before subsiding. In contrast, tension force only caused a notable increase in MMP-1 protein levels after the first hour. These findings suggest that orthodontic forces influence both MMP-1 and MMP-2 protein levels under compression and tension, though the effects differ in magnitude and follow a time-dependent pattern.[16] Evidence suggests that MMP-1 levels increase shortly after laser treatment, reflecting acute inflammation and tissue remodeling. Measurements during the first few hours may be less informative due to the transient inflammatory response, making later time points more relevant. After approximately 7 days, MMP-1 levels seem to stabilize, with limited further changes observed.[17]

Although the role of MMP-1 in accelerating tooth movement has not been directly clarified, studies showed that the expression level of MMP-1 can increase under the mechanical stress of OTM[12-14]; thus, the level of this protein in the gingival crevice fluid may be used as a marker to evaluate the acceleration of tooth movement. Although most of the scientific literature states that LLLT does accelerate the tooth movement, very few authors have studied the effect of LLLT at the molecular level in humans.[18-20] This study aimed to investigate the level of MMP-1 as a marker of bone remodeling in response to LLLT.

Methods

This randomized clinical trial (RCT) was conducted as a split-mouth study, where one side of the mouth was assigned as the case and the contralateral side served as the control. A total of 31 patients met the initial eligibility criteria. From this pool, 24 participants (13 women, 11 men; age range: 14-33 years; mean age: 21.75 years) requiring fixed orthodontic treatment at Yazd Dental School were randomly selected to achieve the predetermined sample size. A minimum of 20 patients per group were required to detect a clinically significant difference between the two groups based on the previously reported standard deviations of 0.0004 for a significant level of 5% (power = 0.8). The sample volume was determined using PASS15 software and the following formula. We selected 24 patients to consider possible dropouts.

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times 2S^2}{d^2}$$

Inclusion criteria included the need for fixed orthodontic treatment, no medication use, and consent to participate in the study. Patients with periodontal and systemic diseases, patients who had poor hygiene during the treatment, and people who did not refer for visits on the scheduled dates were excluded from the study.

In order to reduce confounding factors, the research was conducted with a split-mouth design. Therefore, each patient served as their own control: one side of the mandible (right or left) received LLLT, while the contralateral side acted as the non-irradiated control. Half of the patients were exposed to LLLT for the anterior teeth of the right mandible (Right-side LLLT Group), while the other half received LLLT for the corresponding teeth on the left side (Left-side LLLT Group). The allocation of samples into groups was done using simple randomization with Random Allocation 1 software. Only the person responsible for laser radiation knew the group assignments. The individuals in charge of data collection and performing the ELISA test were unaware of the groupings, ensuring that the study was conducted in a double-blind manner. Before starting the treatment, patients were given oral hygiene instructions, including the correct use of a toothbrush, dental floss, and 0.12% chlorhexidine mouthwash, to be followed for four weeks. Concurrently with the beginning of the first phase of

orthodontic treatment (Aligning & Leveling), laser radiation therapy was initiated.

Low-Level Laser Therapy

In this study, a diode laser with a wavelength of 980 nm (Doctor Smile class 4 laser, Lambda S.p.A., Brendola, Italy, classification CEI EN 60825-1), operating in the infrared range with an output power of 100 mW, was used in continuous mode. Upon the initiation of the first phase of fixed orthodontic treatment, laser radiation was applied to three points on the buccal side and two points on the lingual side of each tooth. The application was conducted two millimeters below the free gingival margin of the two mandibular anterior teeth, with each point receiving laser exposure for 10 seconds. To prevent laser irradiation to neighboring teeth, the probe tip was placed in direct contact with the gingival tissue of the selected tooth, and the tooth root was approximately centered within the probe area. Care was taken to avoid beam dispersion beyond the intended application sites (Figure 1). Laser irradiation was administered on two consecutive days using a probe head area of 1 cm^2, delivering an energy density of 1 J/cm^2 at each point and achieving a total energy density of 5 J/cm^2. In the control side, similar to the intervention side, the laser probe was used but turned off. During laser use, the patient's eyes were closed, and both the patient and the person operating the laser wore protective glasses.

GCF Sampling

GCF sampling was performed at two time points: 1 day (T1) and 7 days (T2) after the last laser irradiation. On the day of sampling, the patients were instructed to brush their teeth thoroughly and to avoid eating for 3 hours prior to sampling. Before sampling, any plaque was removed, and air pressure was applied for 10 seconds to dry the area. An absorbent filter paper strip measuring 2×10 mm was then placed in the gingival sulcus to collect the sample (Rundfilter, Macherey-Nagel & Co., Germany). The periostrip paper (MACHEREY-NAGEL GmbH & Co. KG, Dueren, Germany) was inserted into the gingival sulcus on the buccal side of the incisors until slight tissue resistance was encountered, and then it was held in place for 30 seconds. Care was taken to avoid any mechanical damage to the gums. Samples contaminated with saliva or blood were discarded, and re-sampling was performed. Immediately after preparation, the samples were placed in 1.5 ml impermeable sterile plastic tubes containing 500 µL of phosphate-buffered saline (PBS) and stored at -70 °C until the ELISA test was conducted.

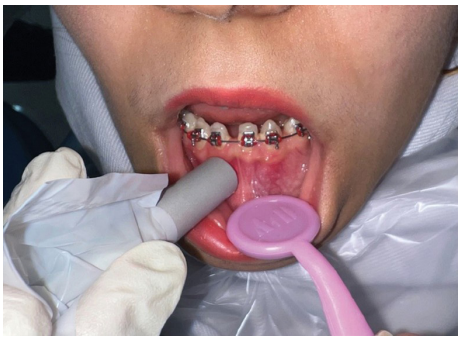

Figure 1. Clinical Positioning of the Diode Laser Probe During Application on Mandibular Anterior Teeth

Quantification of MMP-1

The MMP-1 level was measured using the human MMP-1 ELISA kit (ZellBio GmbH, Lonsee, Germany; Lot No. ZB-OEH634221102-111). The laboratory personnel conducting the tests were blinded to the allocation of patients into different groups.

The wells of the ELISA kit were categorized into three groups:

- Blank wells: Anti-MMP1 antibody with streptavidin-HRP was added without any sample.
- Standard wells: 50 µL of the standard solution and streptavidin-HRP were added.
- Test wells: 40 µL of the sample, followed by 10 µL of anti-MMP1 antibody and 50 µL of streptavidin-HRP, was sequentially added.

After incubating the wells with a coverslip at 37 °C for 60 minutes, the coverslip was removed, and the wells were drained. Subsequently, a washing solution diluted 30 times with distilled water was added to the wells and drained after 30 seconds, repeated up to four times. Each well received 100 µL of chromogen solution and was incubated for 10-20 minutes at 37°C in the dark until staining occurred. Subsequently, 50 µL of stop solution was added to each well to terminate the reactions, resulting in a color change from blue to yellow. Following a 10-minute incubation after the previous step, optical density (OD) was measured at 450 nm for all wells. The blank well served as the zero-concentration reference. A standard curve was constructed using known concentrations and their corresponding OD values. Subsequently, the concentration of MMP1 in the test wells was determined based on their OD readings. OD was measured using a microplate reader at 450 nm, ensuring precise and reliable quantification.

Statistical Analysis

The data were entered into SPSS version 26, and normal distribution was assessed using the Kolmogorov-Smirnov test. Assuming normality, inter-group comparisons were performed using the independent t-test, and intra-group comparisons were conducted using the paired t-test. A significance level of 0.05 was applied to all tests.

Results

In this study, 31 patients were initially identified, but only 24 met the inclusion and exclusion criteria and were

divided into two groups. During the ELISA analysis for MMP-1, samples from one patient in each group were lost to standardize the test, resulting in the evaluation of 11 patients per group, totaling 22 patients (Figure 2).

The results of the Shapiro-Wilk and Kolmogorov-Smirnov tests indicated that MMP-1 levels at T1 and T2 followed a normal distribution ($P>0.05$). Comparison of the two groups showed no significant difference in MMP-1 levels at T1 (1-day post-radiation) ($P=0.804$) or at T2 (7 days post-radiation) ($P=0.581$) between subjects who underwent LLLT on the left versus right teeth. This lack of difference between the right and left sides in MMP-1 levels indicates that the effects of the intervention were consistent regardless of the side of application. This finding supports the reliability of the split-mouth design (Table 1).

Independent t-test results showed that at T1, the average MMP-1 level on the intervention side (6.77 ± 0.54 ng/mL) was significantly higher than on the control side (6.15 ± 0.40 ng/mL) ($P<0.001$). At T2, there was no significant difference in MMP-1 levels between the intervention side (6.20 ± 0.62 ng/mL) and the control side (6.21 ± 0.55 ng/mL) ($P=0.960$) (Table 2).

Intra-group comparisons using the dependent t-test revealed no significant difference in average MMP-1 levels in the control group between T1 (6.15 ± 0.40 ng/mL) and T2 (6.21 ± 0.55 ng/mL) ($P=0.546$). However, in the intervention group, the average MMP-1 level at T1 (6.77 ± 0.54 ng/mL) was significantly higher than at T2 (6.20 ± 0.62 ng/mL) ($P<0.001$) (Figure 3).

Table 1. Comparison of MMP-1 Levels Between the Two Study Groups

		Right-Side LLLT Group (n = 22)		Left-Side LLLT Group (n = 22)		*P* Value*
		Mean	SD	Mean	SD	
MMP-1 levels (ng/mL)	T1	6.44	0.10	6.48	0.10	0.804
	T2	6.25	0.13	6.15	0.13	0.581

* A significance level of $P<0.05$ was considered.

Table 2. The Effect of LLLT on MMP-1 Levels at T1 and T2

		LLLT Side (n = 22)		Control Side (n = 22)		*P* Value*
		Mean	SD	Mean	SD	
MMP-1 levels (ng/mL)	T1	6.77	0.54	6.15	0.40	<0.001
	T2	6.20	0.62	6.21	0.55	0.960

* A significance level of $P<0.05$ was considered.

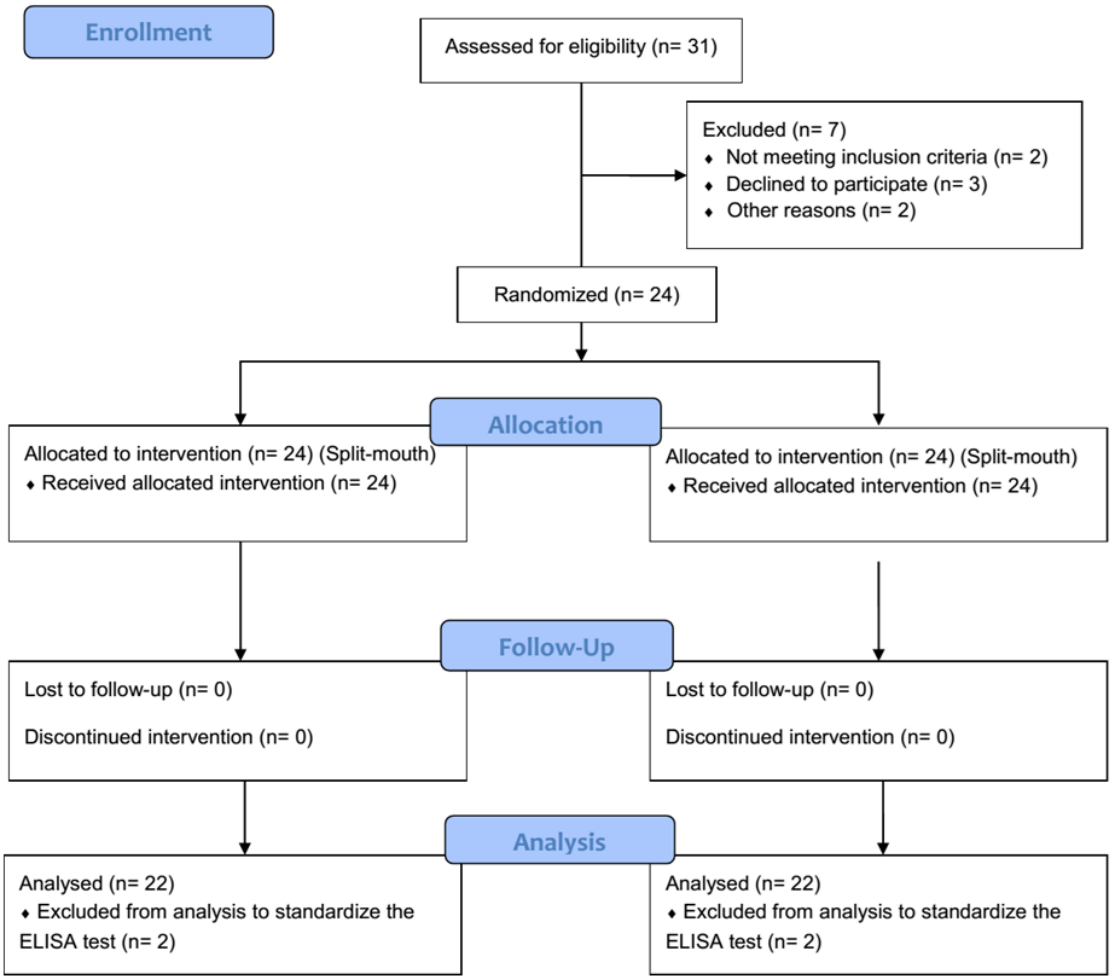

Figure 2. CONSORT 2010 Flow Diagram

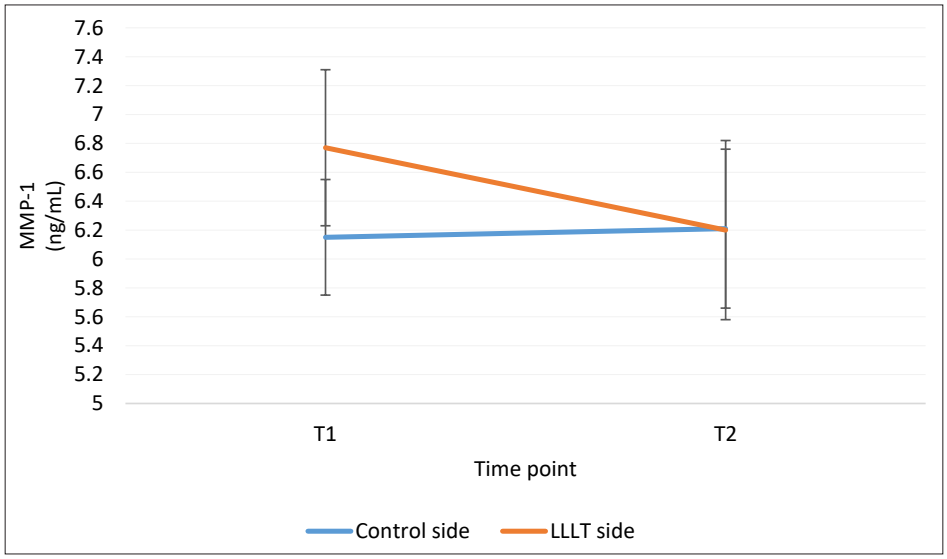

Figure 3. MMP-1 Level Changes in Both Control and LLLT Sides

Discussion

This study aimed to assess the impact of LLLT on MMP-1 levels in the GCF of individuals undergoing fixed orthodontic treatment. Twenty-two participants were enrolled in this double-blind clinical trial. During the initial step of orthodontic treatment (Aligning & Leveling), a low-level diode laser was applied on one side (intervention group), while the laser was kept off on the other side, serving as the control. Twenty-four hours post-LLLT, the MMP-1 levels in the intervention group were significantly higher compared to the control group, demonstrating that LLLT significantly elevated MMP-1 levels in the initial 24-hour period. However, at 164 hours, MMP-1 levels in the intervention group significantly decreased to levels comparable to the control group. These findings indicate that while LLLT can markedly increase MMP-1 levels within the first 24 hours, its effect significantly diminishes over time.

To date, various strategies have been investigated to enhance bone remodeling and accelerate OTM. These include methods such as local drug administration, physical stimuli, and corticotomy.[21] However, systemic unpredictability, local discomfort, and pain associated with injection and corticotomy have restricted their widespread clinical application. Physiotherapeutic modalities like LLLT are increasingly preferred due to their minimal invasiveness and safety profile. LLLT delivers energy levels that maintain temperatures below 36.5°C, ensuring safety during treatment.[22] Consequently, for promoting accelerated tooth movement through minimally invasive means and inducing bone remodeling via biochemical stimulation, photobiomodulation techniques like LLLT and LED light irradiation are increasingly recognized as promising methods.

MMP-1 may play a role in osteoclastic activities and bone remodeling during OTM.[23] Evidence suggests that LLLT accelerates the bone remodeling process through RANKL/OPG modulation and the stimulation of osteoblast and osteoclast proliferation and activity during OTM.[24] The increased MMP-1 levels observed on the intervention side compared to the control side following LLLT may indicate enhanced bone remodeling, thereby accelerating tooth movement. This biostimulatory effect appears to diminish within a week, consistent with findings indicating that intracellular biochemical processes, including ATP and ROS generation, return to baseline levels after approximately one week.[16]

Several studies have investigated the role of LLLT in OTM and bone remodeling. Cantarella et al reported that MMP-1 levels increased shortly after the application of orthodontic force, peaking at three hours and then returning to baseline.[16] Similarly, Almeida et al found that MMP-1 levels increased following the initiation of tooth movement, while other MMP levels showed no significant changes.[25] These findings are consistent with our observation of elevated MMP-1 levels in the first 24 hours post-laser irradiation, highlighting the potential of LLLT to enhance bone remodeling during the aligning and leveling phase of orthodontic treatment.

Animal and human studies further support the efficacy of LLLT in accelerating OTM.[26-28] Yamaguchi et al demonstrated that low-level laser application significantly increased the expression of MMP-9, cathepsin K, and integrin $\alpha(v)\beta_3$, resulting in enhanced bone remodeling and faster tooth movement in a rat model.[20] Similarly, Youssef et al found that laser irradiation (809 nm, 100 mW) resulted in a 98% faster orthodontic movement by the end of the retraction phase.[26] Zheng and Yang reported a 35% faster retraction speed on the laser-treated side within a 4-week period.[29] Conversely, Marquezan et al found that LLLT (830 nm laser, 6000 J/cm^2) had no significant effect on OTM in rats,[30] and Limpanichkul et al observed no

impact of an 860 nm diode laser at 25 J/cm² on OTM in dogs. [31] These conflicting results may be due to variations in experimental protocols, including differences in laser wavelength, output power, laser mode, and irradiation time, highlighting the importance of optimizing laser parameters for effective photobiomodulation.

The present study utilized a 980 nm infrared diode laser with an output power of 100 mW, which falls within the optimal wavelength range for biostimulation (550-980 nm).[32] Infrared radiation has high tissue penetration due to its low absorption coefficient in hemoglobin and water, making it particularly effective for stimulating biological processes.[32] Our findings support the clinical application of LLLT in accelerating tooth movement, as shown by the significant increase in MMP-1 levels during the early phase of treatment.

The safety of LLLT has been well-documented. Chung et al reviewed photobiomodulation techniques and found no harmful effects on the periodontium or teeth, further supporting the clinical viability of LLLT for accelerating OTM.[33] This study adds to the growing evidence supporting the translational application of basic biological knowledge in clinical orthodontics, demonstrating that LLLT can effectively enhance orthodontic treatment outcomes.[34]

The potential mechanisms of LLLT in enhancing OTM remain the subject of ongoing investigation. It has been hypothesized that LLLT may promote photobiomodulation by stimulating mitochondrial activity, potentially leading to increased ATP production and enhanced cellular energy supply. This process could facilitate cell proliferation, differentiation, and tissue regeneration. Additionally, LLLT is suggested to modulate ROS and nitric oxide (NO) levels, which may activate transcription factors and signaling pathways implicated in bone remodeling.[35] Evidence also indicates that LLLT might influence the RANKL/OPG pathway, which regulates osteoclastogenesis, potentially promoting bone resorption on the compression side and deposition on the tension side of the PDL. Furthermore, LLLT has been proposed to enhance angiogenesis by upregulating vascular endothelial growth factors, which are essential for maintaining vascular supply during bone remodeling.[36] While these hypotheses are supported by initial findings, further research is required to fully elucidate these mechanisms and confirm their clinical significance in accelerating tooth movement and improving orthodontic outcomes.

This study has certain limitations that should be considered when interpreting the results. First, the relatively small sample size, despite meeting the minimum statistical requirements, may limit the generalizability of the findings to larger and more diverse populations. Second, the study employed a split-mouth design, which, while effective in minimizing inter-subject variability, may introduce potential bias related to systemic effects influencing both sides of the mouth. Third, the effects of LLLT were only evaluated during the initial phase of orthodontic treatment (aligning and leveling), and long-term effects on tooth movement and bone remodeling were not assessed. Lastly, variations in patient compliance with oral hygiene instructions and the potential influence of undetected confounding factors, such as dietary habits or genetic predispositions, could have affected the outcomes. Future studies with larger sample sizes and longer follow-up periods are needed to validate and expand upon these findings. Investigating the optimal parameters of LLLT, such as wavelength, energy density, and irradiation duration, could further improve treatment outcomes. Furthermore, future research should examine the combined effects of LLLT with other orthodontic interventions, such as corticotomy or local drug delivery, to determine whether synergistic effects can be achieved. Finally, exploring the molecular pathways influenced by LLLT over multiple time points, including biomarkers related to inflammation and bone turnover, would provide a more comprehensive understanding of its mechanisms of action.

Conclusion

The level of MMP-1 in GCF significantly increases in the short term (24 hours) following low-level laser irradiation in conjunction with the application of orthodontic force. However, this elevated MMP-1 level returns to baseline, comparable to the control side, after 164 hours.

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Authors' Contribution

Conceptualization: Hossein Agha Aghili, Fariba Zadbin.
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Investigation: Fariba Zadbin.
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Writing–original draft: Fariba Zadbin.
Writing–review & editing: Fariba Zadbin.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (license number: IR.SSU.

DENTISTRY.REC.1401.055) and registered at Iranian Registry of Clinical Trials (identifier: IRCT.20210221050435N3). Informed consent was obtained from all human adult participants.

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