Impact of Photobiomodulation on External Root Resorption During Orthodontic Tooth Movement in Humans – A Systematic Review and Meta-analysis

by Nida Nayyer

Submission date: 19-May-2022 10:42AM (UTC+0530)
Submission ID: 1839609702
File name: Text_aob___reduced_sim_REVISED_18_may_2022_1.docx (127.28K)
Word count: 5034
Character count: 29304

Impact of Photobiomodulation on External Root Resorption During Orthodontic Tooth Movement in Humans – A Systematic Review and Meta-analysis

ABSTRACT

Background- Photobiomodulation has been gaining traction as a plausible therapy to control orthodontically induced root resorption.

Aim -The aim of the present review was to systematically appraise randomized controlled trials conducted to study the influence of photobiomodulation on external root resorption during orthodontic movement in humans.

Methodology - A systematic search was carried out employing keywords in various electronic databases namely MEDLINE (Pubmed), Cochrane Library, Google Scholar, Semantic Scholar, ScienceDirect and Opengrey.eu for studies upto March 2020. Pre-defined inclusion and exclusion criteria were used to select the studies. Data extraction was carried out and the risk of bias was assessed by means of Cochrane Risk of Bias tool. Meta-analysis was done using random effects model for selected studies. Subgroup analysis was conducted for resorption on each axial surface of the tooth root viz. mesial, buccal, distal and palatal as well as for vertical thirds viz. cervical, middle and apical third. Summary of Findings was formulated according to GRADE Profile.

Results- The search retrieved 1509 results out of which six studies were included for the systematic review. Two studies showed low overall risk of bias and the remaining four showed unclear risk of bias. The meta-analysis was conducted for three studies with an overall sample size of 120 teeth which showed a pooled mean difference of 0.08 (95% CI 0.15 – (-0.02) to 1.96, p=<0.0001) in favour of photobiomodulation group with respect to mean total resorption per tooth. I^2 index revealed 88% heterogeneity.

Conclusion - It is concluded that there is moderate grade of evidence to suggest beneficial effect of photobiomodulation on root resorption. Further high-quality randomized controlled trials with standardized intervention parameters are recommended.

Registration- PROSPERO registration number - CRD42020167291

Conflict of interest- None.

KEYWORDS- Photobiomodulation, Root resorption, systematic review, meta-analysis, Low-level laser therapy.

BACKGROUND

One of the commonly associated iatrogenic effects of fixed orthodontic treatment is the occurrence of orthodontically induced inflammatory root resorption (OIIRR)[1]. It is described as the loss of root structure manifesting as root length reduction or outward defects which decrease root volume [2]. A prospective study showed that 94% of the patients undertaking orthodontic treatment displayed root resorption of more than 1mm [3]. Root resorption may jeopardize the functional ability of teeth by introducing mobility, especially when superimposed with periodontal disease [4,5].Consequently, countering iatrogenic root resorp-

tion has become one of the prime objectives of researchers around the globe. Various methods such as shortening of the treatment duration, controlled mechanics or awareness of factors of individual susceptibility such as systemic disorders, genetics, previous trauma or age have been known to display reduced occurrence of OIIRR [6]. Newer non-invasive techniques such as low-level laser, light-emitting diodes and low intensity pulsed ultrasound (LIPUS) are also being investigated for the same lately [7,8].

Photobiomodulation (PBM) therapy entails exposure of biologic cells or tissues to low levels of red and near-infrared light. The devices consist of semiconductors such as arsenic, aluminium, gallium or indium which convert electrical energy to light energy [9]. The energy thus generated acts on cellular and molecular levels to influence bone and cementum remodeling mechanisms. The core mechanisms involve stimulation of mitochondrial activity and ATP production, activation of ion channels and subsequent modulation of the inflammatory process [10]. It was formerly believed that photobiomodulation required the usage of coherent laser light, however, of late, light-emitting diodes (LEDs) have also been serving as a cheaper alternative. The basic tenet of operation for LEDs and diode lasers is the same and termed as the PIN (positive-intrinsic-negative) semiconductor diode [11]. Currently, photobiomodulation is being tested extensively in orthodontics for pain management and accelerating tooth movement during fixed mechanotherapy, wound healing, bone regeneration after rapid maxillary expansion, root resorption control and post-treatment retention [8, 12,13, 14,15].

Although the effect of photobiomodulation on root resorption has been described by various trials, there continues to exist, a discrepancy in the correlation between OIIRR and photobiomodulation. In view of this background, the present systematic review and meta-analysis was conducted to assess the influence of photobiomodulation on root resorption during orthodontic tooth movement in human subjects enrolled in randomized controlled trials.

MATERIALS AND METHODS

Protocol and registration

The systematic review was registered in PROSPERO on 28th April 2020 (CRD42020167291). It was conducted and reported according to the Cochrane Handbook [16] of systematic reviews and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [17,18].

Eligibility criteria

The PICOS (Participants, Intervention, Control, Outcome and Study design) scheme was utilized to assess the eligibility.

Inclusion Criteria-

P – Human teeth subjected to orthodontic force application in any direction.

I – Photobiomodulation therapy using either low-level laser or light-emitting diode.

C – Human teeth subjected to orthodontic force application without any intervention (photobiomodulation).

O – Studies reporting quantitative measurements of root resorption.

S - Randomized controlled trials conducted on humans.

Exclusion Criteria-

1. Non-randomised clinical trials
2. In-vitro studies or animal studies
3. Studies without a control/comparison group.
4. Studies conducted on replanted teeth, teeth with periodontal and/or periapical pathologies or primary teeth.
5. Review articles, case reports, case series, letters to editor.
6. Studies available only in languages other than English.

Sources of Information and Research Strategy

The search was carried out by two review authors in several electronic bibliographic databases namely MEDLINE via Pubmed, Cochrane Library (Cochrane database of systematic reviews, Cochrane central register of controlled trials (CENTRAL), Google Scholar, Semantic Scholar, ScienceDirect and Opengrey.eu for studies up to March 2020. Reference lists of eligible studies and review articles were also explored. All articles and manuscripts published in English or with English translations available were incorporated in the search.

The search strategy devised included the terms relating to or describing the intervention using MeSH (medical subject headings) terms and subsequently was adapted for use according to different databases.

The search strategies employed for various databases are listed in *Table 1*.-

Study Selection

Two authors screened the titles and/or abstracts of studies obtained from the search results to shortlist articles that potentially met the inclusion criteria. The full text of these studies were then read and independently assessed for eligibility by the same review team members. A third author opined in case of any disagreements.

Data Items and Collection

Data extraction was executed and tabulated under the headings : a) author, year, b) general study characteristics, c) patient demographics, d) details on intervention e) outcome details.

Risk of Bias of individual studies

The risk of bias of included studies was evaluated according to Cochrane guidelines for RoB 2.0 tool for randomized trials. The assessment of risk for individual studies was carried out by two authors independently followed by resolution of discrepancies after discussion with the third author. The studies were categorized as low, high or unclear risk of bias referring to Cochrane Handbook where a low risk of bias was assigned where all the categories were judged as low risk, high risk if a majority of the categories were at high risk and unclear risk if the data was insufficient to formulate a decision.

Summary measures, data synthesis and assessment of heterogeneity

A narrative synthesis of the data extracted from the included studies concerning the type of their intervention, target population characteristics, type of outcome and intervention content was completed. Absolute anticipated effect was calculated and the summary of evidence using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Evidence Profile was formulated with mean difference as the effect estimate [19].

The level of heterogeneity in the outcome measures of the studies was determined using I^2 index with significance indicated by p value < 0.05 and the pooled mean difference was calculated. Sub-group analysis was also done to assess root resorption of different axial surfaces and vertical thirds of the root. The heterogeneity for the same was calculated using I^2 index. Forest plots were plotted for both mean total root resorption as well as mean resorption volumes on individual axial surfaces and vertical thirds. Funnel plot was plotted for mean total root resorption.

RESULTS

Study selection:

The electronic search retrieved 1509 results from all the databases. Seven hundred and one results remained after removal of duplicates which were then screened by titles and abstracts. Full texts of eight articles were downloaded to be tested for eligibility out of which two were excluded [20,21,22,23,24,25,26,27]. The

study by Cruz et al was excluded due to missing quantitative data and Nimeri et al was excluded because of missing control group [20, 22]. The level of agreement between the two authors screening the titles, abstracts and full texts were 0.81, 0.89 and 0.91 as assessed by Kappa's calculation method. Clinical and statistical heterogeneity across the six studies was gauged, on the basis of which three (Ng et al, Ang-Khaw et al and Goymen et al) were selected for quantitative analysis [23,25,27]. The results retrieved from the search along with reasons behind exclusion have been depicted in the *PRISMA Flowchart (Figure 1)* and *Table 1*.

General characteristics of included studies

We included six studies for qualitative analysis. The general characteristics of the studies are reported in *Table 2*. The studies by Ang-Khaw et al (2018) and Ng et al (2017) conducted on 20 patients each were double-blind, randomized controlled trials having split-mouth designs and requiring bilateral maxillary first premolar (MFP) extractions for orthodontic treatment [23,25]. Ang-Khaw et al study comprised 8 males and 12 females and the study of Ng et al had an equal number patients in both the genders while the mean age of the patients were 16.4 ± 1.3 years and 16.7 ± 1.1 years respectively. Both the studies had a test group and a placebo group. However, the root resorption was assessed after a duration of 70 and 28 days by Ang-Khaw et al and Ng et al respectively. Goymen et al conducted their randomized controlled trial in three different groups of 10 patients each - LLLT group, LED group and control group [27]. Fernandes et al equally divided their total sample of 30 patients into Control group, only 'Orthodontic Force' group and 'Orthodontic Force and PBM' group [26]. The mean age of subjects in Goymen's study was 16.27 ± 0.87 years with 14 males and 16 females; the data was not reported by Fernandes et al. The study by Sousa et al comprised 10 subjects (6 female and 4 male) involved in a split-mouth design while Okla et al studied 26 patients who were divided into two groups namely, LLLT and control [21,24]. Both the studies were of six months duration. Out of the six studies, four studies (Ng et al, Ang-Khaw et al, Goymen et al and Fernandes et al) assessed root resorption three-dimensionally subsequent to photobiomodulation [23,25, 26,27]. Three studies used micro-CT for resorption measurement (Ng et al, Ang-Khaw et al, Goymen et al) while Fernandes et al employed conventional computed tomography. The remaining two studies by Okla et al and Sousa et al assessed root resorption two-dimensionally by using intra-oral periapical radiographs subsequent to the clinical procedure [21,24].

Characteristics of the interventions

The type of orthodontic movement carried out varied across the studies. Ng et al, Ang-Khaw et al, and Goymen et al., exerted 150g of buccal tipping force on maxillary first premolars. Sousa et al applied 150g retractive force on canines using NiTi coil spring, Okla et al studied maxillary central incisors undergoing non-specific decrowding, and Fernandes et al exerted intrusive force on maxillary molars.[21,23,25,26,27] Details of the intervention (PBM), namely, the laser type, wavelength, manufacturer, output power, flu-

ence/energy density, total dose per tooth, site of irradiation and duration and frequency were recorded (*Table 3*). Goymen et al, Ng et al and Sousa et al employed Gallium Aluminium Arsenic laser at a wavelength of 810nm (LLLT group), 808nm and 780nm respectively [21,23,27]. Ang-Khaw et al used Aluminium-Gallium-Indium-Phosphorus (AlGaInP) at 660nm [25]. Fernandes et al used an 808nm diode but the semiconductor has not been specified [26]. The powers used by the authors were 100mW by Fernandes et al, 75mW by Ang-Khaw et al, 20mW by Sousa et al and 180mW (continuous delivery group) and 360mW (pulsed delivery group) by Ng et al [21,25,26]. The other two studies did not specify the power used [24,27]. Goymen et al used LED at 850nm for their second test group [27]. Okla et el reported to have used the OrthoPulse® device kit (Biolux Research Ltd. ,Vancouver, BC, Canada) for photobiomodulation (850nm wavelength) and Biolux devices as a placebo (24). In the trials by Ang-Khaw et al & Ng et al, PBM was applied on 4 buccal and 4 palatal points around the roots of the MFP and Fernandes et al applied it around 5 buccal and 5 palatal points [23,25,26]. Sousa et al did not specify the details of the points of irradiation while Okla et al exposed the entire arch. Goymen et al irradiated 10 points in total. In all the studies except the study by Okla et al, the laser tip was in direct contact with the tissue surface.

Characteristics of the study outcomes

Ng et al, Ang-Khaw et al and Goymen et al assessed of the total amount of root resorption in a three-dimensional manner by measuring the volume of root surface craters using micro-CT images. Although Fernandes et al employed CT for resorption measurement, resorption data was presented as root length loss (millimeters) [23,25,26,27]. Out of these, three studies (Ang-Khaw et al, Ng et al and Goymen et al) have further described the distribution of the resorption on four axial surfaces and three vertical thirds for each tooth with mean and standard deviations or standard errors [23,25,27]. Fernandes et al provided a graphical representation of root length changes in the mesiobuccal, distobuccal and palatal roots [26]. The remaining two studies by Okla et al and Sousa et al evaluated the amount of the root resorption two-dimensionally by measuring the differences in the root length directly or by using the Levander and Malmgren Index on periapical radiographs respectively [21,24]. The details have been elucidated in *Table 4*.

Risk of bias of included studies

The risk of bias of all the included studies was ascertained within the specified domains of the Cochrane Risk of bias 2.0 tool. Out of the six studies, two clinical studies (Ng et al, Ang-Khaw et al) had a low risk of bias across the various domains of Selection bias, Performance bias, Detection bias, Attrition Bias and Reporting bias as the studies conformed to the guidelines and reported the data in detail [23,25]. The remaining four studies were placed in the category of overall unclear risk of bias as the information provided in the studies was insufficient to allot them to a high risk or a low risk category [21,24,26,27]. Three studies namely Fernandes et al, Sousa et al and Okla et al failed to provide three-dimensional quantitative resorp-

tion data to be included in the meta-analysis, hence have been marked as a high risk of attrition bias [21,24,26]. Performance of various trials in specific domains of the Cochrane Risk of bias tool is depicted in *Table 5* along with pictorial representations generated in Revman software (version 5.4) in *Figures 2 and 3*. The Kappa statistic for inter-observer agreement for overall risk of bias categorization was 0.85.

Results of individual studies, synthesis of results and additional analyses

Based on the magnitude of homogeneity in the methodologies and study outcomes, the number of studies included in the meta-analysis was three out of six (Ng et al, Ang-Khaw et al and Goymen et al) [23,25,27] These studies were split-mouth randomized controlled trials applying 150g buccal tipping on maxillary first premolars and used micro-CT for volumetric analysis. The study by Ng et al showed an average 0.114 mm^3 less root resorption than the placebo which had statistical significance (P = 0.026). In the study by Ang Khaw et al, there was a mean difference of 0.033 mm^3 greater resorption crater volume in the sham group compared with the intervention group which statistically insignificant (P=0.71) [25]. For the purpose of synthesizing the results, the three study groups of Goymen et al were arranged into two sets – first, the laser versus placebo group and second, the LED versus placebo group. In their study, there was a non-significant increase of 0.016 mm^3 in resorption in laser group vis-à-vis placebo group and a non-significant decrease in resorption of 0.154 mm^3 in LED group compared to control group [27].

The overall sample size of the meta-analysis of the 4 groups extracted out of 3 studies consisted of 60 teeth in the photobiomodulation (Laser/ LED) arm and 60 teeth in the placebo arm. Mean difference was used to determine the association and random effect model was applied for meta-analysis. There was high heterogeneity in the included studies as determined by I^2 index (88%) with appreciable variation in the confidence intervals. The pooled mean difference for overall total root resorption was 0.08 (95% CI 0.15 – (-0.02) to 1.96, p=<0.0001) in favour of photobiomodulation group i.e. significantly lesser total root resorption was seen in the photobiomodulation group (*Figure 4*).

Subgroup analysis (*Figure 5*) was done to determine the root resorption on different axial surfaces. I^2 test revealed high heterogeneity in the included studies for resorption data for the buccal (94%, $p < 0.01$) and distal (91%, $p < 0.01$) surfaces while it was lower for palatal surface (43%, p=0.15) and the least for mesial surface resorption values (0%, p=0.44). The pooled mean differences obtained in root resorption between the photobiomodulation groups and control groups were 0.03, -0.02, -0.04, -0.03 for buccal, palatal, mesial and distal surfaces respectively.

Furthermore, subgroup analysis (*Figure 6*) was conducted for resorption volumes on three vertical divisions of a premolar root viz. cervical, middle and apical third. I^2 testing showed high heterogeneity and non-significant pooled mean differences between test and control groups with respect to cervical and apical

thirds. The pooled mean difference for the middle third was 0.08 in favour of photobiomodulation ($p < 0.00001$). The funnel plot is depicted in Figure 7.

DISCUSSION

The present systematic review applied the selection criteria so as to restrict the review to human trials aiming to scrutinize the impact of photobiomodulation on orthodontic root resorption. A systematic review by Michelogiannikis in 2019 included both animal and human studies and concluded that photobiomodulation effects on root resorption were debatable. [8] There is skepticism about the extrapolation of conclusions of animal research onto man since there is a considerable difference between the tooth size of rats and humans [12]. To avoid incoherence in drawing conclusions, the participants included in the present systematic review were limited to human teeth.

The criterion of intervention in this review was selected as photobiomodulation in the form of low-level diode laser or light-emitting diode. In the present study, the final data which was synthesized for meta-analysis included three groups with LLLT and one with LED as intervention group.

The focus of the method of outcome assessment in the current systematic review was laid on quantification of the root resorption so as to enable decisive interpretation of the magnitude of effect of the intervention. Out of the six studies, two studies employed periapical radiographs (Sousa et al, Okla et al) while the remaining used three-dimensional computed tomography. The validities of 2D radiographic analyses can be questionable as demonstrated by Chan et al owing to parallax errors and surface material denudation while preparing specimens for the same. [28] Furthermore, owing to the meagre methodological homogeneity amongst the 6 studies, trials with two-dimensional resorption data were excluded from the meta-analysis (Sousa et al, Okla et al) [21,24]. Although Fernandes et al employed conventional computed tomography for resorption measurement, data was presented as root length shortening (millimeters), permitting the study to be excluded from the meta-analysis [26]. Consequently, three studies, Ng et al, Ang-Khaw et al and Goymen et al qualified and were selected for the meta-analysis [23,25,27]. Mean difference was the calculated summary effect as the outcome was a continuous variable and the random effects model was used due to the heterogeneity amongst the selected studies. The risk of bias assessment using Cochrane's RoB tool revealed that two out three studies chosen for meta-analysis carried 'low' overall risk of bias (Ng et al and Ang-Khaw et al) and one study carried 'unclear' risk of bias (Goymen et al).

The meta-analysis demonstrated a positive effect of photobiomodulation with regards to mean total root resorption per tooth although it depicts considerable statistical heterogeneity and the evidence for the same is strong ($p < 0.05$). The sub-group analyses of axial surfaces show decrease in root resorption in the irradiated teeth on their mesial, distal and palatal surfaces but there is statistically significant heterogeneity for buccal and distal surfaces ($I^2 = 94\%$ and 91% respectively). Further, the low and moderate heterogeneities of mesial and palatal surface resorptions are based on weak statistical evidence. Similarly, in terms of ver-

tical thirds, photobiomodulation groups tended to demonstrate lower resorption per vertical third but only the middle third showed overlapping confidence intervals and insignificant heterogeneity ($I^2 = 0\%$). The Summary of Findings (SoF) table formulated according to GRADE Pro in order to appraise the quality of evidence showed a moderate overall quality of evidence. Risk of bias was not serious as the potential limitations in study design were unlikely to lower the confidence in the estimate of the effect. Inconsistency was graded as serious owing to the considerable heterogeneity in the outcome. Indirectness and imprecision were not serious and hence the certainty of evidence was moderate. (*Table 6*) The funnel plot generated to evaluate publication bias shows asymmetry but the interpretation derived from it should not be relied upon as the number of studies in considerably low.

Limitations and recommendations

A limitation of the present systematic review is the low number of randomized controlled trials conducting quantitative analysis of root resorption using comparable measurement methods. There is also a probability for different biological reactions being elicited by different wavelengths of photobiomodulation lights [29,30]. Even though there may not be significant therapeutic differences between LLLT and LED, the evidence for the same has yet to be established. Furthermore, orthodontic force factors have a bearing on the magnitude and distribution of root resorption along with the duration of study and outcome assessment method which were found to be variable. [31] In view of this knowledge, the results of the meta-analysis must be interpreted with caution. It is strongly recommended that high-quality trials with more uniformity in intervention methodology be executed.

CONCLUSIONS

The following conclusions may be drawn from the present review:

1. There is moderate grade of evidence to suggest that photobiomodulation has a beneficial effect on root resorption.
2. More high-quality randomized controlled trials with similarity in intervention methods are required for better strength of evidence regarding the influence of PBM on root resorption related to orthodontic tooth movement.

ABBREVIATIONS

PBM- Photobiomodulation

OIIRR- Orthodontically induced inflammatory root resorption

ATP – Adenosine Triphosphate

microCT- micro-computed tomography

LLLT- Low-level laser therapy

LED- Light-emitting diode

μm^3 – cubic micrometer

mm^3 - cubic millimeter

DECLARATIONS

ETHICS APPROVAL AND PARTICIPATION CONSENT

Not applicable

CONSENT FOR PUBLICATION

The authors give consent for publication.

FUNDING

The study is self-funded.

AVAILABILITY OF SUPPORTING DATA

The data can be shared on request.

REFERENCES

1. Weltman B, Vig KWL, Fields HW, Shanker S, Kaizar EE. Root resorption associated with orthodontic tooth movement: A systematic review. Am J Orthod Dentofac Orthop 2010;137(4):462–76. Available from: http://dx.doi.org/10.1016/j.ajodo.2009.06.021
2. Brezniak N, Wasserstein A. Orthodontically Induced Inflammatory Root Resorption . Part I : The Basic Science Aspects. Angle Orthod. 2002;72(2):175–79. Available from: http://dx.doi.org/10.1043/0003-3219(2002)072<0175:OIIRRP>2.0.CO;2.
3. Lund H, Grondahl K, Hansen K, Grondahl H. Apical root resorption during orthodontic treatment A prospective study using cone beam CT. Angle Orthod 2012;82:480-87. Available from: http://dx.doi.org/10.2319/061311-390.1
4. Jönsson A, Malmgren O, Levander E. Long-term follow-up of tooth mobility in maxillary incisors with orthodontically induced apical root resorption. Eur J Orthod. 2007;29(5):482–87. Available from: http://dx.doi.org/10.1093/ejo/cjm047.
5. Sondeijker CFW, Lamberts AA, Beckmann SH, Kuitert RB, Westing K Van, Persoon S, et al. Development of a clinical practice guideline for orthodontically induced external apical root resorption. Eur J Orthod. 2020;42(2):115–24. Available from: http://dx.doi.org/ 10.1093/ejo/cjz034.
6. Brezniak N, Wasserstein A. Orthodontically Induced Inflammatory Root Resorption . Part II : The Clinical Aspects. Angle Orthod 2002;72(2):180–84. Available from: http://dx.doi.org/10.1043/0003-3219(2002)072<0180:OIIRRP>2.0.CO;2.

7. Raza H, Major PW, Dederich D, El-Bialy T. Effect of low-intensity pulsed ultrasound on orthodontically induced root resorption caused by torque: A prospective, double-blind, controlled clinical trial. Angle Orthod. 2016;86(4):550–57. Available from: http://dx.doi.org/10.2319/081915-554.1
8. Michelogiannakis D, Al-shammery D, Akram Z, Rossouw PE, Javed F, Romanos GE. SC. Arch Oral Biol. 2019;100:1-13. Available from: https://doi.org/10.1016/j.archoralbio.2019.01.017.
9. Chung H, Dai T, Sharma SK, Huang Y-Y, Carroll JD, Hamblin MR. The Nuts and Bolts of Low-level Laser (Light) Therapy. Ann Biomed Eng 2012;40(2):516–33. Available from: http://link.springer.com/10.1007/s10439-011-0454-7.
10. Zein R, Selting W, Hamblin MR. Review of light parameters and photobiomodulation efficacy: dive into complexity. J Biomed Opt. 2018;23(12):1-17. Available from: https://doi.org/10.1117/1.JBO.23.12.120901.
11. Heiskanen V, Hamblin MR, Diseases M, Hospital MG. Photobiomodulation : Lasers vs Light Emitting Diodes ? Photochem Photobiol Sci 2019;17(8):1003–17. Available from: https://doi.org/10.1039/c8pp00176f.
12. Seifi M, Vahid-Dastjerdi E. Tooth movement alterations by different low level laser protocols: A literature review. J Lasers Med Sci. 2015;6(1):1–5.
13. Deana NF, Zaror C, Sandoval P, Alves N. Effectiveness of Low-Level Laser Therapy in Reducing Orthodontic Pain: A Systematic Review and Meta-Analysis. Pain Res Manag. 2017;2017:8560652. Available from: https://doi.org/10.1155/2017/8560652
14. Cepera F, Torres FC, Scanavini MA, Paranhos LR, Filho LC, Cardoso MA, et al. Effect of a low-level laser on bone regeneration after rapid maxillary expansion. Am J Orthod Dentofac Orthop 2012 Apr;141(4):444-50. Available from: http://dx.doi.org/10.1016/j.ajodo.2011.10.023.
15. Mcgrath C, Gu M. Effects of Low-Level Laser Therapy as an Adjunct for Orthodontic Retention : A Systematic Review of Human and Animal Studies. Pre-screen. Available from: http://dx.doi.org/10.21203/rs.3.rs-28836/v1
16. Atrium T, Gate S, Road TC, Collaboration TC, Kingdom U. Cochrane Handbook for Systematic Reviews of Interventions. 2011.
17. PRISMA checklist. Available from: http://prisma-statement.org/prismastatement/Checklist.aspx. Accessed on: November 2019.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions : Explanation and Elaboration. Journal of Clinical Epi-demiology 2009; 62: e1–34. Available from: http://dx.doi.org/10.1371/journal.pmed.1000100.
19. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines : 12 . Preparing Summary of Findings tables - binary outcomes. J Clin Epidemiol . 2013;66(2):158-72. Available from: http://dx.doi.org/10.1016/j.jclinepi.2012.01.012.
20. Cruz DR, Kohara EK, Ribeiro MS, Wetter NU. Effects of low-intensity laser therapy on the ortho-

dontic movement velocity of human teeth: A preliminary study. Lasers Surg Med. 2004;35(2):117–20. Available from: http://dx.doi.org/10.1002/lsm.20076.

21. da Silva Sousa MV, Scanavini MA, Sannomiya EK, Velasco LG, Angelieri F. Influence of Low-Level Laser on the Speed of Orthodontic Movement. Photomed Laser Surg 2011;29(3):191–6. Available from: https://www.liebertpub.com/doi/10.1089/pho.2009.2652.
22. Nimeri G, Kau CH, Corona R, Shelly J. The effect of photobiomodulation on root resorption during orthodontic treatment. Clin Cosmet Investig Dent 2014;6:1-8. Available from: http://dx.doi.org/10.2147/CCIDE.S49489.
23. Ng D, Chan AK, Papadopoulou AK, Dalci O, Petocz P, Darendeliler MA. The effect of low-level laser therapy on orthodontically induced root resorption: a pilot double blind randomized controlled trial. Eur J Orthod [Internet]. 2017;1–9. Available from: https://doi.org/10. 1093/ejo/cjx065.
24. Okla N, Bader D, Makki L (2018) Effect ofphotobiomodulation on maxillary decrowding and root resorption: a randomized clinical trial. APOS Trends Orthod 8:86–91. https://doi.org/10.4103/apos.
25. Ang Khaw CM, Dalci O, Foley M, Petocz P, Darendeliler MA, Papadopoulou AK. Physical properties of root cementum: Part 27. Effect of low-level laser therapy on the repair of orthodontically induced inflammatory root resorption: A double-blind, split-mouth, randomized controlled clinical trial. Am J Orthod Dentofac Orthop. 2018;154(3):326–36. Available from: https://doi.org/10.1016/j.ajodo.2018.04. 022.
26. Fernandes MRU, Suzuki SS, Suzuki H, Martinez EF, Garcez AS. Photobiomodulation increases intrusion tooth movement and modulates IL-6, IL-8 and IL-1β expression during orthodontically bone remodeling. J Biophotonics 2019;12(10):e201800311. Doi: 10.1002/jbio.201800311.
27. Goymen M, Gulec A. Effect of photobiomodulation therapies on the root resorption associated with orthodontic forces: a pilot study using micro computed tomography. Clin Oral Investig. 2020;24(4):1431-38. doi: 10.1007/s00784-019-03155-w
28. Chan EKM, Darendeliler MA. Exploring the third dimension in root resorption. Orthod Craniofacial Res. 2004;7(2):64–70.
29. Wang Y, Huang Y, Wang Y, Lyu P, Hamblin MR. Biochimica et Biophysica Acta Photobiomodulation of human adipose-derived stem cells using 810 nm and 980 nm lasers operates via different mechanisms of action. BBA - Gen Subj 2017;1861(2):441–9. Available from: http://dx.doi.org/10.1016/j.bbagen.2016.10.008
30. Santana-blank L, Rodrı E, Santana-rodrı K. Theoretic , Experimental , Clinical Bases of the Water Oscillator Hypothesis in Near-Infrared Photobiomodulation. 2010; Photomed Laser Surg . 2010 Aug;28 Suppl 1:S41-52. doi: 10.1089/pho.2009.2647.
31. Nayyer N, Tripathi T, Gopal R. Effect of photobiomodulation on external root resorption during orthodontic tooth movement—a scoping review. Lasers in Dental Science 2019;3(4):219-26. DOI-10.1007/s41547-019-00072-9.

Appendix

Articles whose full texts were downloaded - Cruz et al, Sousa et al, Nimeri et al, Ng et al, Okla et al, Ang Khaw et al, Goymen et al, Fernandes et al.

Reasons for exclusion of studies from systematic review- Nimeri et al- No Control Group; Cruz et al – No quantitative data.

Studies included in systematic review –Sousa et al, Ng et al, Okla et al, Ang Khaw et al, Goymen et al, Fernandes et al.

Studies included in meta-analysis- Ng et al, Ang Khaw et al, Goymen et al.

FIGURE LEGENDS

Figure 1. PRISMA flow chart depicting study selection

Figure 2. Risk of bias of studies in specific domains of Cochrane Risk of Bias tool

Figure 3. Risk of bias of individual studies in each domain of Cochrane Risk of Bias tool

Figure 4. Forest plot of mean total root resorption

Figure 5. Forest plot of mean resorption on each axial surface of root i.e. buccal, palatal, mesial and distal surface

Figure 6. Forest plot of mean resorption on each vertical third of root surface i.e. coronal, middle and apical third

Figure 7. Funnet plot.

TABLE CAPTIONS

Table 1. Search strategies employed for various databases and results retrieved

Table 2. General characteristics of included studies

Table 3. Details of intervention (photobiomodulation) of included studies

Table 4. Characteristics of the study outcomes

Table 5. Risk of Bias Assessment of included studies

Table 6. Summary of Findings according to GRADE Assessment Profile

Impact of Photobiomodulation on External Root Resorption During Orthodontic Tooth Movement in Humans – A Systematic Review and Meta-analysis

ORIGINALITY REPORT

17%	11%	13%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Dimitrios Michelogiannakis, Deema Al-Shammery, Zohaib Akram, P. Emile Rossouw, Fawad Javed, Georgios E. Romanos. "Influence of low-level laser therapy on orthodontically-induced inflammatory root resorption. A systematic review", Archives of Oral Biology, 2019 Publication	3%
2	Nida Nayyer, Tulika Tripathi, Priyank Rai, Ram Gopal. "Effect of photobiomodulation on external root resorption during orthodontic tooth movement—a scoping review", Lasers in Dental Science, 2019 Publication	2%
3	search.bvsalud.org Internet Source	1%
4	hdl.handle.net Internet Source	1%

5	Spyridon N Papageorgiou, Despina Koletsi, Anna Iliadi, Timo Peltomaki, Theodore Eliades. "Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses", European Journal of Orthodontics, 2019 Publication	1 %
6	www.dbc.wroc.pl Internet Source	1 %
7	Jesse Hu, Richard M Rainsbury, Ashvina Segaran, Oana Predescu, Pankaj G Roy. "Objective assessment of clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast-conserving surgery: protocol for a systematic review", BMJ Open, 2018 Publication	1 %
8	meridian.allenpress.com Internet Source	1 %
9	Chun M. Ang Khaw, Oyku Dalci, Matthew Foley, Peter Petocz, M. Ali Darendeliler, Alexandra K. Papadopoulou. "Physical properties of root cementum: Part 27. Effect of low-level laser therapy on the repair of orthodontically induced inflammatory root resorption: A double-blind, split-mouth,	1 %

	randomized controlled clinical trial", American Journal of Orthodontics and Dentofacial Orthopedics, 2018 Publication	
10	academic.oup.com Internet Source	<1 %
11	Corinne Stahli, Theodore Eliades, Spyridon N. Papageorgiou. "Functional appliance treatment for mandibular fractures: a systematic review with meta‐analyses", Journal of Oral Rehabilitation, 2021 Publication	<1 %
12	link.springer.com Internet Source	<1 %
13	www.hrb.ie Internet Source	<1 %
14	progressinorthodontics.springeropen.com Internet Source	<1 %
15	assets.researchsquare.com Internet Source	<1 %
16	Alessandra Sinopoli, Claudia Isonne, Maria Mercedes Santoro, Valentina Baccolini. "The effects of orally administered lactoferrin in the prevention and management of viral infections: A systematic review", Reviews in Medical Virology, 2021 Publication	<1 %

17	Sharon Lechtig-Wasserman, Hans Liebisch-Rey, Nicolas Diaz-Pinilla, Jhosep Blanco et al. "Carbapenem Therapeutic Drug Monitoring in Critically Ill Adult Patients and Clinical Outcomes: A Systematic Review with Meta-Analysis", Antibiotics, 2021 Publication	<1 %
18	aadsm.org Internet Source	<1 %
19	helicojournal.org Internet Source	<1 %
20	journals.sagepub.com Internet Source	<1 %
21	bmcpregnancychildbirth.biomedcentral.com Internet Source	<1 %
22	www.degruyter.com Internet Source	<1 %
23	www.laser-therapy.us Internet Source	<1 %
24	www.science.gov Internet Source	<1 %
25	evidenciasenpediatria.es Internet Source	<1 %
26	pubmed.ncbi.nlm.nih.gov Internet Source	<1 %

Exclude quotes	On	Exclude matches	< 14 words
Exclude bibliography	On		