**Review Article**

# Clinical and Molecular Factors Associated with External Apical Root Resorption Following Orthodontic Treatments; An Umbrella Review

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## Abstract

**Background and Aim:** The aim of this study was to analyze the available evidence on external apical root resorption (EARR) due to orthodontic movement to identify clinical and molecular factors associated to this condition.

**Materials and Methods:** An umbrella review was conducted, encompassing systematic reviews and meta-analyses. Four databases—PubMed, ScienceDirect, Scopus, and Cochrane—were searched. The reviews were critically evaluated according to PRISMA and AMSTAR-2 guidelines. The study protocol was registered with PROSPERO (CRD42020198971).

**Results:** Totally, 124 papers were considered eligible for this investigation. Following title and abstract screening, 10 papers (4 systematic reviews and 6 meta-analyses) were included. The AMSTAR-2 guideline was applied, and the evaluation was conducted in accordance with PRISMA guidelines. Factors such as female gender, adulthood, conventional fixed orthodontic treatment, heavy, continuous and prolonged loads, intrusive movements and anterior superior teeth with abnormal roots increased the risk of developing this condition. At the molecular level, biomarkers such as IL-1β, IL-6, IL-4, and dentin phosphoprotein (DPP) were considered crucial for early diagnosis of external root resorption (ERR). Notably, the IL-1β (+3954) gene polymorphism was the most significant predictor of this condition in patients undergoing orthodontic treatment.

**Conclusion:** Clinical and molecular factors, which are influenced by individual characteristics, must be identified to assess the risk of developing EARR. Prolonged treatments should be avoided, and immunoassays to analyze proteins in gingival crevicular fluid (GCF) should be utilized for early diagnosis.

**Key Words:** Orthodontic; Root Resorption; Gingival Crevicular Fluid; Biomarkers; Cytokines

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## Introduction

External apical root resorption (EARR) is one of the undesired biological effects of orthodontic treatments [1-3]. Permanent loss of root structure is originated by excessive pressure, leading to capillary collapse, reduced blood flow and overwhelming of the repair capacity of supporting tissues. Consequently, necrotic areas, referred to as hyaline zones are formed, triggering an inflammatory response that activates cellular and molecular mechanisms promoting EARR [1,2,4-7]. The formation of hyaline areas during orthodontic treatment is inevitable; however, the incidence and severity of EARR vary widely, ranging from 26% to 100%, depending on biological, mechanical, and molecular factors [6,8,9]. Orthodontic movements are not the sole contributors to the onset of EARR [6,10-13].

Various investigative approaches have associated several factors with an increased risk of developing EARR, including age, gender, nutritional status, medication use, systemic diseases, genetics, oral habits, malocclusion, tooth type, root morphology, history of dental trauma, previous orthodontic treatments, pulp vitality, infections, and inflammation [2,3,7,11, 14-16]. Mechanical factors include type of orthodontic appliances, orthodontic movement type, extractions, treatment time and level or force magnitude [7,17-25]. In addition, several biomarkers are related with the progress of EARR as a response to the orthodontic dental movement. Tissue tension induces structural reorganization within tissues, leading to the release of neurotransmitters, growth factors, and cytokines. These substances, which are released into the gingival crevicular fluid (GCF), have been studied extensively to understand their roles and effects [5,6,16,26-28].

Interleukins are a complex of cytokines or low-molecular weight proteins that act as messengers and are physiologically secreted during the bone remodeling process in response to local stress (IL 1 β, IL-6, IL-7, IL-8, TNFα, IL-4, IL-10, IL-13, IL18, and IFN-γ). The human genome codifies around 50 interleukins and associated proteins. However, their association with EARR has not been conclusive as data convergence has not been obtained [6,8,10,16-33].

Diagnosis of EARR depends on early detection using routine radiographs. Root shortening begins between the second and fifth treatment weeks, but such change will be only visible in panoramic or periapical radiographs at three or four months after the beginning of the orthodontic treatment. As these diagnostic aids underestimate the extension and produce negative false cases, the “gold standard” to diagnose EARR is the Cone Beam Computed Tomography (CBCT) because it accurately detects EARR without the existing limitations of other techniques. CBCT offers high-resolution structural analysis in the three planes of space and superimposition elimination, which provide high sensitivity and specificity in the identification of these type of conditions [2,3, 10,33-35].

There are multiple clinical and orthodontic variables associated with EARR. However, investigations show contradictory results, so careful analysis is necessary due the high heterogeneity within original studies. Therefore, the main objective of this umbrella review was to analyze current evidence on orthodontically-induced EARR to identify clinical and molecular factors associated with this condition.

## Materials and Methods

### Design

An umbrella review was performed beginning with a PICO question (Population, Intervention, Comparison and Outcome). A search strategy, inclusion criteria and quality assessment with analysis of results were carried out. The study protocol was inscribed in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42020198971).

### Search strategy

Four electronic databases were used: PubMed, Science Direct, Scopus and Cochrane. Systematic reviews and meta-analyses were identified using the terms orthodontic AND root resorption. The search was conducted including articles from 2015 to 2020. In order to guarantee the exhaustivity of the protocol, an additional search using thesaurus terms and different word combinations was performed. This addition search included (((((“orthodontal”[All Fields] OR “orthodontic” [All Fields]) OR “orthodontical”[All Fields]) OR “orthodontically”[All Fields]) OR “orthodontics” [MeSH Terms]) OR “orthodontics”[All Fields]) AND ((“root resorption”[MeSH Terms] OR (“root”[All Fields] AND “resorption”[All Fields])) OR “root resorption” [All Fields]))))).

**Inclusion and exclusion criteria**

The PICO question used in the current work according to the main objective was: (P) patients from different age, gender and ethnicity; (I) previous orthodontic treatment; (C) during orthodontic treatment; (O) what clinical and molecular factors are associated with the incidence of EARR? Systematic reviews and meta-analyses performed from human subjects and published between 2015 and 2020 were included. Exclusion criteria included other types of investigations (analytical, clinical, guidelines, review articles, letters to the editor, opinion articles and observational studies)

The following inclusion criteria were applied upon title and abstract reading:

a. Search terms in the title or abstract.
b. Publications in human subjects
c. Systematic review or meta-analysis

**Article selection**

A total of 124 potentially eligible articles were identified. After duplicate elimination, 118 articles remained, which were then screened for title and abstract. One-hundred articles were not related to the topic and were discarded. The remaining 18 articles were read and analyzed and 8 were subsequently discarded because the studied population was animals. Ten articles (4 systematic reviews and 6 systematic reviews with meta-analysis) were selected for data analysis and validation using the PRISMA and AMSTAR-2 guidelines. The flow of article selection is shown in figure 1.

**Critical analysis**

Three independent investigators assessed the validity of the selected articles. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR-2 (Admeasurement Tool to Assess Systematic Reviews) guidelines were used to verify their quality. A calibration process was then performed and a 90% concordance index was obtained.

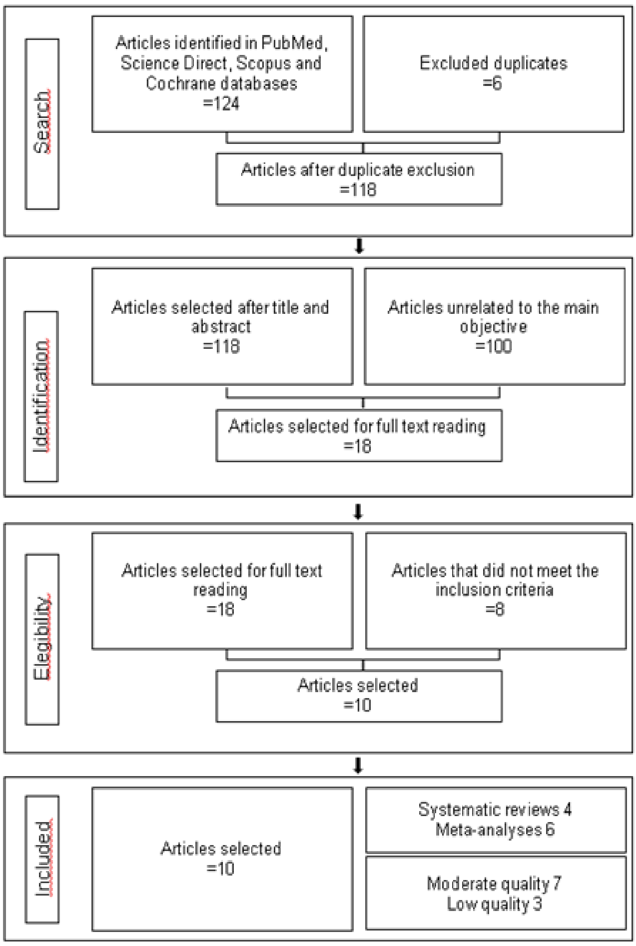

**Figure 1.** Selection process of included articles

All the evaluations were performed using the PRISMA checklist applying the identification, screening, selection and inclusion phases from the guidelines using 27 questions. Then, the AMSTAR-2 guideline was applied to assess the quality of the articles and four levels of quality were obtained: high, moderate, low and critically low.

The risk of bias, classified as low, high or undefined, was assessed for every single article. In addition, whether heterogeneity was reported was also established. A descriptive analysis of the main characteristics of the included revisions was carried out.

## Results

Quality assessment of systematic reviews and meta-analyses

Quality assessment of the 10 included articles in this umbrella review is shown in Table 1. According to the AMSTAR-2 guideline, 7 studies were classified as having moderate quality and 3 as low quality. According to the PRISMA guideline, the articles with the best scores were the investigations performed by Shifat A Nowrin et al [5], Vaibhav Gandhi et al [2], Jianru Yi et al [35] and Xuanwei Fang [36]. Out of the 27 items included in the PRISMA checklist, only one article matches all the criteria and the score was over 18 points. Besides, 9 out of 10 articles reported high heterogeneity and the remaining articles did not report it.

Quality assessment instruments reported in these studies are the GRADE (Grading of Recommendations, Assessment, Development and Evaluations), which was used in three articles, the STREGA (Strengthening the Reporting of Genetic Association Studies) statement in two articles, the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool in 1 study, the MINORS (Methodological index for non-randomized studies) index in 1 work, the QAI (Quality Assurance International) certification in 1 article, the PRISMA guideline in 1 article and the Methodologic Scoring System adopted by Roscoe MG et al. [7]in 2015 in the remaining article.

Cochrane evaluation of individual studies identified sources of bias (Table 2) and assessed the presence of a prism algorithm, the report of inter observer evaluation and the presence of a funnel plot in each study. The results for this study showed that all investigations exposed the use of prism algorithm, resulting in low risk of selection bias. Assessment of inter observer concordance was reported in all articles, leading to a low risk of bias. Due to the presence of a funnel plot, only 2 studies showed low risk of report bias and it was undefined or unclear in the remaining articles as some doubts about the results arose.

With the purpose of reducing systematic errors, possible bias in the included articles was identified. Due to the high variability among ethnic groups, a selection bias may be found in genetic studies as genotypes vary according to ethnicity. Samples of fewer than 100 patients were considered a potential bias. The difference in precision among radiographies and measurement and quantification methods was also considered a measurement bias. Absence of control groups, lack of high quality prospective studies, non-homogeneity at the GCF collection time, different methods to collect this fluid and measurement of applied force magnitude were other biases.

**Main characteristics of reports**

The main characteristics of articles included in this umbrella review compared different clinical and molecular variables that increase the risk of developing external apical root resorption during the orthodontic treatment. Out of 10 investigations, 4 were performed in Asia, 2 in North America, 1 in South America, 2 in Europe and 1 in Oceania.

Most investigations were randomized controlled clinical trials performed in human subjects under orthodontic treatment or about to begin one. Sample size was established according to each investigation and most works only include 3D diagnostic aids. For qualitative studies (systematic reviews), the minimum number of included studies was 2 and the maximum was 30. For quantitative studies (meta-analysis), the minimum number of included studies was 3 and the maximum was 16.

As for age, the minimum age to participate in the studies was 8 years and the maximum was 75 years. Only 6 papers reported gender information and more females than males were included. Diagnostic aids ranged from lateral cephalograms, panoramic, occlusal radiographies, periapical radiographies and scanning electron microscopy (SEM). However, 80% of the authors preferred the CBCT as the measurement method due to its high precision. Samples from GCF were obtained using filter papers, paper strips and micropipettes and analyses were performed using techniques such as Taqman, Ncoi sequencing, ELISA immunoassays, among others. Only two types

**Table 1.** Assessment and quality for the selected articles

| Article | Prisma Guideline Information Qualification | AMSTAR-2 Guideline General Quality | Heterogeneity | Quality Assessment Instrument Used In The Study |
|---|---|---|---|---|
| Shifat A Nowrina<br>Saidi Jaafarb<br>Norma Ab Rahmana<br>Rehana Basric<br>Mohammad Khursheed Alamd<br>Fazal Shahida 2018 [5] | 24/27 | LOW | CC vs. TT: p-value: 0.020 I2: 60.136<br>CT vs. TT: p-value: 0.019 I2: 60.371<br>CC + CT vs TT: p-value: 0.032 I2: 56.520<br>CC vs. CT + TT: p-value: 0.000 I2: 76.917 | (STREGA) statement |
| Arwa Aldeeri, Lulu Alhammad, Amjad Alduham, Waad Ghassan, Sanaa Shafshak, Eman Fatani 2018 [4] | 18/27 | MODERATE | NR | The Methodologic Scoring System Adopted from Roscoe MG et al, 2015.[7] |
| Marina G. Roscoe, Josete B. C. Meira, and Paolo M. Cattaneo 2015 [7] | 21/27 | MODERATE | Heterogeneity in study design and treatment protocols | PRISMA 2009 checklist |
| Francesco Tarallo, Claudio Chimenti, Giordano Paiella, Massimo Cordaro and Michele Tepedino 2019 [6] | 20/27 | LOW | Heterogeneity in the studies | Quality Assessment Instrument (QAI) |
| Vaibhav Gandhi , Shivam Mehta, Marissa Gauthier, Jijian Mu, Chia-Ling Kuo, , Ravindra Nanda and Sumit Yadav 2020 [2] | 27/27 | MODERATE | Heterogeneity among studies was modeled by a the effect of a random study in the mixed-effects meta-regression model | Methodological index for non-randomized studies (MINORS) |
| Aikaterini Samandara, Spyridon N Papageorgiou, Ioulia Ioannidou-Marathiotou, Smaragda Kavvadia-Tsatala, Moschos A Papadopoulos 2018 [3] | 23/27 | MODERATE | P <0.10 | Grading of Recommendations, Assessment, Development and Evaluations (GRADE)<br>Downs and Black checklist |
| Scott Derek Currell, , Andrew Liaw, A y Alan Nimmo 2019 [1] | 21/27 | MODERATE | NR | Grading of Recommendations, Assessment, Development and Evaluations (GRADE) |
| Hatem A. Alhadainy, Carlos Flores, Jacqueline Crossman 2016 [13] | 18/27 | LOW | P <0,05; I2 = 69%). Because I2 was 69%, a random effects model was performed that showed a funnel plot with asymmetric distribution of the included studies | Grading of Recommendations, Assessment, Development and Evaluations (GRADE) |
| Jianru Yi, Meile Li y Zhihe Zhao 2016 [35] | 23/27 | MODERATE | (I2> 50%) The hypothesis test was set at p <0.05 | STREGA statement |
| Xuanwei Fang, Rui Qi, Chufeng Liu 2019 [36] | 22/27 | MODERATE | Chi2= 17,14 df= 12 (P= 0,14) I2= 30% | Grading of Recommendations, Assessment, Development and Evaluations (GRADE) |

**Table 2.** Cochrane evaluation for individual studies

| | | | |
|---|---|---|---|
| "Shifat A Nowrina, Saidi Jaafarb, Norma Ab Rahman, Rehana Basric Mohammad Khursheed Alamd, Fazal Shahida" | - | - | - |
| Arwa Aldeeri, Lulu Alhammad, Amjad Alduham, Waad Ghassan, Sanaa Shafshak, Eman Fatani | ? | - | - |
| Marina G. Roscoe, Josete B. C. Meira, and Paolo M. Cattaneo | ? | - | - |
| Francesco Tarallo, Claudio Chimenti, Giordano Paiella, Massimo Cordaro and Michele Tepedino | ? | - | - |
| Vaibhav Gandhi, Shivam Mehta, Marissa Gauthier, Jijian Mu, Chia-Ling Kuo, , Ravindra Nanda and Sumit Yadav | - | - | - |
| Aikaterini Samandara, Spyridon N Papageorgiou, Ioulia Ioannidou-Marathiotou, Smaragda Kavvadia Tsatala, Moschos A Papadopoulos | ? | - | - |
| Scott Derek Currell, Andrew Liaw, A y Alan Nimmo | ? | - | - |
| Hatem A. Alhadainy, Carlos Flores, Jacqueline Crossman | ? | - | - |
| Jianru Yi, Meile Li y Zhihe Zhao | ? | - | - |
| Xuanwei Fang, Rui Qi, Chufeng Liu | ? | - | - |
| 🔴 HIGH RISK OF BIAS<br>🟢 LOW RISK OF BIAS<br>🟡 UNDEFINED RISK OF BIAS | Funnel Plot | Prisma Algorithm | Interobserver Assessment |

of orthodontic appliances were reported (clear dental aligners or fixed orthodontic appliances). For the volumetric measurement of the EARR, the following methods were reported: linear measurements, radiometric, millimeters and voxel 3D. Four studies classified EARR as light, moderate and severe. As for biological factors, one study analyzed ethnicity and found higher prevalence in Caucasian and Hispanic populations than Asians. As for patient type (children, adolescents or adults), the most severe form of EARR was found more frequently in adults than adolescents (Table 3). Immunological factors were referred as variables such as genetic polymorphism expression and the presence of cytokines, interleukins, RANK, OPG, DPP, DSP and ALP among other biomarkers. All these factors and the main conclusions are summarized in table 4.

**Table 3.** Main characteristics of included systematic reviews and meta-analyses. Description of individual studies

| Article | Average Age | Gender | Radiographies | Treatment Type | Root Resorption Quantification Method |
|---|---|---|---|---|---|
| Association between genetic polymorphisms and external apical root resorption: A systematic review and meta-analysis [5] | 8.0-55.4 years | NR | Lateral cephalogram, panoramic, CBCT, occlusal, periapical | "Treatment type" confounding factor was not considered | Radiographic analysis |
| Association of Orthodontic Clear Aligners with Root Resorption Using Three-dimension Measurements: A Systematic Review [4] | 8.3-33.7 years | NR | CBCT, micro computerized tomography | Orthodontic treatment with transparent aligners (Invisalign and ClearSmile®). Light load (25 g) and heavy load (225 g) | Volumetric measurement |
| Association of orthodontic force system and root resorption: A systematic review [7] | 10.2-41.8 years | 66% females<br>43% males | Periapical | 12 split-mouth studies assessed the influence of load level on OIIRR in premolars. Except the study by Harry and Sims, the remaining studies compared a light (25g) with a heavy load (225g), light torque (2.5°) with heavy torque (15°), and light distal inclination (2.5°) with heavy distal inclination (15°) as the most studied, followed by intrusión | Volumetric measurements and histologic analyses |
| Biomarkers in the gingival crevicular fluid used to detect root resorption in patients undergoing orthodontic treatment: a systematic review [6] | 9.0-44.0 years | 73% females<br>27% males | Panoramic | 2 split-mouth studies, one in canines and one in premolars. 5 clinical trials with control group. Studies with GCF collection during and after orthodontic treatment to verify the presence of ERR biomarkers | Low, moderate and severe; cytokine measurement with GCF collection |
| Comparison of external apical root resorption with clear aligners and pre-adjusted edgewise appliances in non-extraction cases: a systematic review and meta-analysis [2] | 10.0-75.0 years | 65% females<br>35% males | Panoramic, periapical, CBCT | Treatment with Invisalign and Smart Track aligners and Roth and MBT prescriptions for fixed orthodontic treatment | Radiometric measurements in millimeters |
| Evaluation of orthodontically induced external root resorption following orthodontic treatment using cone beam computed tomography (CBCT): a systematic review and meta-analysis [3] | 11,4 - 26,6 years | 37,7% males<br>62,3% females | CBCT | Fixed orthodontic treatment, anterior maxillary intrusion or rapid maxillary expansion | Changes in length and volume |
| Orthodontic mechanotherapies and their influence on external root resorption: A systematic review [1] | 12,3 - 20, 9 years | NR | Computerized tomography, SEM, periapical, CBCT | 3 studies assessed continuous and intermittent forces with different force magnitudes and follow-up periods. All the studies used a split-mouth design with fixed orthodontic brackets bonded to the premolars | Volumetric measurement |
| Orthodontic-induced External Root Resorption of Endodontically Treated Teeth: A Meta-analysis [13] | 12,8 - 34,5 years | NR | CBCT, periapical, panoramic, lateral cephalogram | Fixed orthodontic treatment on vital and non-vital teeth | Linear measurement of the EARR |
| Root resorption during orthodontic treatment with self-ligating or conventional brackets: a systematic review and meta-analysis [37] | 12 - 30 years | 40,6% males<br>59,4% females | CBCT, periapical | Self-ligation and conventional fixed orthodontic treatment | Volumetric measurement |
| Root resorption in orthodontic treatment with clear aligners: A Systematic Review and Meta-Analysis [36] | 12- 58 years | 40% males<br>60% females | CBCT, periapical, panoramic | Fixed orthodontic treatment vs aligners | Volumetric measurement |

**Table 4.** Summary of contributing factors to the development of EARR according to results from systematic reviews and meta-analyses

| Category | Factor | Description | Article |
|---|---|---|---|
| Mechanical Factors | | | |
| | Force Magnitude | Under the same mechanical stress, many subjects exhibit low and some severe ERR | [1] |
| | | There are positive correlations between ERR and continuous forces | [3] |
| | | There is a positive correlation between ERR and an increase in the orthodontic force magnitude regardless of force direction | [6] |
| | Treatment Duration | The higher the treatment time, the higher the root resorption | [3] |
| | | A pause in dental movement is beneficial to reduce ERR | [3,6,10] |
| | | A reduction in root resorption was observed in patients who received orthodontic treatment in two phases | [6] |
| | Movement Direction or Type | Buccal inclination was associated with ERR in the Bucco cervical and linguoapical regions | [3] |
| | | Buccal root torque was associated with ERR in the Bucco apical and palatocervical regions | [3] |
| | | Distal inclination was associated with ERR in the distal aspect of the apical and middle thirds and in the mesial aspects in the cervical third | [3] |
| | | Extrusion movement was associated with increased resorption on the distal surfaces | [3] |
| | | There are positive correlations between ERR and intrusive forces | [3,6] |
| | Type Of Orthodontic Device | Transparent aligners do not reduce the risk of developing ERR, although the incidence and severity might be reduced | [1, 2] |
| | | Similar results are observed when patients are treated with light forces using aligners or brackets | [3] |
| | | Teeth subjected to super elastic NITI arch wires show higher ERR | [3] |
| | | Differences were not found in the prevalence or severity of ERR when straight-wire appliances were compared with standard appliances | [6] |
| | | Class-II elastics is a risk factor for ERR | [8] |
| | | Meta-analysis results suggest that self-ligating brackets are better than conventional brackets at protecting maxillary central incisors against ERR | [9] |
| Biologic Factors | | | |
| | Age | No age predilection was found | [2] |
| | Race | ERR is higher in Caucasians and Hispanics than Asians | [2] |
| | Gender | Proportion of ERR cases was higher in females than males | [8] |
| | | No predilection of ERR for males or females | [2] |
| | Tooth Type | The highest root resorption was found on the maxillary lateral incisors followed by maxillary central incisors and canines | [2,7,8] |
| | | The highest ERR was observed in the anterior maxilla followed by the anterior mandible, posterior mandible and posterior maxilla | [7] |
| | Root Morphology | Root morphology (abnormal shape, long and narrow roots) is associated with ERR | [8] |
| | Provious Extractions | Orthodontic treatment involving extractions are more associated with reduction in root size | [7] |
| | | Dental extraction to resolve severe dental crowding may be considered a risk factor for ERR | [10] |
| | Pulp Vitalitry | An increase in ERR in endodontically treated teeth after orthodontic treatment was not observed | [8] |
| | | No difference was found in the degree of ERR between endodontically treated teeth vs contralateral vital teeth | [8] |
| | | Endodontic treatment in males exhibited a significant increased ERR | [8] |
| Molecular Factors | | | |
| | Expression Of Genetic Polymorphisms | IL-1B (+3954) polymorphism is considered a promising gene to predict ERR | [1] |
| | | Patients who are homozygous for allele 1 of the IL-1B (+3954) gene have a 95% probability of developing ERR > 2mm | [1] |
| | Cytokines | Levels of IL- 4, IFN- γ and GMCSF are higher in light ERR cases | [5] |
| | | Dentin matrix protein (DMP - 1) is not a useful biomarker because it is not possible to differentiate between its physiological and pathological activities | [5] |
| | | Dentin phosphoprotein (DPP) is a relatively useful biomarker for ERR diagnosis | [5] |
| | | RANKL concentration in the GCF is higher in patients with light and severe ERR | [5] |
| | | There are higher concentrations of DPP, DSP and IL-6 in patients with severe ERR | [5] |
| | | Overall alkaline phosphatase (ALP) activity increased with higher rates of tooth movement at 150 g of force | [5] |
| | | Cytokine levels are different depending on sampling sites and occurring time | [5] |

## Discussion

Due to the absence of pathognomonic signs, EARR is casually detected in routine panoramic radiographies. However, underestimation of its severity may lead to permanent loss of important root structure since other risks patients are subjected to from their biological background, their interaction with the environment and factors related to the mechanics employed in the orthodontic treatment are mostly unknown. Results presented in this umbrella review may be used as a foundation to develop more solid investigations on this topic.

In 2019, Currel et al. analyzed the degree of root resorption in teeth subjected to orthodontic treatment considering mechanical factors such as type of device and orthodontic force magnitude and direction. It was found that continuous forces increase EARR regardless of magnitude and direction. Bracket type, ligation and archwire sequence did not influence the severity of EARR [1]. In 2019, Samandara reported that root shortening is significantly increased after orthodontic therapy and confirmed that heavy forces, extractions and anterior teeth with abnormal root morphology are factors that increase the prevalence and severity of this condition [3]. Similar results are reported by Fernandes et al [38] stating that orthodontic therapy with extractions increases the risk of EARR by 70% and also considering other variables, such as increased overjet and long dilacerated roots . Harris et al. [39], Barbagallo et al. [25], Cheng et al. [40] and Paetyangkul et al. [34] concurred that there is a directly proportional relation between force and EARR and that the type of orthodontic movement is a significant mechanical factor as forces intensify on certain areas of the root according to the orthodontic action. For instance, pressure accumulates on the root apex during intrusion movements, thus increasing the risk of EARR in that zone. During extrusion movements, EARR is more frequently found on the cervical third toward mesial and distal, which are the areas where pressure accumulates. However, it is important to mention that extrusion movements have four times lower resorption probabilities than intrusions [41].

The type of appliance used in the orthodontic treatment is another variable that may influence the behavior of the root resorption process. Conventional brackets have been compared with self-ligating ones to determine whether significant differences are found between both bracket types in the incidence of EARR. It is established that self-ligating systems may produce lighter forces durign aligning movements since no ligature is needed, which may prduce a protective effect for maxillary central incisors that are most vulnerable. However, it has also been concluded that it is not possible to suggest the superiority of one system over another due to the lack of investigations that follow solid methodologies to identify the exact differences between both systems [35,37].

Regarding molecular factors, articles suggest that EARR has an important genetic component. Homozygous patients for allele 1 of IL-1B exhibit 5 to 6 times higher risk of developing EARR >2 mm than other groups. Data show that allele 1 in IL-1B gene, known for reducing the production of IL-1 cytokine, significantly increases the risk of resorption. In addition, it has been suggested that EARR is a complex condition influenced by many different factors that are important to know to understand the contribution of environmental factors, such as habits and biomechanics [5,42].

The search for EARR biomarkers intensified after finding dentin specific proteins (dentin phosphoprotein –DPP- and dentin sialoprotein – DSP) that are byproducts found in the GCF, even though such proteins are not routinely released within the periodontal ligament space. ELISA immunoassays were analyzed by James et al., and later confirmed by Balducci et al., which identified and quantified these proteins in patients under orthodontic treatment. DMP-1 was found in large quantities in the GCF as it is eliminated from bone and dentin during resorption processes. However, based on the results of the current work, DMP-1 is not dentin-specific and its presence may be explained not only because of EARR, but also due to the remodeling process during the orthodontic movement. As such, it is not an adequate biomarker of this condition as it is not possible to differentiate between its normal and pathological activities. Likewise, DSP protein was found in control groups, so no consensus is reached in the scientific literature to classify them as exact molecular biomarkers of EARR as they are not exclusive of dentin and are expressed in the osseous tissue. Their presence in the GCF may be explained by physiological remodeling processes, which are increased in patients under orthodontic treatment [42, 43].

Perinetti et al.[44] assessed the activity of alkaline phosphatase (ALP) in the GCF to evaluate its utility in the diagnosis of EARR during the orthodontic treatment. The authors observed a significantly higher ALP activity in tension sites compared to compression zones, which increases as the force increase. However, this finding only reflects the biological activity of such compound in the periodontium during the dental movement and must be further studied.

As for dental pulp status and root resorption, Alhadainy et al.[13] concluded that the endodontic treatment does not seem to increase root resorption as no significant differences are found between vital and endodontically-treated teeth.

## Conclusion

- Different factors or individual characteristics are paramount to define the risk of root resorption. The dental professional must carry out a comprehensive medical record of patients, including their background, to make the best treatment decision possible
- Biomarkers such as I-1B, I-6, I-4 interleukins and dentin phosphoprotein are potential indicators of root resorption and such molecules might be used to establish the individual risk and/or reach early diagnosis of EARR to reduce the negative impact of this condition on orthodontic treatments

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