

Review Article

Clinical and molecular factors associated with external apical root resorption by orthodontics: Umbrella review

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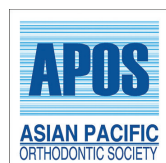
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Received: 27 September 2022
Accepted: 24 May 2024
Epub Ahead of Print: 07 October 2024
Published: 19 November 2024

DOI

10.25259/APOS_176_2022

Quick Response Code:



ABSTRACT

The objective 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 with this condition. An umbrella review that included systematic reviews and meta-analysis was performed. Four databases were used (PubMed, Science Direct, Scopus, and Cochrane), and critical evaluation following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and admeasurement tool to assess systematic reviews (AMSTAR-2) guidelines were carried out. The study protocol was registered in PROSPERO (International prospective register of systematic reviews, CRD42020198971). One hundred and twenty-four papers were eligible for this investigation. After exclusion by title and abstract, 10 papers (four systematic reviews and six meta-analyses) were included in the study. Guideline AMSTAR-2 was applied, and evaluation was performed using the PRISMA guideline. Factors such as female gender, adulthood, conventional fixed orthodontic treatment, heavy, continuous, and prolonged loads, intrusive movements, and anterior superior teeth with abnormal roots increase the risk of developing this condition. At the molecular level, some biomarkers, such as interleukins (IL) I-1B, I-6, I-4, and dentin phosphoprotein, are significant to reach an early diagnosis of external root resorption (ERR), especially the gene of polymorphism IL-1B (+3954), which is the most important predictor of this condition in patients under orthodontic treatment. Clinical and molecular factors respond to individual characteristics that must be identified to define the risk of developing EARR. Cone-beam computed tomography is the most accurate tool to evaluate the dimension of this condition. Prolonged treatments must be avoided, and immunoassays to analyze proteins in the gingival crevicular fluid should be included to reach an early diagnosis.

Keywords: Orthodontic, Root resorption, Gingival crevicular fluid, Biomarkers, Cytokines

INTRODUCTION

External apical root resorption (EARR) is one of the undesired biological effects of an orthodontic treatment.^[1-3] Permanent loss of root structure is originated by excessive pressure, which leads to capillary collapse, reduction in blood flow, and override of the repair capacity of supporting tissues. These, in turn, lead to the formation of necrotic areas, known as hyaline zones, and activation of the inflammatory response, activating cellular and molecular mechanisms that promote EARR.^[1,2,4-7]

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Formation of hyaline areas during orthodontic treatment is unavoidable, but the incidence and severity of EARR are variable,^[7-9] ranging from 26% to 100% as a function of biological, mechanical, and molecular factors, as the orthodontic movements are not the only factor that influences the onset of EARR.^[7,10-13]

Different investigative approaches associate the following factors with a risk of developing EARR: age, gender, nutrition status, medication, systemic diseases, genetics, oral habits, malocclusion, tooth type, root morphology, history of dental trauma, previous orthodontic treatments, pulp vitality, infections, and inflammations are the most relevant biological factors.^[2,3,6,11,14-18] Mechanical factors include the type of orthodontic appliances, orthodontic movement type, extractions, treatment time, and level of force magnitude.^[6,19-27]

In addition, several biomarkers are related to the progress of EARR as a response to the orthodontic dental movement. Tissue tension generates tissue structural reorganization that releases neurotransmitters, growth factors, and cytokines, which have been attempted to study in-depth by analyzing the gingival crevicular fluid (GCF) that constitutes their releasing medium.^[4,7,16,28-30]

Interleukins (ILs) 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, TNF α , IL-4, IL-10, IL-13, IL18, and Interferon- γ). The human genome codifies around 50 ILs and associated proteins. However, their association with EARR has not been conclusive, as data convergence has not been obtained.^[7,8,10,16,29-34]

Diagnosis of EARR depends on early detection using routine radiographies. Root shortening begins between the second and fifth treatment weeks, but such change will be only visible in panoramic or periapical radiographs 3 or 4 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 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 types of conditions.^[2,3,10,35-37]

Consequently, multiple clinical and orthodontic variables are associated with EARR. However, investigations show contradictory results, so careful analysis is necessary due to 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.

MATERIAL AND METHODS

Design

An umbrella review was performed, beginning with a Population, Intervention, Comparison, and Outcome (PICO) question. A search strategy, inclusion criteria, and quality assessment with analysis of results were carried out. The study's 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. 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 as follows: (P) patients from different ages, genders, and ethnicities; (I) previous orthodontic treatment; (C) during orthodontic treatment; and (O) what clinical and molecular factors are associated with the incidence of EARR? Systematic reviews and meta-analyses performed on human subjects and published between 2015 and 2020 were included in the study. 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 to the 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 eight were subsequently discarded because the studied population was animals. Ten articles (four systematic reviews and six systematic reviews with meta-analysis) were selected for data analysis and validation using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Admeasurement Tool to Assess Systematic Reviews (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 and AMSTAR-2 guidelines were used to verify their quality. A calibration process was then performed, and a 90% concordance index was obtained.

All the evaluations were performed using the PRISMA checklist, which applied 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 ten included articles in this umbrella review is shown in [Table 1]. According to the AMSTAR-2 guideline, seven studies were classified as having moderate quality and 3 as low quality. According to the PRISMA guideline, the articles with the best scores were investigations performed by Nowrin *et al.*^[4], Gandhi *et al.*^[2], Yi *et al.*^[37], and Fang X. *et al.*^[38]. Out of the 27 items included in the PRISMA checklist, only one article matches all the criteria and the score is over 18 points. Besides, nine out of ten articles report high heterogeneity and the remaining article does not report it.

Quality assessment instruments reported in these studies are the Grading of Recommendations, Assessment, Development, and Evaluations, which was used in three articles; the Strengthening the Reporting of Genetic Association Studies statement in two articles; the Risk of bias in Non-randomized Studies-of Interventions tool in 1 study, the Methodological index for non-randomized studies index in 1 work, the Quality Assurance International certification in 1 article, the PRISMA guideline in 1 article, and the Methodologic Scoring System adopted by Roscoe *et al.* in 2015 in the remaining article.^[6]

Cochrane evaluation of individual studies identified sources of bias [Table 2] and assessed the presence of a prism algorithm, the report of interobserver evaluation, and the presence of a funnel plot in each study. The results of this study showed that all investigations exposed the use of the prism algorithm, resulting in a low risk of selection bias. Assessment of interobserver concordance was reported in all articles, leading to a low risk of bias. Due to the presence of a funnel plot, only two studies showed a 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. The 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.

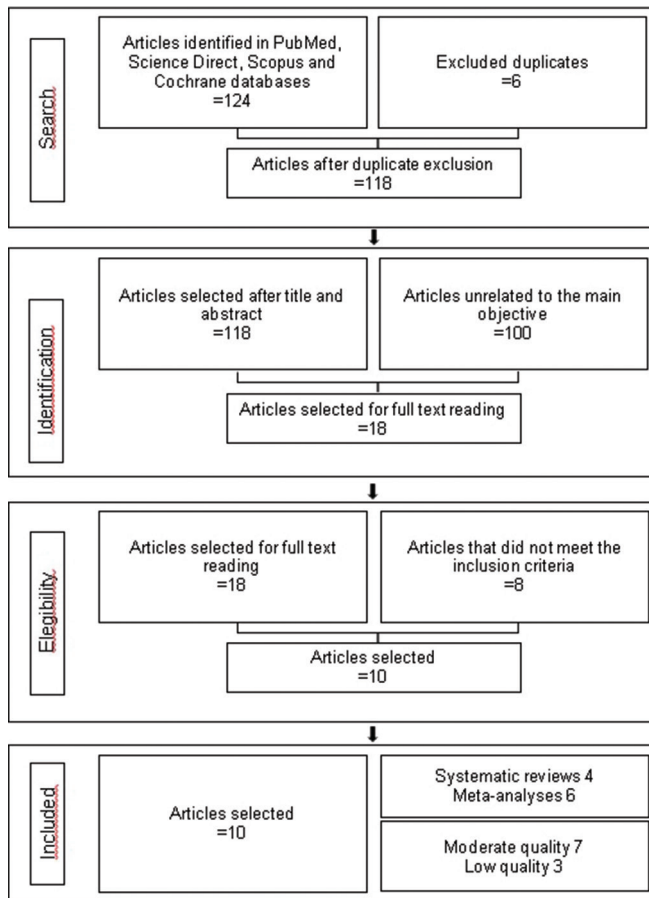


































Figure 1: Selection process of included articles.

Table 1: Assessment and quality control of selected articles				
Article	Prisma guideline information qualification	Amstar-2 guideline general quality	Heterogeneity	Quality assessment instrument used in the study
Shifat A Nowrina ^[4] Saidi Jaafarb Norma Ab Rahmana Rehana Basric Mohammad Khursheed Alamd Fazal Shahida 2018	24/27	Low	CC vs. TT: p -value: 0.020 I ² : 60.136 CT vs. TT: p -value: 0.019 I ² : 60.371 CC + CT vs TT: p -value: 0.032 I ² : 56.520 CC vs. CT + TT: p -value: 0.000 I ² : 76.917	(STREGA) statement
Arwa Aldeeri, Lulu Alhammad, Amjad Alduham, Waad Ghassan, Sanaa Shafshak, Eman Fatani 2018 ^[5]	18/27	Moderate	NR	The Methodologic Scoring System Adopted from Roscoe MG <i>et al</i> , 2015.9 ^[6]
Marina G. Roscoe, Joseite B. C. Meira, and Paolo M. Cattaneo 2015 ^[66]	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 ^[7]	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) 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	$P < 0.05$; $I^2 = 69\%$). Because I^2 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 2019 ^[37]	23/27	Moderate	($I^2 > 50\%$) The hypothesis test was set at $p < 0.05$	STREGA statement
Xuanwei Fang, Rui Qi, Chufeng Liu 2019 ^[38]	22/27	Moderate	$\text{Chi}^2 = 17.14$ $df = 12$ ($P = 0.14$) $I^2 = 30\%$	Grading of Recommendations, Assessment, Development and Evaluations (GRADE)
CC: Control, TT: Treated, STREGA: Strengthening the reporting of genetic association studies, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis, NR: Not reported				

Table 2: Cochrane assessment for individual studies

Shifat A Nowrina, Saidi Jaafarb, Norma Ab Rahman, Rehana Basic			
Mohammad Khurshed 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			
	Funnel plot	Prisma algorithm	Interobserver assessment
 Low risk of bias			
 Undefined risk of bias			

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 EARR during the orthodontic treatment. Out of ten investigations, four were performed in Asia, two in North America, one in South America, two in Europe, and one in Oceania.

Most investigations are randomized controlled clinical trials performed in human subjects under orthodontic treatment of 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 six papers reported gender information, and more females than males were included. Diagnostic aids ranged from lateral cephalograms, panoramic, occlusal radiographs, periapical radiographs, and scanning electron microscopy. 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, and enzyme-linked

immunosorbent assay (ELISA) immunoassays, among others. Only two types 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 a higher prevalence in Caucasian and Hispanic populations than in 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 to as variables such as genetic polymorphism expression and the presence of cytokines, ILs, RANK, OPG, dentin phosphoprotein (DPP), dentin sialoprotein (DSP), and alkaline phosphatase (ALP), among other biomarkers. All these factors and the main conclusions are summarized in [Table 4].

DISCUSSION

Due to the absence of pathognomonic signs, EARR is casually detected in routine panoramic radiographs. However, underestimating 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 orthodontic treatment are mostly unknown. Results presented

Table 3. Main characteristics of included systematic reviews and meta-analyses and 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	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	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	10.2-41.8 years	66% females 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 intrusion	Volumetric measurements and histologic analyses
Biomarkers in the gingival crevicular fluid used to detect root resorption in patients undergoing orthodontic treatment: a systematic review	9.0-44.0 years	73% females 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	10.0-75.0 years	65% females 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	11,4 - 26,6 years	37,7% males 62,3% females	CBCT	Fixed orthodontic treatment, anterior maxillary intrusion or rapid maxillary expansion	Changes in length and volume

(Contd)...

Table 3. (Continued)

Article	Average age	Gender	Radiographies	Treatment type	Root resorption quantification method
Orthodontic mechanotherapies and their influence on external root resorption: A systematic review	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	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	12 - 30 years	40,6% males 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	12- 58 years	40% males 60% females	CBCT, periapical, panoramic	Fixed orthodontic treatment vs aligners	Volumetric measurement

CBCT: Cone beam computed tomography, SEM: Scanning electron microscopy, NR: Not reported, GCF: Gingival crevicular fluid

in this umbrella review may be used as a foundation to develop more solid investigations on this topic.

In 2019, Currel *et al.*^[11] 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.^[11]

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. Similar results are reported by Fernandes 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.^[3,39]

Harris *et al.*,^[40] Barbagallo *et al.*,^[27] Cheng *et al.*,^[25] and Paetyangkul *et al.*^[36] concurred that there is a directly proportional relationship 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 the mesial and distal, which are the areas where pressure accumulates. However, it is important to mention that extrusion movements have 4 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. Yi J. *et al.*^[37] established that self-ligating systems may produce lighter forces during aligning movements since no ligature is needed, which may produce a protective effect for maxillary central incisors that are most vulnerable. However, Aras *et al.* concluded that it is not possible to suggest the superiority of one system over another due to the lack of investigations that follow solid

Table 4: Contributing factors to the development (ERR) according to results provided by 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	7
	Treatment duration	The higher the treatment time, the higher the root resorption	3
		a pause in dental movement is beneficial to reduce ERR	3,7,10
		a reduction in root resorption was observed in patients who received orthodontic treatment in two phases	7
	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	3,7
	Type of orthodontic device	Transparent aligners do not reduce the risk of developing ERR, although the incidence and severity might be reduced	2,1
		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	7
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	2,6,8
		The highest ERR was observed in the anterior maxilla followed by the anterior mandible, posterior mandible and posterior maxilla	6
	Root morphology	Root morphology (abnormal shape, long and narrow roots) is associated with ERR	8
	Previous extractions	Orthodontic treatment involving extractions are more associated with reduction in root size	6
		Dental extraction to resolve severe dental crowding may be considered a risk factor for ERR	10
	Pulp vitality	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	4

(Contd)...

Table 4: (Continued)

Category	Factor	Description	Article
		Dentin matrix protein (DMP - 1) is not a useful biomarker because it is not possible to differentiate between its physiological and pathological activities	4
		Dentin phosphoprotein (DPP) is a relatively useful biomarker for ERR diagnosis	4
		RANKL concentration in the GCF is higher in patients with light and severe ERR	4
		There are higher concentrations of DPP, DSP and IL-6 in patients with severe ERR	4
		Overall alkaline phosphatase (ALP) activity increased with higher rates of tooth movement at 150 g of force	4
		Cytokine levels are different depending on sampling sites and occurring time	4

EARR: External apical root resorption, ERR: External root resorption, NITI: Nickel titanium, IL-1B: Interleukin-1beta, IFN: Interferon, GM-CSF: Granulocyte macrophage colony-stimulating factor, GCF: Gingival crevicular fluid, DSP: Dentin sialoprotein, DPP: Dentin phosphoprotein, DMP: Dentin matrix protein

methodologies to identify the exact differences between both systems.^[37,42]

Regarding molecular factors, articles suggest that EARR has an important genetic component. Homozygous patients for allele 1 of IL-1B exhibit 5–6 times higher risk of developing EARR >2 mm than other groups. Data show that allele 1 in the 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.^[4,43]

The search for EARR biomarkers intensified after finding dentin specific proteins (DPP-and 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.*,^[44,45] who identified and quantified these proteins in patients under orthodontic treatment. Dentin matrix protein-1 (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.^[43,46]

Perinetti *et al.* assessed the activity of ALP in the GCF to evaluate its utility in the diagnosis of EARR during orthodontic treatment. These authors observed a significantly

higher ALP activity in tension sites compared to compression zones, which increases as the force increases. However, this finding only reflects the biological activity of such compound in the periodontium during the dental movement and must be further studied, as proposed by Tarallo *et al.* in 2019.^[7,33,47]

As for dental pulp status and root resorption, Alhadainy *et al.* and Huzar *et al.* concurred that the endodontic treatment does not seem to increase root resorption as no significant differences are found between vital and endodontically-treated teeth.^[13,48]

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 ILs, and DPP are potential indicators of root resorption, and such molecules might be used to establish the individual risk and/or reach an early diagnosis of EARR to reduce the negative impact of this condition on orthodontic treatments.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Pineda Vélez EL, Alzate Rivera D, Salgado Amaya AM, Hernandez JC, Arboleda Toro D, Vélez Trujillo N. Clinical and molecular factors associated with external apical root resorption by orthodontics: Umbrella review. *APOS Trends Orthod.* 2024;14:214-24. doi: 10.25259/APOS_176_2022