Orthodontic mechanotherapies and their influence on external root resorption: A systematic review

Scott Derek Currell,[a] Andrew Liaw,[b] Peter Donald Blackmore Grant,[c] Adrian Esterman,[d,e] and Alan Nimmo[a]
Beenliegh, Cairns, and Launceston, Australia

Introduction: This systematic review assesses the literature regarding the association between orthodontic tooth movement and external root resorption. By determining the evidence level supporting the association, the results could provide clinical evidence for minimizing the deleterious effect of orthodontic tooth movement. **Methods:** Electronic databases, including MEDLINE, PubMed, Embase, Scopus, CINAHL, Cochrane Library, and LILACS, were searched up to February 2018, with hand searching of selected orthodontic journals undertaken to identify any preelectronic publications. Searches were undertaken with no restrictions on year, publication status, or language. Selection criteria included randomized controlled trials conducted with the use of fixed orthodontic appliances or sequential thermoplastic aligners on human patients. The quality of included studies was assessed with the use of the Cochrane Risk of Bias Tool and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Inter-rater agreement of the review authors was used for the inclusion of primary articles, risk of bias assessment, and evaluation of the quality of evidence (GRADE), and it was calculated with the use of the Cohen kappa statistic. **Results:** A total of 654 articles were retrieved in the initial search. After the review process, 25 articles describing 24 individual trials met the inclusion criteria. Sample sizes ranged from 6 to 154 patients. Most articles were classified as having unclear risks of bias and very low to low quality of evidence. **Conclusions:** There is very low to low evidence for supporting positive associations between root resorption and increased force levels, force continuity, intrusive forces, and treatment duration. Moreover, by including a pause in treatment for patients experiencing root resorption, it may be possible for the clinician to reduce the severity of the condition. Of the included studies, the most common methodologic flaws include the absence of a control group, appropriate randomization strategy, and adequate examinations before and after treatment. (Am J Orthod Dentofacial Orthop 2019;155:313-29)

Orthodontics is the only dental specialty that uses the body's inflammatory system to solve functional and esthetic dental problems. Orthodontically induced external root resorption (OIERR) is a common, deleterious, side-effect of this inflammation-driven tooth movement.[1,2] As early as 1932, it was shown that this physiological problem may be the result of orthodontic pressure exceeding that of capillary pressure within the periodontium, causing collapse and thus localized loss of the blood supply.[2-5] This resulting ischemic necrosis in the periodontal ligament results in the degradation of the protective outer layers of the tooth (hyalinized zone). The loss of precementum and its formative layer of cementoblasts activate the body's clastic cells which results in root resorption during the active removal of the hyalinized necrotic tissue.[6,7] Root resorption thus occurs when the reparative capacity of the cementum is exceeded, exposing the dentine to activated odontoclasts causing irreversible loss of root structure.[8] The formation of hyalinized areas during orthodontic treatment is seen to be unavoidable, and it is expected that OIERR will occur in ~80% of patients.[9-11] Often considered to be insignificant, a loss

[a]College of Medicine and Dentistry, James Cook University, Queensland, Australia.
[b]Oral Health Services Tasmania, Tasmania, Australia.
[c]Private Practice, Queensland, Australia.
[d]University of South Australia Cancer Research Institute, University of South Australia, South Australia, Australia.
[e]Australian Institute of Tropical Health and Medicine, James Cook University, Queensland, Australia.
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Address correspondence to: Adrian Esterman, Australian Institute of Tropical Health and Medicine, McGregor Road, Smithfield, Queensland, Australia; e-mail, adrian.esterman@jcu.edu.au.
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in root length of 3 mm is biomechanically shown to be equivalent to a 1 mm loss of crestal alveolar bone.[12,13] Severe resorption is considered to be a loss of >4 mm, or more than one-third overall root length, and is estimated to affect up to 15% of orthodontically treated patients.[11,14-16] It is reported that ~46% of adults are diagnosed with periodontitis, therefore highlighting the importance of mitigating this adverse effect of orthodontic treatment.[17]

It is proposed that OIERR is a result of the interrelationship between mechanical factors and individual predisposition. The current body of scientific literature fails to identify a clear approach that an orthodontist may use to prevent OIERR from occurring. It is therefore pertinent that clinical evidence regarding treatment-related factors that may mitigate the irreversible destruction of tooth structure be evaluated. Many reviews, systematic reviews, and meta-analyses exist, attempting to elucidate possible patient- and treatment-related factors that are associated with OIERR.[18-26] The results of these studies show that high-quality studies on OIERR are limited, with evidence to guide orthodontists' treatment decisions lacking. Of these reviews, only 2 created an assessment of different mechanical therapies. Initially, studies assessing mechanical orthodontic factors influencing OIERR were reviewed by Weltman et al.[24] That review used a comprehensive search method to evaluate randomized controlled trials (RCTs); however, only a small number of articles published up to the year 2008 were included, with the results of the study showing limited evidence. Most recently, a systematic review by Roscoe et al[22] also evaluated the mechanical aspects of orthodontics resulting in OIERR. That review also evaluated non-RCTs and included studies to the end of 2013. An assessment of the individual studies for methodologic quality was performed with the use of their own tool and did not evaluate the quality of the evidence. These 2 reviews were limited by a small number of included studies and sample sizes. In addition, heterogeneity in the included studies have led to varying results.

The primary aim of the present systematic review was to examine the current available evidence regarding orthodontic mechanotherapies resulting in OIERR by critically analyzing RCTs. The secondary aim was to evaluate the patient-related outcomes of OIERR, including pain, perception, and dental prognosis. By determining the risk of bias (RoB) and quality of evidence supporting the association, the results of the present review aim to provide the clinician an update and analysis of the clinical evidence for minimizing the risk of OIERR during orthodontic tooth movement.

MATERIAL AND METHODS

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement[27] and the Cochrane Handbook for Systematic Reviews of Interventions.[28] The review protocol was registered with the Prospero international prospective registry of systematic reviews: CRD42018088981.

Inclusion criteria were: 1) population: human patients receiving orthodontic mechanotherapy; 2) intervention: orthodontic tooth movement with conventional fixed appliances or sequential thermoplastic aligners (STAs); 3) comparator: individuals or teeth within the same individual (including the split mouth technique) not subjected to the same mechanical variable; 4) outcome: OIERR; and 5) study design: RCT, published or unpublished.

Exclusion criteria were: 1) studies of human patients with craniofacial abnormalities or nonhuman studies; 2) studies that include concomitant exogenous drug use, external stimulus, or adjunctive maxillofacial surgery; 3) studies including patients who previously received orthodontic treatment or combined surgical and orthodontic treatment; and 4) non-RCTs, cohort studies, case reports, case series, reviews, abstracts, systematic reviews, opinions, or studies where the diagnosis/measurement of OIERR was performed only on lateral cephalograms.

A computerized systematic search was performed, including 7 electronic databases: PubMed, MEDLINE, Embase, Scopus, CINAHL, Cochrane Library, and LILACS. The search strategy included the use of MeSH (Medical Subject Headings), Emtree (Embase Subject Headings), and DeCS (Health Sciences Descriptors), key words, boolean operators "AND" and "OR," and truncations that were adjusted for each database. The search strategy for PubMed is presented in Table I. The full electronic search strategy for all of the included databases can be viewed online at the Prospero review protocol (CRD42018088981).

Hand searching of 5 selected journals (*American Journal of Orthodontics and Dentofacial Orthopaedics, Angle Orthodontist, European Journal of Orthodontics, Orthodontics and Craniofacial Research, and Progress in Orthodontics*) was also undertaken to ensure that additional articles were not missed in the electronic search (including early view and accepted articles). Ongoing trials were searched from the World Health Organization International Clinical Trials Registry Platform and Clinicaltrials.gov for relevance, as well as gray literature found at Opengrey and System for Information on Grey Literature in Europe. To locate additional studies,

Table I. Search strategy for PubMed

Search	Search term	Results
1	exp Orthodontics/	49,401
2	orthodontic*.mp.	65,021
3	braces.mp.	6,105
4	1 OR 2 OR 3	77,986
5	exp Tooth Resorption/	3,978
6	resorp* or resorb*	64,157
7	root AND (erosion OR shortening OR blunting OR length).mp.	13,765
8	5 OR 6 OR 7	77,501
9	exp Randomized Controlled Trial/	115,956
10	"randomized controlled trial" OR "randomised controlled trial"	607,843
11	rct.mp.	16,373
12	9 OR 10 OR 11	613,142
13	4 AND 8 AND 12	97

The full electronic search strategy for MEDLINE, Embase, PubMed, Scopus, CINAHL, Cochrane Library, and LILACS can be viewed online at the Prospero review protocol (CRD42018088981).

reference lists of review articles and all included studies were checked. Requests were also sent to experts in the field, to identify unpublished and ongoing studies. Searches were performed with no restrictions on year, publication status, or language. The results obtained were exported to the reference management software (Endnote version X7.1; Clarivate Analytics, Philadelphia, Pa) and any duplicates were removed. Searches were initiated in December 2017 and updated in February 2018.

The process of article selection, screening according to title and abstract, then full text, data extraction, RoB, and quality assessment were undertaken independently and in duplicate by 2 authors (S.D.C. and A.L.). For all steps in the systematic review process, instances where no decision could be reached after discussion between the 2 authors, a third author (A.E.) was used to resolve the problem. Titles and abstracts were primarily used to screen the searched studies and identify full text articles relating to external root resorption due orthodontic mechanotherapies. Full text articles were retrieved after their selection from the screening process and further assessed for suitability. Full text articles were also retrieved for articles in which eligibility was uncertain based on title and abstract alone. These articles were subjected to prespecified inclusion and exclusion criteria and assessed for suitability.

Studies that fulfilled the inclusion and exclusion criteria were collated for data extraction. A specially designed electronic spreadsheet was piloted and modified before data extraction. For each included study, quantitative and qualitative information was extracted, including: the author's name, country of study, year of publication, setting, study design, teeth assessed, sample size, gender of patients, examiner characteristics (number and calibration method), force system, force direction, force magnitude, loading protocol, study duration, outcome of interest, duration of study, and assessment method (quantifiable measure and instrument). Extraction of quantitative data presented in tables or text was preferred over graphs or figures to avoid measurement errors from data approximation; however, if data were presented only in graphs or figures, the review authors used the aforementioned data extraction protocol to ensure that measurement error was mitigated. Data were simplified to include the difference between experimental groups, regardless of the time of follow-up. Authors were contacted in cases where it was suspected that the included studies presented data from repeated observations on the same sample participants.

The RoB of included studies was assessed with the use of the Cochrane Collaboration bias assessment tool.[28] With the use of this tool, the RoB was determined from selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (bias from other sources). Key domains for the assessment of OIERR due to orthodontic mechanotherapies were selected to be selection bias, performance bias, and detection bias, which were used to determine the RoB. Each study was classified as having low (low RoB for all key domains), unclear (unclear RoB in $\geq$1 key domain), or high (high RoB in $\geq$1 key domain) risk. For studies in which an unclear RoB was decided, the authors were contacted to clarify the domain and an appropriate judgement was made. In cases where the authors did not respond or supply sufficient evidence to make a judgement, the domain was left as having an unclear risk.

The principal summary measure was the difference in the amount of OIERR after the application of orthodontic force. This may be presented as the volumetric measurement of root resorption or change in root length. The secondary outcome measure included patient-related outcomes such as perception, further complications (mobility, tooth loss), or quality of life data. To assess the effect of interventions, the association or difference between the mechanical variable and root resorption was compared. The quality of evidence for each outcome was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[29] The level of certainty was downgraded by 1 level for serious concerns (or by 2 levels for very serious concerns) about

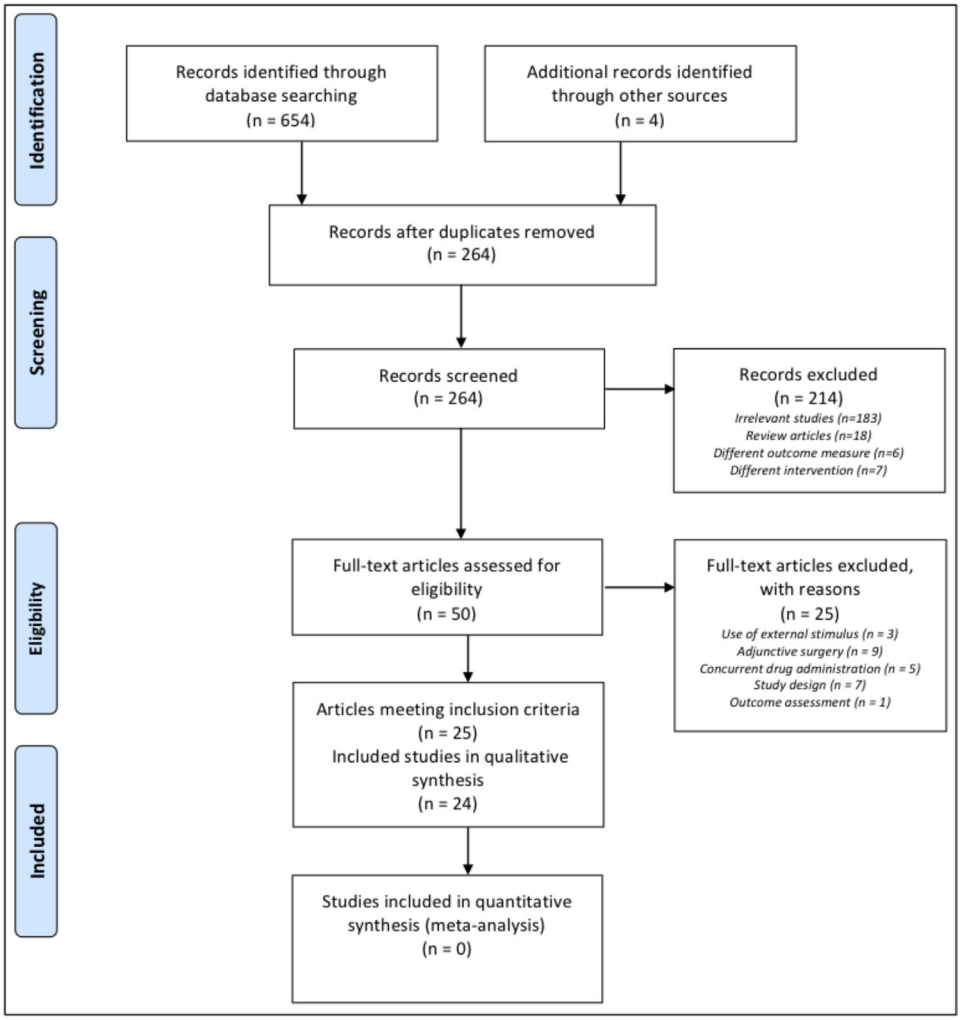

Fig 1. PRISMA flow diagram summarizing the literature search.

RoB, inconsistency, indirectness, imprecision, or publication bias. This was used to determine the level of certainty in the evidence and the strength of recommendations as high, moderate, low, or very low quality.

The inter-rater agreement of the review authors was calculated with the use of the Cohen kappa statistic for the inclusion of primary articles, RoB assessment, and evaluation of the quality of evidence.[30] Any disagreements were resolved by discussion and consensus of all authors.

RESULTS

Electronic and manual searches of the literature revealed 654 unique citations. After the removal of duplicates and the addition of 3 further articles found by hand searching, title and abstract evaluation resulted in the acquisition of 263 full text articles. Of these full text articles, a total of 50 met the prespecified inclusion and exclusion criteria. After evaluation, it was determined that 25 articles (describing 24 trials) fulfilled the requirements for inclusion in this systematic review. It was found that 2 articles[31,32] were conducted on the same sample of patients and were therefore included in the review as 1 study, with their results combined. No unpublished studies of relevance could be obtained after consultation with academic orthodontists and gray literature search. The inter-reviewer agreement for the inclusion of primary articles can be considered very good ($\kappa = 0.885$). Figure 1 shows the PRISMA flowchart of the literature selection process.

The included studies were published from 1994 to 2017, with samples sizes ranging from 6 to 154 male and female patients, with a mean age range of 12.3-

20.9 years. All studies experimentally applied orthodontic force to teeth, but the measurement tool varied among studies. OIERR was evaluated with the use of microcomputerized tomography (MicroCT) in 11 studies,[33-43] electron microscopy (EM) in 4 studies,[31,32,44-46] intraoral periapical radiography (IOPA) in 6 studies,[47-52] and cone-beam computerized tomography (CBCT) in 3 studies.[53-55] Table II provides a summary of the characteristics of the included studies, including data regarding participants, interventions, comparison, outcomes, and study design ("PICOS") as well as study size and follow-up.

Data pooling of the included studies was not suitable owing to methodologic and clinical heterogeneity. Because the included studies used different methodologies and reporting strategies, a narrative synthesis was conducted rather than a meta-analysis.

Four studies[47,50-52] had a low RoB for randomization because they used adequate random allocation sequences. Randomization methods of the other studies were unclear, because the authors merely indicated that allocation was randomized in their articles. Low RoB for allocation concealment was considered in only 3 studies which included information about using envelopes[50] or third parties,[47,51] with all other studies providing unclear information in this domain. The effect of patient and personnel blinding was deemed not to influence the outcome of most studies and thus considered to be low risk. However, in 2 studies[44,46] the intervention was considered to have a high potential to be influenced by lack of blinding, and 2 studies[35,45] provided insufficient information, resulting in an unclear RoB. All studies used methods of outcome assessment in which blinding was deemed not to influence the outcome and considered to be low RoB. Only 12 studies[31,32,38,41,42,44,47,49-54] were considered to be low RoB for attrition bias because they adequately described patients lost to follow-up or omitted data, whereas the remaining 12[33-37,39,40,43,45,46,48,55] did not report dropouts. Reporting bias was unclear for all studies because no links to protocols were published and 9 studies[36,37,47,50-55] published statistically insignificant findings. One study[44] was judged to have a high RoB for the "other bias" domain because it failed to include a sample size calculation or perform any statistical testing. Eighteen studies[31-43,45,46,48,49,51,55] were considered to have an unclear RoB for the "other bias" domain owing to failure to present sample size calculations, and in 5[47,50,52-54] no other sources of bias were detected. The inter-reviewer agreement (kappa) value for RoB was 0.972, indicating very good agreement between reviewers. The summary of the RoB assessment for each included study is presented in Figure 2.

Three split-mouth studies investigated the difference in OIERR caused by continuous and interrupted orthodontic force.[33,34,44] Sample sizes ranged from 8 to 32 patients per study. All 3 studies used different force magnitudes, follow-up periods, and methods to assess OIERR. However, all of them found that OIERR was observed when orthodontic force was applied. In addition, all 3 studies found that continuous force, compared with intermittent force, resulted in a significant increase in OIERR. Aras et al,[33] who also investigated reactivation timing, found the difference to be significant only when orthodontic forces were reactivated every 3 weeks instead of 2. The same study also found that despite the increase in OIERR, continuous forces produced significantly greater tooth movement for both activation periods. Studies by Aras et al[33] and Ballard et al[34] implemented a 3-day rest period in their intermittent force model, which resulted in a significant decrease in OIERR. In comparison, Acar et al[44] used a 12-hour activation-deactivation cycle in their model.

Eleven studies[31,32,35-43,45] evaluated the effect of light or heavy orthodontic forces on OIERR. All studies used a split mouth design with segmented fixed orthodontic brackets on the premolars of 222 patients (range 10-36 patients). Of the light or heavy orthodontic forces that were applied, 6 studies[31,32,35,37,41,42,45] used buccally directed tipping force and 1 study each examined intrusive force,[38] extrusive force,[39] distal root tipping force,[40] buccal root torqueing force,[36] buccal-palatal jiggling force,[37] and rotational force.[43] All studies found that OIERR was observed when orthodontic force was applied, although only 4 studies included a control (no force).[31,32,35,38,45] Compared with control, all studies except a single low force experimental group[31,32] showed a significant increase in OIERR when the orthodontic force was applied. Similarly, all studies except 1, by Bartley et al,[36] found a positive association between OIERR and an increase in magnitude of orthodontic force regardless of the direction. The duration in which light and heavy forces were applied to teeth was assessed by Pae et al,[41] showing significantly more OIERR with increased duration of force.

One study, by Barbagallo et al,[35] assessed OIERR induced due to STAs by comparing these forces with those provided by fixed orthodontic appliances and a control (no force). This split-mouth design study experimenting on maxillary premolars allocated 27 patients into the STA group, with the contralateral premolar

Table II. Characteristics of the included studies

Study (year)	*Study design*	*Participants*	*Interventions*	*Comparisons*	*Outcomes*	*Follow-up*
Acar et al[44] (1999)	RCT, SMD, parallel	28 first PMs from 14 patients (gender not stated); ages 14-23 y, mean age not stated	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Loading protocol: G1: Continuous force (100 g) G2: Intermittent force (100 g) C: No force (0 g)	Extracted PM: • RR surface area • Apical morphology • RR severity	9 wk
Alzahawi et al[47] (2014)	RCT, parallel	656 Mx and Md incisors from 82 patients (42 F, 40 M); ages 11-22 y, mean age 13.5 y	Fixed orthodontic appliances	Archwire sequence: G1: Superelastic wire (sequence: 0.014-inch and 0.016-inch Sentalloy and 0.018 × 0.025-inch Bioforce)* G2: Conventional steel wire (sequence: 0.0175-inch Penta-One multistranded,† 0.016-inch Australian regular,‡ and 0.016 × 0.022-inch resilient)§	• Change in root length • Time to complete Mx and Md leveling	Time until leveling phase complete: 40 wk
Aras et al[33] (2012)	RCT, SMD, parallel	64 Mx first PMs from 32 patients (25 F, 7 M); ages 12-18 y, mean age 14.4 y	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Loading protocol and activation period: G1: Continuous force (150 g), 2 wk G2: intermittent force (150 g), 2 wk G3: Continuous force (150 g), 3 wk G4: intermittent force (150 g), 3 wk	Extracted PM: • Volumetric measurement of RR • Tooth movement • Location and distribution of RR	12 wk
Ballard et al[34] (2009)	RCT, SMD	16 Mx first PMs from 8 patients (6 F, 2 M); ages 13.4-18.6 y, mean age 16.5 y	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Loading protocol: G1: Continuous force (225 cN) G2: Intermittent force (225 cN)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	8 wk
Barbagallo et al[35] (2008)	RCT, SMD, parallel	54 Mx first PMs from 27 patients (15 F, 12 M); ages 12.5-20 y, mean age 15.3 y	Fixed orthodontic appliances (segmented technique) and TAs;	Force magnitude and system: G1: Low force (25 g)	Extracted PM: • Volumetric measurement of RR	8 wk

Table II. Continued

Study (year)	Study design	Participants	Interventions	Comparisons	Outcomes	Follow-up
			buccally directed tipping force	G2: Heavy force (225 g) G3: STA (Clearsmile)‖ C: No force (0 g)	• Location and distribution of RR	
Bartley et al[36] (2011)	RCT, SMD	30 Mx first PMs from 15 patients (8 F, 7 M); ages 12.8-16.8 y, mean age 14.3 y	Fixed orthodontic appliances (segmented technique); buccally directed root torque	Force magnitude: G1: Low force (47.5 g) G2: Heavy force (285 g)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	4 wk
Brin et al[48] (2003)	RCT, parallel	552 Mx central and lateral incisors from 138 patients (66 F, 79 M); ages not stated, mean age not stated	Fixed orthodontic appliances	Force system: G1: 1-phase fixed orthodontics G2: 2-phase Bionator, fixed orthodontics G3: 2-phase Headgear, fixed orthodontics	• Change in root length • Prevalence of RR • Treatment duration of fixed appliances • Influence of root morphology on RR • Influence of incisal trauma on RR	Full treatment: Mean 1-phase 110 wk (SD 40.8), 2-phase bionator 106.9 wk (SD 45.6), and 2-phase headgear 117.6 wk (SD 46.84)
Chan and Darendeliler[31,32] (2005, 2006)	RCT, SMD, parallel	36 Mx first PMs from 27 patients (15 F, 12 M); ages 12.5-20 y, mean age 15.3 y	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Force magnitude: G1: Low force (25g) G2: Heavy force (225 g) C: No force (0 g)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	4 wk
Chan et al[45] (2004)	RCT, SMD, parallel	20 Mx first PMs from 10 patients (gender not stated); ages not stated, mean age not stated	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Force magnitude: G1: Low force (25 g) G2: Heavy force (225 g) C: No force (0 g)	Extracted PM: • Volumetric measurement of RR	4 wk
de Almeida et al[53] (2018)	RCT, parallel	112 Mx and Md incisors from 28 patients (12 F, 16 M); ages 12-30 y, mean age not stated	Fixed orthodontic appliances	Force system: G1: Intrusion arch (0.017 × 0.025-inch Connecticut Intrusion Arch)¶ G2: Intrusive straight wire mechanics (0.014 × 0.025-inch NiTi)	• Change in root length • Amount of vertical incisor movement	26 wk
Eross et al[37] (2015)	RCT, SMD	60 Mx first PMs from 30 patients (15 F, 15 M);	Fixed orthodontic appliances (segmented technique); buccally	Loading protocol, force magnitude and direction:	Extracted PM: • Volumetric measurement of RR	12 wk

Table II. Continued

Study (year)	*Study design*	*Participants*	*Interventions*	*Comparisons*	*Outcomes*	*Follow-up*
		ages 13-18 y, mean age not stated	directed tipping force; buccal-lingual jiggling force	G1: Low force (25 g), continuous G2: Heavy force (225 g), continuous G1: Low force (25 g), jiggling G2: Heavy force (225 g), jiggling		
Han et al[46] (2005)	RCT, SMD	11 Mx first PMs from 6 patients (5 F, 4 M); ages 12.7-20 y, mean age 15.3 y	Fixed orthodontic appliances	Force direction: G1: Extrusion (100 cN) G2: Intrusion (100 cN) C: No force (0 cN)	Extracted PM: • RR surface area • Severity of RR • Location and distribution of RR	8 wk
Harris et al[38] (2006)	RCT, SMD, parallel	54 Mx first PMs from 27 patients (15 F, 12 M); ages 11.9-19.3 y, mean age 15.6 y	Fixed orthodontic appliances (segmented technique); intrusive force	Force magnitude: G1: Low force (25 g) G2: Heavy force (225 g) C: No force (0 g)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	4 wk
Jiménez Montenegro et al[39] (2012)	RCT, SMD	20 Mx first PMs from 10 patients (7 F, 3 M); ages 12-18 y, mean age not stated	Fixed orthodontic appliances (segmented technique); extrusive force	Force magnitude: G1: Low force (25 g) G2: Heavy force (225 g)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	4 wk
King et al[40] (2011)	RCT, SMD, parallel	30 Mx first PMs from 15 patients (4 M, 11 F); ages 12.8-16.11 y, mean age 14.2 y	Fixed orthodontic appliances (segmented technique); distal root tipping force	Force magnitude: G1: Low force (25 g) G2: Heavy force (225 g)	Extracted PM: • Volumetric measurement of RR	4 wk
Leite et al[54] (2012)	RCT, parallel	152 Mx and Md incisors from 19 patients (11 F, 8 M); ages 11-30 y, mean age 20.9 y	Fixed orthodontic appliances	Bracket ligation: G1: Self-ligating brackets (0.022 × 0.027-inch slot, Easyclip bracket)[#] G2: Conventionally-ligated brackets (0.022 × 0.030-inch slot, 3M Unitek)[§]	• Change in root length	24 wk
Levander et al[49] (1994)	RCT, parallel	62 Mx incisors from 40 patients (25 F, 15 M); ages 12-18 y, mean age 15 y	Fixed orthodontic appliances	Loading protocol: G1: Continuous orthodontic therapy G2: 2–3-month treatment pause then continuation of treatment	• Change in root length	Full treatment: Continuous mean 84 wk and treatment pause mean 80 wk

Table II. Continued

Study (year)	*Study design*	*Participants*	*Interventions*	*Comparisons*	*Outcomes*	*Follow-up*
Liu and Guo[55] (2016)	RCT, parallel	200 Mx incisors from 50 patients (gender not stated); ages not stated, mean age not stated	Fixed orthodontic appliances	Bracket ligation: G1: Self-ligating brackets (0.022-inch slot; DamonQ)** G2: Conventionally-ligated brackets (0.022-inch slot, APC)§	• Change in root length	104 wk
Mandall et al[50] (2006)	RCT, parallel	154 Mx left central incisors from 154 patients (92 F, 62 M); ages 10-17 y, mean age not stated	Fixed orthodontic appliances	Force system (archwire sequence)**: G1: 0.016-inch NiTi, 0.018 × 0.025-inch NiTi, and 0.019 × 0.025-inch SS G2: 0.016-inch NiTi, 0.016-inch SS, 0.020-inch SS, and 0.019 × 0.025-inch SS G3: 0.016 × 0.022-inch CuNiTi, 0.019 × 0.025-inch CuNiTi, and 0.019 × 0.025-inch SS	• Change in root length • Time to reach Mx and Md working archwire (0.019 × 0.025-inch SS)** • Number of visits • Patient discomfort	Time until working archwire placed: 37.2 wk (SD 17.6)
Paetyangkul et al (2011)[41]	RCT, SMD, parallel	54 Mx first PMs from 36 patients (21 F, 15 M); ages not stated, mean age 14.9 y	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Force magnitude and duration: G1: Low force (25 g), 4 wk G2: Heavy force (225 g), 4 wk G3: Low force (25 g), 8 wk G4: Heavy force (225 g), 8 wk G5: Low force (25 g), 12 wk G6: Heavy force (225 g), 12 wk	Extracted PM: • Volumetric measurement of RR	12 wk
Paetyangkul et al[42] (2009)	RCT, SMD	40 Mx and Md first PMs from 10 patients (6 F, 4 M); ages 12.7-18.2 y, mean age 14.3 y	Fixed orthodontic appliances (segmented technique); buccally directed tipping force	Force magnitude: G1: Low force (25 g) G2: Heavy force (225 g)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	12 wk
Reukers et al[51] (1998)	RCT, parallel	298 Mx central incisors from 149 patients (85 F, 64 M); ages 10.6-15.7 y, mean age 12.3 y	Fixed orthodontic appliances	Bracket prescription: G1: Standard edgewise brackets (0.022-inch slot; Roth prescription, "A"-company)††	• Change in root length • Prevalence of RR	Full treatment: Mean 20.4 wk (SD 6.00)

Table II. Continued

Study (year)	*Study design*	*Participants*	*Interventions*	*Comparisons*	*Outcomes*	*Follow-up*
				G2: Straight-wire brackets (0.018-inch slot; Microloc bracket)*		
Scott et al[52] (2008)	RCT, parallel	62 Md right central incisors from 62 patients (30 F, 32 M); ages not stated, mean age 16.27 y	Fixed orthodontic appliances	Bracket ligation: G1: Self-ligating brackets (0.022-inch slot; Damon3)** G2: Conventionally ligated brackets (0.022-inch slot; Synthesis)**	• Rapidity of tooth alignment • Change in root length • Change in arch dimension	Full treatment: Mean self-ligating 34.7 wk (SD 11.8) and conventional 36.1 wk (SD 9.08)
Wu et al[43] (2011)	RCT, SMD	30 Mx first PMs from 15 patients (10 F, 5 M); ages 11.9-16.9 y, mean age 14.15 y	Fixed orthodontic appliances (segmented technique); rotational force	Force magnitude: G1: Low force (25 g) G2: Heavy force (225 g)	Extracted PM: • Volumetric measurement of RR • Location and distribution of RR	4 wk

C, control; *CuNiTi*, Copper-nickel-titanium archwire; *F*, female; *G*, group; *M*, male; *Md*, mandibular; *Mx*, maxillary; *PM*, premolar; *RCT*, randomized controlled tial; *RR*, root resorption; *TM*, tooth movement; *NiTi*, nickel-titanium archwire; *SMD*, split-mouth design; *SS*, stainless steel archwire; *STAs*, sequential thermoplastic aligners.
*Dentsply GAC, Bohemia, NY; †Masel Orthodontics, Carlsbad, Calif; ‡A.J. Wilcock, Whittlesea, Australia; §3M Unitek, Saint Paul, Minn; ‖Clearsmile, Woollongong, Australia; ¶Ortho Organizers, Carlsbad, Calif; #Aditek, Cravinhos, São Paulo, Brazil; **Ormco, Orange, Calif; ††"A"-company, San Diego, Calif.

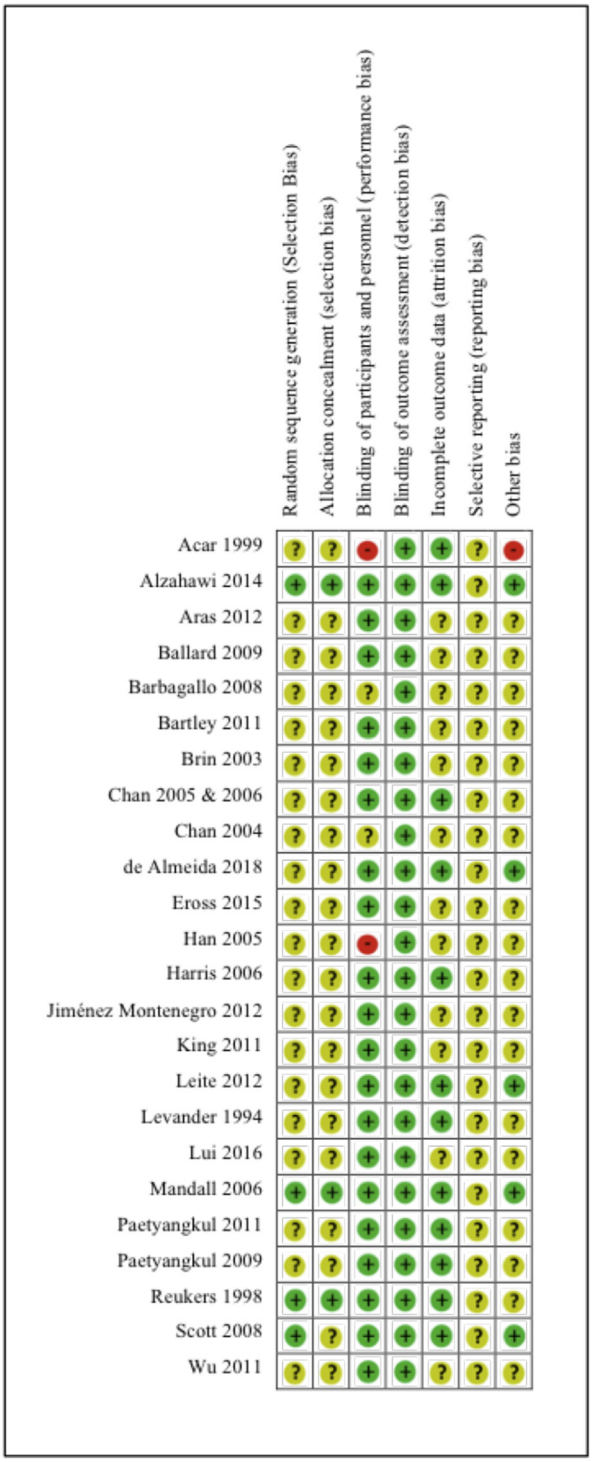

Fig 2. Cochrane risk of bias summary.

allocated into control (no force), heavy (225 g), or low (25 g) continuous force. Compared with the control (no force), STAs caused 5.9 times the amount of root resorption. STAs were also shown to result in resorption similar to that caused by light orthodontic forces (1.1 times) and significantly less than that caused by heavy forces (0.63 times).

Three studies,[38,46,53] with a subject range of 6-28 patients, evaluated the effect of intrusive orthodontic force on OIERR. All 3 studies used different force magnitudes, follow-up periods, and methods to assess the effect of intrusive force, but all of them found that OIERR was observed when intrusive orthodontic force was applied. In addition, 1 study, by Han et al,[46] found that intrusive forces of 100 cN caused 11 times more resorbed root area than control (no force) and 4.5 times more than extrusive forces. Similarly, Harris et al[38] showed about 2 and 4 times greater resorption volume in the light (25 g) and heavy (225 g) intrusive force groups, respectively than in the control group. Unlike the previous 2 studies, de Almeida et al[53] compared intrusive forces provided by orthodontic archwires using the Connecticut Intrusion Arch (Ortho Organizers, Carlsbad, Calif) and straight-wire mechanics. The study showed that although the intrusion arch resulted in a significant increase in vertical incisor movement, there was no difference found in the amount of OIERR between the archwire groups.

One split-mouth study, by Eross et al,[37] assessed the difference in OIERR caused by the application of light (25 g) and heavy (225 g) jiggling force and continuous buccally directed tipping forces during fixed orthodontic therapy. The study included 10 patients for each of the 3 experimental groups (30 patients) and found no significant difference in OIERR with the use of heavy and low jiggling orthodontic forces compared with buccally directed tipping forces of the same magnitude. However, it was found that the use of heavy jiggling forces led to a significant increase in OIERR compared with light jiggling forces.

One study, by Reukers et al,[51] investigated the difference in OIERR caused by treatment with a partly programmed edgewise appliance and a fully programmed edgewise appliance in 149 patients. Although both groups were treated with different wires and brackets, the results of this study showed that straight-wire appliances resulted in no significant difference in prevalence or severity of OIERR compared with standard edgewise appliances.

Two studies with 262 patients compared different archwire sequences in relation to OIERR. Both studies assessed the loss in root length in millimeters with the use of IOPA but varied in treatment method. Alzahawi et al[47] measured the OIERR after the initial leveling phase of treatment. Comparing a sequence of superelastic archwires to a sequence of conventional multistranded stainless steel archwires, all evaluated teeth

except 1 did not have a statistically significant difference in OIERR. The study showed that the use of a superelastic archwire sequence during leveling led to a statistically significant increase in OIERR in the single mandibular left central incisor. Mandall et al[50] evaluated the OIERR caused by different archwire sequences used to reach the working archwire (0.029 × 0.025-inch stainless steel wire) in maxillary and mandibular incisors. This study assessed OIERR in maxillary left central incisors and found no statistically significant difference between 3 different archwire sequences. The study also showed that there was no statistically significant difference in the proportion of patients with OIERR between the 3 groups.

Three studies investigated the difference in OIERR caused by self-ligating and conventionally ligated orthodontic brackets in 131 patients.[52,54,55] All studies evaluated a change in root length, but 2 studies did this by way of CBCT[54,55] and 1 used IOPA.[52] One study[54] assessed OIERR after the initial leveling and alignment phase of treatment, and the others assessed OIERR after comprehensive treatment. All of the studies showed that orthodontic therapy resulted in OIERR, but it was also shown that no statistically significant difference in OIERR existed between the groups. Scott et al[52] also showed that no statistically significant difference was found in the alignment efficiency of the 2 brackets.

A study by Brin et al[48] evaluated the effect of increased treatment duration on OIERR by performing Class II correction on 138 patients with the use of fixed orthodontic appliances. A partial proportional odds model indicated that an increase in treatment duration led to a significant increase in OIERR. The average group differences in treatment duration were reflected in the percentage of children who had moderate to severe root resorption. This was also found to be associated with the degree of overjet reduction required during treatment.

A study by Levander et al[49] investigated the difference in OIERR caused by a treatment pause in 40 patients experiencing OIERR. During the initial 6 months of fixed orthodontic treatment, patients experiencing OIERR were assigned to either continuous or pause groups. It was shown that the overall loss of root length was statistically significantly greater in patients treated continuously compared with those who were treated with a pause.

A study by Brin et al[48] evaluated the difference in OIERR caused by 2-phase orthodontic therapy, compared with single-phase treatment, during Class II correction of 138 patients with the use of fixed orthodontic appliances. The study showed that patients treated with a 2-phase treatment plan had a lower proportion of incisors with moderate to severe OIERR (2-phase functional, 5%; 2-phase headgear, 12.5%; single-phase control, 20.4%), but the finding was not statistically significant. Although also not statistically significant, the use of a 2-phase treatment plan was shown to lead to a reduction in mean initial overjet for fixed orthodontic therapy. An increase in the magnitude of overjet reduction required by fixed orthodontic therapy was shown by means of a partial proportional odds model to lead to a significant increase in OIERR.

No included studies reported any patient-related factors due to OIERR.

Because no meta-analysis was undertaken, no test for publication bias was performed.

With the use of the GRADE tool, the overall certainty of the evidence for each intervention was judged to be predominantly low to very low, with 1 intervention graded as moderate. This grading of evidence suggested limited to very little confidence in the effect estimate for the majority of the reviewed interventions and moderate confidence for 1 intervention. That is, the true effect may or was likely to be substantially different to the estimate effect for most interventions. Table III outlines the reasons for these judgements. The inter-investigator agreement (kappa) value for assessment of the quality of evidence was 0.864, indicating very good agreement between reviewers.

DISCUSSION

It is widely accepted that the use of orthodontic force often results in the unwanted effect of external root resorption on the treated dentition. Owing to the absence of pathognomonic symptoms, OIERR is often detected by routine radiographic examinations. This systematic review included 25 articles, describing 24 RCTs assessing 1004 patients for external root resorption. The included studies investigated OIERR in incisors and premolars undergoing orthodontic mechanotherapies. When assessing OIERR, the greatest advantage of RCTs compared with non-RCTs and cohort studies is the random allocation process. Because of known patient factors that predispose for OIERR[18] (such as ethnicity, genetics, and local factors), randomization is deemed to be essential in ensuring an even distribution of these factors and thus confounding within the study groups. This is thought to be an integral factor when studying OIERR and therefore justifies the inclusion of only these types of studies.

When assessing reported outcome parameters within the included studies, significant heterogeneity was observed. For many clinicians, radiographic apical blunting and/or loss of root length is the first apparent sign that OIERR is occurring. For patients undergoing

Table III. GRADE summary of findings: orthodontic mechanotherapies resulting in external root resorption (outcome)

Intervention	*No. of participants (studies)*	*Risk of bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Publication bias*	*Effect*	*Overall quality of evidence*
Continuity of force activation	54 (3 RCTs)	Very serious*	Serious†	Serious‡	Very Serious§,‖	Suspected¶	All studies showed increased resorption with continuous force.	⊕○○○ VERY LOW
Force magnitude	222 (11 RCTs)	Serious#	Serious†	No	No	Not suspected	All studies showed increased resorption with heavy forces.	⊕⊕○○ LOW
Removable thermoplastic aligners	27 (1 RCT)	Serious#	No	No	Serious§	Suspected¶	A single study showed no effect on resorption compared with light forces and less then with heavy forces.	⊕○○○ VERY LOW
Intrusive force	61 (3 RCTs)	Very serious*	No	Serious‡	Serious§	Suspected¶	All studies showed increased resorption with intrusion	⊕○○○ VERY LOW
Jiggling force	30 (1 RCT)	Serious#	No	No	Serious§	Suspected¶	A single study showed no effect on resorption.	⊕○○○ VERY LOW
Bracket prescription	149 (1 RCT)	No	No	No	Serious§	Not suspected	A single study showed no effect on resorption.	⊕⊕⊕○ MODERATE
Archwire sequence	236 (2 RCTs)	Serious#	Serious†	No	No	Not suspected	All studies showed no effect on resorption	⊕⊕○○ LOW
Bracket ligation	131 (3 RCTs)	Serious#	Serious†	Serious‡	No	Not suspected	All studies showed no effect on resorption	⊕○○○ VERY LOW
Treatment duration	138 (1 RCT)	Serious#	Serious†	No	Serious§	Not suspected	A single study showed increased resorption with increased duration.	⊕○○○ VERY LOW
Treatment pause	40 (1 RCT)	Serious#	No	No	Serious§	Suspected¶	A single study showed reduced resorption.	⊕○○○ VERY LOW
2-Phase treatment	138 (1 RCT)	Serious#	No	No	Serious§	Not suspected	A single study showed no effect on resorption.	⊕⊕○○ LOW

Outcome of interest: external root resorption (for which a single pooled effect estimate was not available and only a narrative synthesis of the evidence was provided). Note that because the outcome for all interventions was the amount of OIERR, individual GRADE summary of findings tables were collated into this single table for publication purposes. GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: Any estimate of effect is very uncertain.

*The evidence was downgraded by 2 levels because of very serious concern regarding the risk of bias; 1 included study has high risk of bias; †The evidence was downgraded by 1 level because of high degree of heterogeneity in methodology; ‡The evidence was downgraded by 1 level because of the use of uninformative measurement tool; §The evidence was downgraded by 1 level because the results come from small studies and number of participants and insufficient event rates for dichotomous and continuous outcomes; ‖The evidence was downgraded by 1 level because the results did not include a statistical test or the test statistic; ¶The evidence was downgraded by 1 level because the results come from small studies and number of participants; #The evidence was downgraded by one level because of serious concern regarding the risk of bias; ≥1 included study has unclear risk of bias.

orthodontic therapy, the use of CBCT or panoramic and IOPA radiography is primarily used to assess the presence and severity of the OIERR. Many of the included studies used volumetric measurement of OIERR on extracted premolars (13 assessed only maxillary first premolars[31-41,43,45,46]; 2 assessed both maxillary and mandibular premolars[42,44]). Premolars are the teeth most frequently bilaterally extracted for orthodontic treatment, making it possible to perform split mouth–designed RCTs, with the contralateral premolar often serving as a control. This method may be the only ethical way to measure OIERR using the most reliable instruments for the diagnosis of OIERR (ie, MicroCT and EM), although these teeth are not shown to be the teeth most often affected.[18] Of the 10 studies assessing incisors, a low RoB was detected in only 3,[50-52] with a high risk detected in 1.[55] For these studies, the use of more sensitive and specific diagnostic instruments after dental extraction is not suitable. This therefore results in potential bias due to possible underestimation of the treatment effect.[56] Quality-of-life data were recorded in only 1 study,[50] but it was measured as discomfort following archwire change not as a result of OIERR. Other outcomes, such as genetic predisposition, patient's perception, tooth mobility, and prognosis, were not recorded in any of the studies. Because of methodologic heterogeneity of the included studies and incompatibility of original data, a meta-analysis was not possible. In addition, many of the studies that were characterized by study design and methodologic similarities were conducted by the same research group. To then conduct a meta-analysis in this case could result in a biased conclusion.

Of the 24 included studies, only a few included a control group, adequately described the randomization process, or measured OIERR before commencement of the intervention. To determine the actual effect of OIERR due to the orthodontic mechanotherapies, the use of a control group and pretreatment screening is strongly recommended. Despite this, most authors compared 2 interventions, with only 5 studies[31,32,35,38,44,45] including no-treatment control. Finally, without assessing subjects for OIERR before commencement of the study, it is impossible to discern the actual effect of the interventions. Three of the included studies appropriately described and applied a valid randomization protocol,[50-52] and only 9 performed pretreatment OIERR assessment.[47-55]

The results of the present review show that induction of external root resorption is associated with the application of orthodontic force.[31,32,35,38,44,45] The influence of force loading continuity was assessed by 3 articles, with the results showing that continuous forces, regardless of force magnitude or direction, resulted in more OIERR than interrupted forces. This finding is argued to be due to intermittent loading allowing the healing of resorbed cementum.[2,33,44,49] Of the 11 studies[31,32,35-43,45] evaluating force magnitude, only 1 did not show a statistically significant increase in OIERR when heavy forces were applied.[36] That study also found increased OIERR with the application of heavy force, although it may be argued that the 4-week duration of the trial may have been insufficient to determine relationship with OIERR.[41] To date, only 1 RCT assessing STAs exists, and it showed that STAs result in OIERR similar to that of light forces with the use of conventional fixed orthodontic brackets.[35] Notably, although the authors reported that the STAs were passive before delivery of the next aligner, the amount of movement provided by an STA is variable and subject to patient compliance. This has the ability to influence results, because it has been shown that intermittent forces allow for healing of resorbed cementum and may reduce OIERR. The effect of intrusive forces on OIERR were reviewed with the use of multiple methodologies, but all of the studies showed an increase in OIERR.[38,46,53] This finding was typified by a single study comparing intrusion with extrusive forces.[46] That study aimed to compare the effect of compression and tension of the periodontal ligament in OIERR, and showed that intrusive forces resulted in a >4-fold increase compared with extrusion. The use of jiggling forces by Eross et al[37] found that that compressive forces resulted in similar OIERR regardless of the direction. It must be noted that this finding was interpreted as a sum of all resorption, because the introduction of jiggling buccal-lingual directed forces resulted in 2 intermittent compression areas, compared with a single compression area in the buccally directed tipping force group.

Of the studies assessing orthodontic brackets and wires, it was shown that bracket prescription,[51] ligation method,[52,54,55] and archwire sequence[47,50] resulted in no statistically significant association with an increase or decrease in OIERR. The reason for this may be assumed to be similarities in force magnitude and activation protocol between groups, which have been shown to be associated with OIERR, rather than the appliance design. The effect of treatment duration[48] and a treatment pause[49] showed a positive and an inverse relationship with OIERR, respectively. Interestingly, 13 of the included studies used an intervention period of >8 weeks.[33,37,41,42,47-55] Paetyangkul et al[41] observed statistically significant increases in OIERR when 12 weeks of treatment had been reached and suggested that it was due to an increase in clastic

activity after 8 weeks of treatment. The effect of increased treatment duration was supported by a finding of a large observational study by Apajalahti and Peltola,[57] which showed that a longer treatment duration of fixed orthodontics increased the risk of severe OIERR. Despite invariably increasing treatment duration, it has also been shown that the inclusion of a treatment pause in patients experiencing OIERR may mitigate its severity. This is proposed to be due to the resolution and healing of resorptive craters and complete clearance of hyalinization zones before recommencing treatment.[2,18,24] Finally, the results of the effect of a 2-phase orthodontic treatment plan on OIERR was evaluated by 1 study, in comparison with a single-phase treatment plan.[48] Although there was a decrease in resorption seen in patients receiving 2-phase treatment, the association may be related to the reduction in overjet provided by the first phase of treatment. By reducing initial overjet, the treatment duration of fixed orthodontic therapy may be reduced and thus a decrease in OIERR.

During the systematic review process, heterogeneity among the included studies presented a profound limitation of the study. Primarily, the methodology in which the primary articles measured OIERR limits the ability to compare studies within the same intervention. Of the 24 included studies, 13 assessed OIERR by means of volumetric measurement,[31-43,45] 9 by means of change in root length,[47-55] and 2 by means of root surface area affected.[44,46] This heterogeneity in assessment was exacerbated by the use of various measuring instruments (IOPA, CBCT, EM, and MicroCT), force magnitude, force direction, and duration. When assessing follow-up, the duration of treatment ranged from 4 to 117 weeks. Although various time points were used for assessment, this review assessed the overall range of mean differences, with changes at specific time intervals not directly compared. No studies were excluded in this review on the basis of RoB, and no secondary meta-analysis could be performed. Therefore, the impact that the unclear/high-RoB studies had on the overall treatment effect was not determined.

Although a comprehensive search strategy was used, a shortage of high-quality clinical trials is apparent. With the use of the GRADE tool, the overall certainty of the evidence for each intervention was determined to be predominantly low to very low, with 1 intervention graded as moderate (Table III). For the other outcomes of this review, no published data fulfilled the criteria required for inclusion. Further studies are recommended to overcome the methodologic limitations of the included trials. Standardization of OIERR measurement techniques, the inclusion of pretreatment assessment of OIERR in included patients, and standardized reporting methods will allow for quantitative evaluation and stronger clinical recommendations.

CONCLUSION

From the available literature, the following is shown.

1. There is an shortage of well designed and reported RCTs on OIERR.
2. There is predominantly low- to very-low-quality evidence regarding orthodontic mechanotherapies and their influence on external root resorption.
3. An increase in incidence and severity of OIERR is seen when orthodontic forces are applied.
4. Positive correlations exist between OIERR and continuous force, heavy forces, intrusive force, and treatment duration.
5. Extent of external root resorption was shown to reduce with the provision of a treatment pause.

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