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Published in:
European Journal of Orthodontics

DOI:
10.1093/ejo/cjaa058

Publication date:
2021

Document Version
Peer reviewed version

Orthodontic treatment and root resorption: An overview of systematic reviews

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ABSTRACT

Background: Root resorption can be considered the most unfortunate complication of orthodontic treatment.
Objective: To evaluate the available evidence regarding orthodontically induced inflammatory root resorption (OIIRR).
Search Methods: A comprehensive literature search was conducted for the systematic reviews investigating OIIRR published up to 24 May, 2020. This was accomplished using electronic databases: MEDLINE via OVID, EMBASE, AMED (Allied and Complementary Medicine Database), PubMed, and Web of Science. Any ongoing systematic reviews were searched using Prospero and a grey literature search was undertaken using Google Scholar and OpenGrey (www.opengrey.eu/). No language restriction was applied.
Selection Criteria: Only studies investigating OIIRR were included.
Data Collection and Analysis: Screening, quality assessment [using the AMSTAR 2 tool (A Measurement Tool to Assess Systematic Reviews)], and data extraction were performed by two authors independently. Information was categorized and narratively synthesized for the key findings from moderate and high-quality reviews.
Results: A total of 2033 potentially eligible studies were identified. After excluding the non-relevant studies, 28 systematic reviews were included. Of which, 20 systematic reviews (71.5%) were of moderate and high-quality level of evidence. The incidence and severity of OIIRR increase with the fixed appliance, especially with heavy force, intrusion, torquing movements, increased treatment duration, and treatment with extractions or with long apical displacement (particularly for maxillary incisors). There was insufficient evidence regarding most other treatment- and patient-related factors on OIIRR. Following all precautionary measures, pausing treatment and regular monitoring benefits patients with OIIRR.
Conclusions: There is a limited number of high-quality studies in terms of OIIRR. The influence of fixed appliance on root resorption was noted however the cause and effect relationship between OIIRR and orthodontic biomechanics has not been confirmed. Avoiding heavy, continuous forces and a greater amount of apical displacement over a long duration of treatment is recommended. Precautionary measures should be carefully considered when treating patients with a high risk of OIIRR.
Registration: CRD42020166629
Conflict of Interest: None to declare.
Keywords: Root resorption, Fixed appliance, Overview of systematic reviews, OIIRR

INTRODUCTION

External apical root resorption (EARR) is a permanent/irreversible loss of the apical part of a tooth root **(1)**. It can be a physiologic or pathologic process. Root resorption is a common iatrogenic complication of orthodontic treatment, where the term of "orthodontically induced inflammatory root resorption" (OIIRR) is used **(2-5)**. During orthodontic treatment, mechanical forces are applied to move teeth and this results in sterile inflammatory response which is the biological basis of OIIRR **(2,3)**.

When orthodontic pressure exceeds that of the periodontal capillary pressure, ischemic necrosis in the periodontal ligament occurs due to collapse and localized loss of the blood supply **(2,6-8)**. This results in the degradation of the outer protective layers of the tooth (hyalinized zone). Consequently, clastic cells are activated as a result of the loss of precementum and its formative layer of cementoblasts, and root resorption is initiated during active removal of the hyalinized necrotic tissue **(9,10)**. Thus, when the reparative capacity of the cementum is exceeded, dentine is exposed and odontoclasts cause irreversible loss of root structure **(11)**.

Since orthodontic treatment is usually associated with the formation of hyalinized areas, OIIRR is anticipated for the majority of orthodontic patients **(12-14)**.

Detection of EARR can be either histologically using microscopic investigation or clinically using two-dimensional (2D) radiography or three-dimensional (3D) cone beam computed tomography (CBCT) **(15,16)**. Nevertheless, due to the three-dimensional (3D) nature of the resorption, 3D imaging is more accurate and reliable than 2D methods **(15,17-19)**.

Methods of measuring root resorption usually include subjective assessment using a scoring system **(20)**, linear measurements of root length and root ratios **(21,22)**, and digital reconstruction/subtraction using computer software **(23,24)**.

Although it is a complex process that is not completely understood, OIIRR is deemed to have a multifactorial etiology, that essentially can be categorized into treatment-related factors and patient-related factors. Treatment-related risk factors include treatment duration, appliance type, type and magnitude of force applied, type of tooth movement, amount of apical displacement, corticotomy, low-level laser therapy, and ultrasound therapy. Whereas, patient-related risk factors include among others the genetic predisposition, biologic factors, systemic factors and medications, age, gender, ethnicity, root morphology, type of malocclusion, previous history of trauma or root resorption, and endodontic treatment **(3,25-28)**.

Root resorption and orthodontic treatment has been investigated using different study designs, including reviews. Some of these reviews have not been systematic in nature **(3,29-32)**, however several systematic reviews have been conducted to evaluate the association of EARR with different patient- or treatment-related factors **(25,27,28,33-57)**. The aim of this study is to provide an overview of these systematic reviews in order to evaluate the available evidence regarding OIIRR.

MATERIALS AND METHOD

Due to the nature of this study, ethical approval was not required as no intervention was carried out, there was no patient participation and personal data collection was not required. This overview was prepared in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement **(58)**.

Protocol and registration

The protocol for the present review was registered with PROSPERO. Registration number: CRD42020166629.

Eligibility criteria

The eligibility criteria were determined according to Population, Intervention, Comparison, Outcome, and Study design (PICOS) scheme:

Populations: humans or animals receiving orthodontic mechanotherapy.

Intervention: orthodontic treatment with any type of appliances or treatment modality.

Comparison: any type of orthodontic treatment at another time-point or untreated controls (if available).

Outcome: OIIRR measured by any method.

Study design: systematic reviews with or without meta-analysis. In case of Cochrane reviews, the most recent publication was included, and all previous versions were excluded. Studies with any other design or without orthodontic treatment were also excluded.

Different treatment- and patient-related factors were also taken into consideration during selecting of intervention and comparison.

Information sources, search strategy and study selection

A comprehensive literature search was conducted for studies published up to 24 May, 2020 using the following key terms: “root resorption”, “root shortening”, “root alternation”, “adverse effect”, “orthodontic treatment”, “systematic review”, and “meta-analysis”. This was accomplished using electronic databases: MEDLINE via OVID (1946 to 24 May, 2020), EMBASE (1974 to 24 May, 2020), AMED (Allied and Complementary Medicine Database) (1985 to 24 May, 2020), PubMed (inception to 24 May, 2020) and, Web of Science (1900 to 2020). Any ongoing systematic reviews were searched using Prospero and a grey literature search was undertaken using Google Scholar and OpenGrey (www.opengrey.eu/). No restrictions were applied in terms of language, date, and status of publication, type of orthodontic treatment, age of treated patients, and animal species. All relevant articles were identified, retrieved and assessed for eligibility of inclusion by two authors (Y.A.Y. and G.T.M.). Any disagreements were resolved by discussion or alternatively by a third author (D.R.B.).

Data extraction

After screening the eligible systematic reviews, the following data were extracted independently and in duplicate by the same two authors (Y.A.Y and G.T.M.): (1) year of publication; (2) study design; (3) number of studies included; (4) type of studies; (5) number of participants; (6) period of search; (7) name of journal; and (8) objectives of the study (Table 1).

Quality assessment

Both authors (Y.A.Y and G.T.M.) assessed the included reviews independently using the AMSTAR 2 quality assessment tool (A Measurement Tool to Assess Systematic Reviews) **(59)** (Table 2). Any disagreements were initially resolved by discussion or in conjunction with a third author (D.R.B.), if necessary.
AMSTAR 2 categorizes the level of evidence according to the following:

- **High:** No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
- **Moderate:** More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
- **Low:** One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
- **Critically low:** More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence

Data synthesis

Data pooling was planned to quantitatively assess the effect of orthodontic treatment on OIIRR in the case of clinical homogeneity. Various study characteristics, such as similarity in interventions, method of OIIRR detection and measurement, and type of sample (human or animals) was planned to be examined to evaluate the homogeneity of the included reviews. On the other hand, where clinical heterogeneity was detected, qualitative analysis would be applied instead.

RESULTS

Search selection

A total of 2033 potentially eligible studies were identified. After exclusion of the duplicates, 1988 were left for screening the titles and abstracts. This shortened the number to 37 systematic reviews. After full text

assessment, five reviews were not systematically designed and four reviews were not relevant to the aim leaving 28 for inclusion (Figure 1).

Study characteristics

A summary of the characteristics of the included systematic reviews is presented in Table 1. The included studies were published from 2004 to 2020. Four of the included studies have animals in their sample.

Data synthesis

Due to heterogeneity of the included systematic reviews in terms of type of treatment, participants, methods of detecting and assessment of OIIRR, meta-analysis was not possible. The data were, therefore, synthesized qualitatively using *thematic synthesis* by identifying the most prominent and important themes with the findings summarized accordingly. Thematic synthesis was used with the following thematic headings identified: (1) quality of evidence; (2) OIIRR and treatment-related factors; (3) OIIRR and patient-related factors.

Quality of the Evidence

The quality of the included reviews was variable: 5 (17.9%) critically low, 3 (10.7%) low, 19 (67.9%) moderate, and 1 (3.6%) high (Figure 2). Meta-analyses were carried out in 39.3% of the systematic reviews (11 systematic reviews with meta-analysis) (Table 1). Most of the AMSTAR 2 items were covered to a varying degree. Only one review reported the source of funding of the included studies **(47)** (Table 2). There was complete consensus between the reviewers regarding the quality assessment.

In this umbrella review, the main findings from the moderate and high-quality systematic reviews will be considered.

OIIRR and treatment-related factors

Incidence, prevalence, and severity of root resorption with orthodontic treatment

The incidence and severity of root resorption was found to increase with comprehensive fixed appliance treatment **(25,45,46)**. However, generally all the systematic reviews included in this overview reported that there is a relationship between orthodontic treatment and root resorption.

Type of tooth movement and force level

OIIRR increased with the application of heavy forces. This positive and significant correlation between orthodontic force level and OIIRR was reported by several systematic reviews **(25,37,46)**. However, this correlation was supported by low evidence as reported by **Currell et al. (2019) (46)**.

It has also been reported that intrusive movements **(25,46)**, anteroposterior apical root displacement, and retraction mechanics **(36)** were associated with OIIRR.

Intrusion movements with TADs placed between the maxillary lateral incisors and canines results in greater OIIRR than when TADs were placed between the maxillary second premolar and the first permanent molar **(28)**. It has also been noted that continuous force results in greater root resorption than intermittent forces **(25, 46)**.

Type of orthodontic appliance

Although the evidence is low, OIIRR was not affected by the type of bracket ligation method (conventional/self-ligating) **(25,28,46)**, bracket prescription **(25)**, or straight wire/standard edgewise brackets **(25,46)**. **Yi et al. (2016) (44)** on the other hand reported that root resorption with self-ligating brackets was

only lower for the maxillary central incisors, but not significantly different for other incisors when compared with root resorption associated with conventional brackets. Again, the evidence for this finding was low.

No difference in OIIRR with different archwire sequences was identified **(25,46)**. Nevertheless, the use of superelastic archwires showed a very mild tendency, although non-significant, to an increase of OIIRR **(46)**.

The incidence and severity of root resorption was less with aligners than with fixed appliance and it is comparable to the resorption with light forces **(25,37,39,40,46)**. However, **Ghandi et al. (2020) (41)**, in general, could not find a significant difference between the two types of appliances.

No information is available yet regarding root resorption with removable appliances, while rapid maxillary expansion is associated with a higher degree of root resorption **(28)**, especially for the first permanent molars **(28)**. Further evidence is required about the effect of functional appliances, and particularly for fixed-functional appliances such as Herbst appliance **(28)**.

Phases of treatment

Although one-phase of treatment of Class II malocclusions was associated with greater OIIRR compared with two-phase treatment **(25,46)**, this was not statistically significant **(25)**.

Treatment duration

A positive correlation was reported between increased treatment duration and root resorption **(28,36,37,45,46)**. This correlation was however weak to moderate **(36)**.

Extraction vs. non-extraction

The risk of OIIRR was found to increase when the treatment included dental extractions **(28,45)**.

Interventions

Conflicting results were observed regarding the use of low-level laser therapy during orthodontic tooth movement. This ranged from reducing OIIRR, a reparative effect for OIIRR to increasing OIIRR **(47)**. **Haugland et al. (2018) (27)** detected that low-level laser therapy and mechanical vibration in humans and rats did not affect OIIRR. Similarly, with orthodontic patients, **Lyu et al. (2019) (48)** reported insufficient evidence to support the positive effect of supplemental vibrational forces on root resorption during orthodontic treatment.

Corticotomy was found, with meta-analysis outcomes, to significantly increase OIIRR in rats, while in humans the results were contradictory. On the other hand, low-intensity pulsed ultrasound might reduce OIIRR in humans **(27)**.

OIIRR and patient-related factors

Age and gender

Chronological age at the start of treatment and gender did not influence root resorption. Studies that considered these factors did not find any conclusive association **(36,56)**.

Type of malocclusion

Orthodontic treatment for Class II division 1 malocclusion could increase the risk and severity of OIIRR **(36)**. However, no systematic review investigated the influence of other types of malocclusions on OIIRR.

Teeth and jaws

The risk of OIIRR is higher for anterior teeth than posterior teeth especially for maxillary central and lateral incisors and then canines **(28,45)**. Regarding the location within the dental arch, OIIRR is greater in the following regions within each arch: anterior maxilla, anterior mandible, posterior mandible, and posterior maxilla respectively **(28)**.

History of trauma and root canal filling

It has been reported that a history of trauma was not found to correlate with or influence OIIRR **(25)**. One systematic review revealed that OIIRR was comparable for root-filled teeth and those with vital pulp **(56)**, while another discovered that root resorption following orthodontic treatment is less for endodontically treated teeth in comparison with teeth with vital pulp **(57)**.

Root morphology

Unusual root morphology was not found to correlate with OIIRR **(25)**.

Genes

Inconclusive results were found regarding the role of genetic polymorphisms for OIIRR, as some studies found an association while others did not. However, some genetic polymorphisms and biological modifiers may increase the incidence of OIIRR **(49)**.

Systemic supplements, medications, and hormones

Systemic supplements (in animal studies) such as prostaglandin did not affect OIIRR, while fluoride administration on the other hand, reduces OIIRR in animals **(27)** and for a short-term only in humans **(52)**. Administration of prostaglandin E2 **(51)** and Ca++ **(51,53)** did not influence OIIRR in animal studies.

Medications: Bisphosphonate may inhibit OIIRR, however no meta-analysis confirmed this in animals or humans **(27,53,54)**. The effect of NSAIDs on OIIRR in rats did not show a significant result in a meta-analysis and this was similar to the effect of acetaminophen in rats. Other drugs also showed no significant effects, in animal studies, on OIIRR, such as statins, lithium chloride, and fluoxetine **(27)**. **Makrygiannakis et al. (2019) (53)** found, in animal studies, that administration of Vitamin C may increase the possibility of OIIRR. They also reported no difference in OIIRR with acetaminophen, aspirin, fluoxetine, atorvastatin, zinc, zoledronic acid, and misoprostol. On the other hand, they noted a decrease in root resorption after the administration of ibuprofen, meloxicam, simvastatin, alendronate, lithium chloride, and strontium ranelate. In regards to humans, nabumetone (NSAIDs) was reported to reduce OIIRR, however this was with a very low confidence **(52)**.

Non-conclusive results assessing the relationship of OIIRR and interleukins (IL-4, IL-12) were also found in animal studies **(51)**.

Hormones: OIIRR was increased in rats with oestrogen reduction **(27)**. Whereas, it was significantly inhibited in rats with the administration of thyroxine **(27,51)**, especially in low doses **(51)**, insulin, recombinant human growth hormone, and steroids (particularly prednisolone) **(27)**. **Makrygiannakis et al. (2019) (53)** found the same result in rats for the recombinant human growth hormone, but with inconsistent effect of administrating prednisolone and L-thyroxine on OIIRR.

Asthma and allergy

Asthmatic orthodontic patients and allergic sensitization in animals were reported to increase OIIRR significantly when compared to control groups **(27)**.

DISCUSSION

This study was designed to provide a contemporary overview of the available evidence-based information regarding root resorption in association with orthodontic treatment. As such, synthesis was at the systematic review level rather than at the individual study level. The searching process revealed 28 systematic reviews (of these 11 included meta-analysis) that were published during the last 16 years in high quality journals. Unfortunately, most of the systematic reviews reported a deficiency in the available evidence, particularly at the level of RCTs and genetic studies. In order to determine the actual OIIRR for any intervention, a control group should be compared with the intervention group and a pre-intervention assessment of root resorption should be undertaken. Nevertheless, most of the studies did not carry out these and thus their results must be interpreted with caution **(46)**.

The method of assessing the systematic reviews was based on AMSTAR 2, which is a 16-item tool to assess the methodological quality/level of evidence of systematic reviews (including randomized and non-randomised studies) **(59)**. It is a modified and updated version of the 11-item AMSTAR that has been internally and externally validated with adequate reliability **(60,61)** along with a simpler and more comprehensive categorical rating of study quality. Only one of the included systematic reviews, representing 3.6% of the available evidence, was considered to be "High level" evidence while the rest were approximately divided into moderate and low/critically low. This was attributed primarily to the lack of meta-analysis, weaknesses in methodology, inferior searching processes, or poor explanations of the results.

Due to the heterogeneity of the included reviews for different treatment- and patient-related factors in addition to the difference in detecting and assessing root resorption, thematic analysis was used to provide a narrative review. Thematic analysis is a form of analysis that can be used in qualitative research **(62)**, by examining, emphasising, pinpointing and recording themes within data **(63)**. Themes are patterns within sets of data that are associated to a specific research question and are essential to the description of a phenomenon **(64)**. The main findings of moderate and high-quality systematic reviews, which comprise 71.5% of the total systematic reviews, were included to avoid any misleading outcomes from low/critically low-quality systematic reviews.

OIIRR and treatment-related factors

Incidence, prevalence, and severity of root resorption with orthodontic treatment

It is clear from the evidence that the incidence, prevalence, and severity of root resorption increases with comprehensive fixed appliance orthodontic treatment. This is due to the mechanism of orthodontic tooth movement where the applied pressure results in ischemic necrosis and the formation of a hyalinized zone in the periodontal ligament due to the loss of the blood supply. Therefore, as a consequence of the reparative process, root resorption occurs **(2,6-11)**. This would significantly increase when force levels are higher **(25,37,46)**.

Type of tooth movement and force levels

Intrusion, retraction, and torque movements may not by themselves be responsible for increasing the risk of OIIRR, but the amount of force applied, stress distribution area, and total apical displacement may exacerbate their influential effect on OIIRR **(25)**. Greater distance of apical displacement may reflect the longer duration of force application with subsequent hyalinization and OIIRR **(36)**.

The effect of intrusion on OIIRR may also be attributed to the greater compression of the periodontal ligament on a small surface area of the root **(25,46)**. A study by **Han et al. (2005) (65)** showed that intrusive forces increases OIIRR greater than four-fold when compared to extrusive forces **(46)**.

The presence of TADs more anteriorly (between the maxillary lateral incisor and canine) for incisor intrusion could provide heavier apical forces and more compression of the blood vessels and therefore resulting in greater OIIRR when compared to more posteriorly placed TADs (between the maxillary second premolar and the first permanent molar) **(28)**.

The association of OIIRR with force application, particularly continuous forces when compared to intermittent forces may be due to remission periods as a result of treatment pauses with the intermittent force allowing

healing of the resorbed cementum **(46)**. **Weltman et al. (2010) (25)** agreed with this finding but reported that the evidence was limited.

Type of orthodontic appliance

The reason for the non-significant influence of bracket design, prescription, or archwire sequence on OIIRR may be that all these appliance variations result in similar force magnitudes which is correlated with root resorption rather than the appliance design itself **(46)**. The meta-analysis by **Samandara et al. (2018) (28)** revealed non-significant differences between self-ligating and conventional brackets but they highlight the low level of evidence due to bias and imprecision in addition to the low numbers of clinical trials. **Yi et al. (2016) (44)** found that self-ligating brackets could provide a protective effect for long-term treatment to the maxillary central incisors. This may be attributed to the lower amount of force with self-ligating brackets compared to conventional brackets due to loose ligation, but as mentioned above due to the low level of evidence, these results should be interpreted with caution.

There is a very mild tendency of inducing OIIRR with superelastic archwires when compared to stainless steel wires **(46)**, and this can be explained by the continuous nature of force with superelastic wires and the intermittent force with stainless steel wires **(46,66,67)**. However, greater evidence is required in this area.

The evidence related to OIIRR with aligner appliances is scarce, however the available studies revealed that aligners are associated with a lower risk of OIIRR when compared to fixed appliances **(25,37,39,40)** and this may be due to the nature of intermittent and relatively light forces with these appliances, the simpler types of tooth movement resulting in smaller amounts of tooth movement/apical displacement. Hence, there is a greater chance of root healing by promoting the cementum repair process. Moreover, aligners are usually indicated for cases with minor crowding where no extractions are indicated and with shorter treatment duration **(41)**. Aligners are also subject to patient compliance, where any lack of compliance results in more intermittent force delivery with shorter duration of force application resulting in less OIIRR **(46)**, but this may also produce jiggling forces which may increase the risk of OIIRR **(40)**. This may not be easily determined and hence is not readily reported **(37)**. In light of the above differences between fixed and aligner appliances, the results of these comparisons with fixed appliances should be interpreted with caution **(37,40)**. The most recent systematic review and meta-analysis could not find a significant difference between preadjusted edgewise fixed appliance and aligners in terms of OIIRR, except for the maxillary right lateral incisor which showed less OIIRR with aligners. Yet, all the differences for the maxillary central and lateral incisors were not of clinical importance (less than 1 mm) **(41)**.

Surprisingly, removable appliances were not investigated in terms of OIIRR in any of the included reviews. but only in one critically low-quality of evidence systematic review **(43)**

The systematic review by **Samandara et al. (2018) (28)** found that OIIRR with tooth-and-tissue-anchored Hass-type rapid maxillary expander was less than that with a tooth-anchored Hyrax-type expander. However, more RCTs are required to confirm this.

The effect of functional appliances and with fixed-functional appliances, in particular the Herbst appliance needs to be confirmed as this appears to increase root resorption for the upper and lower first permanent molars **(28)**.

Phases of treatment

The reduction in OIIRR with two-phase treatment compared to that of one-phase **(46)** may be explained by the severity of malocclusion being decreased in the first phase and therefore, the duration of fixed appliance treatment and the amount of tooth movement would be decreased in the second phase. Furthermore, this interruption will act similar to the intermittent force by increasing the possibility of root healing that could happen during the 1st phase. Nevertheless, the evidence regarding phases of treatment and OIIRR is scarce **(25)**.

Treatment duration

Despite the positive correlation between duration of treatment and OIIRR **(28,36,37,45,46)**, it may not be the treatment duration that matters rather than the active treatment time that increases the risk of OIIRR. The treatment duration could be increased due to lack of patient cooperation (missing appointments), or when clinicians preferred longer interval between appointments. This would increase overall treatment duration but diminish force level between appointments and may decrease the risk of OIIRR. Although, these were not investigated, but may explain the weak correlation between treatment duration and OIIRR in some studies **(36)**.

Extraction vs. non-extraction

The presence and pattern of extractions plays a significant role in OIIRR, as extraction of four bicuspids was associated with a greater risk of OIIRR when compared to non-extraction treatment **(28,45)**. This may be explained due to the greater distance that the teeth will move when treatment includes extractions. The longer the distance means the greater the associated force and duration of treatment and consequently OIIRR **(28)**.

Interventions

The non-significant influence of low-level laser therapy, and mechanical vibration on OIIRR occurs due to heterogeneity in the method of application, doses used, and duration of application **(27)** or due to limited available studies **(48)**. Low-level laser therapy is supposed to have a potential promising role in clinical orthodontics, especially for increasing the rate of tooth movement, decreasing the treatment duration **(68)**, decreasing pain levels in humans **(69)**, and promoting bone regeneration **(70-72)**. However, due to methodological incoherence and inconsistencies of the available studies, the influence of low-level laser therapy on OIIRR is still unclear. The results of studies involving low-level laser therapy are confounded by several factors, such as type of the sample (humans or animals), amount of orthodontic force, duration of treatment, design and material of orthodontic appliance, site of tooth movement, using of split mouth design, presence of other interventions (such as corticotomy or grafting procedures), laser wavelength, output power, dose, exposure time, contact or non-contact application, type of tissue, and administration method. Therefore, further high-quality studies with adequately calculated sample size are required to determine this effect **(47)**.

Low-intensity pulsed ultrasound, on the other hand, might seem to reduce OIIRR **(27)**. However, all the above-mentioned interventions were not investigated comprehensively.

Corticotomy is implemented with intention to increase bone remodelling, increase the speed of tooth movement, and reduce OIIRR, but the opposite was confirmed by the meta-analysis with a rat sample. This may be due to this procedure enhancing inflammatory reaction associated with the release of biomedical mediators that induce osteoclastic activity. In human, the influence of corticotomy with OIIRR has not been confirmed **(27)**.

OIIRR and patient-related factors

Age and gender

Age and gender were not found to influence OIIRR and even studies that reported a difference with these factors this was not statistically significant **(36,56)**. However, these potential risk factors were not investigated extensively. Regarding the age, there is a tendency that younger roots with open apex might tolerate pulpal changes and root resorption more than fully developed teeth **(36)**.

Type of malocclusion

Tieu et al. (2014) (36) concluded that there was a limited evidence suggesting that treatment of Class II division 1 malocclusion could increase the severity and prevalence of root resorption when compared to the pre-treatment situation. Furthermore, when Class II division 1 was treated with any type of treatment strategies it could produce a similar amount of root resorption and it is comparable to that reported for treatment of any

other type of malocclusion. However, other types of malocclusion were not investigated in that systematic review.

It is expected that treatment for Class II division 2 malocclusion with fixed appliances may be associated with a higher risk for OIIRR due to the need for the correction of deep overbite and overjet using a combination of torqueing, intrusive, and retraction movements.

Teeth and jaws

The higher risk of root resorption for the maxillary incisors during orthodontic treatment can be related to the greater amount of distance that these teeth usually move **(36)** and the torqueing/intrusive movement compared to other teeth adding to this the smaller and finer root surface of these teeth. Generally, root resorption is greater in the high-pressure zones than that in the high-tensile zones **(37)**. **Samandara et al. (2018) (28)** in their meta-analysis found that the greatest amount of OIIRR was for the anterior maxilla (0.82 mm), followed by the anterior mandible (0.60 mm), posterior mandible (0.28 mm), and posterior maxilla (0.22 mm). This amount of resorption in the anterior maxilla and mandible is almost similar to that found by **Deng et al. (2018) (45)**, however it may differ from those reported by other studies due to variation in the method of assessment. Though, it does not reflect an amount of resorption of clinical importance. This was supported by **Deng et al. (2018) (45)** meta-analysis who reported that the average OIIRR was approximately 1 mm and did not exceed 2 mm in its upper limit.

History of trauma and root canal filling

It has been postulated that OIIRR will be increased if the traumatized tooth showed a sign of root resorption **(20,56)**. Whereas, the risk of OIIRR for traumatized teeth with no signs of root resorption will be less **(20,56)** and comparable to that with non-traumatized teeth. The systematic review by **Weltman et al. (2010) (25)** agreed with the above postulation but they mentioned that there is a lack of RCTs for patients with traumatized teeth and showing a sign of root resorption before orthodontic treatment. Therefore, the evidence regarding this information is week.

It was found **(57)** that the amount of root resorption is significantly less in endodontically treated teeth compared to teeth with vital pulp. However, this difference was 0.31 mm **(57)** which can be considered as non-clinically significant and it may be the result of measurement error. This partially agreed with another systematic review **(56)** which reported, although the results were inconclusive, that root-filled teeth are not at higher risk of root resorption than vital teeth during orthodontic treatment (the difference is not clinically relevant, i.e. less than 1 mm). The absence of dental pulp in endodontically treated teeth, which may play an important role in inflammatory process, degenerative changes and root resorption can explain this result, however the evidence is not robust **(57)**. Several drawbacks that limit the level of evidence and render the interpretation of such results with caution are as follows: there is a lack in the information about previous trauma and its interaction with root resorption of orthodontically moved vital and root-filled teeth, no standardization of root resorption measurement, presence of root resorption prior to treatment **(55,56)**, no information available about the type of material used as a sealer or root canal filling (whether it is favorable such as calcium hydroxide or induces inflammation such as zinc oxide and eugenol or iodoform-containing root canal filling), the time of endodontic treatment to the onset of orthodontic treatment was not reported (with or without inflammation, as starting orthodontic treatment with the presence of inflammation could exacerbate the inflammatory reaction and consequently root resorption), small number and low quality of the original studies and their sample size, and heterogenous data.

Root morphology

The systematic review by **Weltman et al. (2010) (25)** found that the influence of unusual root morphology on OIIRR is very slight and did not reach the level of significance. Further investigations are required to determine if unusual root morphology, especially with fine tips, can withstand the force during orthodontic treatment similarly to normal roots.

Genes

Although the genetic predisposition to OIIRR is not fully understood yet, some evidence is available reporting that genetic polymorphism may be responsible for EARR, which means that the primordial cells within the dental pulp are probably playing this role **(49)**. However, the limited adequately-controlled genetic studies available as well as the non-adherence to the genetic guidelines or "STrengthening the REporting of Genetic Association studies" (STREGA), heterogeneity in ethnic background and genotyping methods could subject this evidence to bias due to lack of; power calculation, matching cases and controls, adjusting for confounders, odd ratios, reporting genetic analysis with the Hardy-Weinberg equilibrium among other methodological errors. Therefore, up-to-date, genetic polymorphism and biological modifiers cannot be considered as an actual cause for EARR, but perhaps an additional risk factor **(49)**.

Systemic supplements, medications, and hormones

Prostaglandins have the potential to accelerate tooth movement, and it has been concluded from the systematic review by **Haugland et al. (2018) (27)** according to their included animal studies that prostaglandins did not significantly increase OIIRR. On the other hand, the high doses of angiogenic cytokine basic fibroblast growth factor was found to reduce OIIRR in high doses in rats **(27)**. Furthermore, the combined use of prostaglandin E2 and Ca++ was not confirmed to increase OIIRR in animals **(51)**.

The inhibition effect of fluoride to OIIRR can be explained by: the fluoride increases mineral density and bone mass (hence it can be used for treating osteoporosis) **(73)**, therefore higher doses with longer exposure to fluoride can inhibit OIIRR **(74)**. Although this may not be practically applicable for humans and it may explain the short-term effect of fluoride administration on the reduction of OIIRR in human with an overall no significant long-term effect **(52)**. Secondly, sodium fluoride has the ability to reduce the number of active osteoclasts and inhibit osteoclastic activity **(27,75)**.

The influence of all the medications investigated, in humans and animals, by **Haugland et al. (2018) (27)**, **Kaklamanos et al. (2019) (52)**, **Makrygiannakis et al. (2019) (53)**, and **Zymperdikas et al. (2019) (54)** was not confirmed by a meta-analysis. Although some tendency may be anticipated from bisphosphonates and NSAIDs to reduce OIIRR, but due to the heterogeneity within their studies and methodological limitations, this could not be confirmed with a high level of confidence.

Thyroxine (T4) effect, especially in low doses, on reducing OIIRR is related to its effect on intestinal calcium absorption so it can affect bone turnover indirectly **(76)**. However, administration of thyroxine to patients susceptible to OIIRR may not be recommended due to other adverse effects that may occur. Moreover, the more relevant systematic review by **Makrygiannakis et al. (2019) (53)** did not confirm the influence of thyroxine on OIIRR. Administration of insulin could reduce OIIRR in diabetic patient as it controls the adverse effects of diabetes on bone metabolism and hence its impact on OIIRR. Administration of recombinant human growth hormone and its significant reduction in OIIRR might not be of great application as the dosage and frequency of administration used was greater than that normally required for growth hormone deficient patients **(77)**. Deficient oestrogen level enhances OIIRR similar to the effect of low oestrogen after menopause. This situation could modulate osteoclastogenesis via the OPG/RANK/RANKL system **(78,79)**. Therefore, when planning orthodontic treatment for post-menopausal women, OIIRR should be carefully considered. Prednisolone, in contrast to methylprednisolone, could reduce OIIRR, and this could be due to its anti-clastic activity of prednisolone, while methylprednisolone could inhibit blastic activity and enhance or result in unchanged clastic activity **(27)**. But the above influence of prednisolone was inconsistent with the **Makrygiannakis et al. (2019) (53)** finding. A decision algorithm by **Jadad et al., (1997) (80)** regarding the influence of prednisolone slightly outweighed the evidence of reducing OIIRR by **Haugland et al. (2018) (27)**. There is no robust evidence to determine the effect of intrinsic hormone-like molecule on OIIRR as all studies were carried out on animals and it may not ethically viable for humans. Therefore, their results should be interpreted with caution and further high-quality studies are required to completely understand this relationship **(51)**.

In general, studies including systemic supplements, medications, and hormones showed high risk of bias, poor methodological quality, scarce of clinical studies (the majority are experimental on animals that cannot be directly inferred to humans), lack of clear information regarding dosage, timing, method of administration and side effects of these substances **(27,51)**.

Asthma and allergy

The relationship between asthma and allergy and OIIRR are not fully understood and no clinical study supports the available information which reveals that these conditions could increase OIIRR in humans and animals due to an increase in osteoclastogenesis due to allergen-induced inflammation **(27)**.

Methods of detection

There is evidence that using 2D measurements to evaluate root resorption is inferior to 3D measurements in terms of accuracy and reliability **(25,39,45)**. Furthermore, it has been found that root resorption value was overestimated and less accurate with 2D compared to CBCT **(41,45)**.

Cephalometric radiographs are associated with inherent problems such as superimposition, magnification, and distortion. Similarly, panoramic radiographs are associated with distortion of tooth position and inclination **(37)**. The use of this technique may maximize or shorten the root length due to differences in tooth inclination/angulation **(36)**.

Generally, root resorption is difficult to be detected with 2D radiographs when associated with maxillary expansion, or when there is minor root resorption, or resorption at the mesial, distal, mid-apical or buccal aspects. It is only the frank root resorption that can be easily visible by 2D radiographs **(35,45)**. The most reliable methods of microscopic or histologic examination can only be used for extracted teeth. CBCT which is the best clinical method for detection is costly and associated with a high dose of ionized radiation **(28,37,56)**, with perhaps limited clinical relevance as showed by **Samandara et al. (2018) (28)** meta-analysis. Therefore, periapical radiographs can be still used as a screening tool for root resorption. The paralleling technique tends to produce more accurate image with less magnification and distortion to this produced by bisecting technique **(36)**.

A recent systematic review by **Tarallo et al. (2019) (81)** revealed that dentine phosphoprotein could be considered a relatively useful biomarker for OIIRR. This was attributed because it is the major organic and non-collagenous component of dentine and seems more indicative of the loss of root structure than cementum proteins.

Precautionary measures to reduce OIIRR / Recommendations for clinical practice

The clinical recommendations have been classified as strong or weak/conditional recommendations based on the guidance provided in the GRADE handbook **(82)**.

1. Root resorption is a progressing iatrogenic effect of orthodontic treatment and can be considered as the major complication of treatment. Therefore, every effort should be paid to detect it and manage it as soon as possible. The orthodontist should be aware about the possible causes, consequences, and management of root resorption. It is also important that the informed consent should include information about the potential risk and impact of OIIRR **(25,36,45)** (strong recommendation).
2. Special attention should be paid for anterior teeth particularly when movement is intended for a long distance and over a long duration (strong recommendation).
3. Light intermittent force should be used especially for intrusive and torqueing movements **(25)**. Avoid starting with heavy gauge wires and skipping wire sizes. Additionally, the interval between appointments should be elongated as possible (conditional recommendation).
4. To detect and monitor root resorption, a periapical radiograph should be taken after six months from the start of treatment and supplemented by 3-month radiographic follow-up (specially for the anterior teeth of patients at risk) **(36)** (conditional recommendation).
5. When root resorption is detected during treatment, the treatment plan should be reassessed with the patient and/or parent, the treatment should be paused for at least 2-3 months or up to 6 months without active movements (with a passive archwire) to allow healing to take place **(25,37,46)**. Pausing the treatment for patients suffering from OIIRR may allow the reparative process to take place and give the chance for clearance of the hyalinized zone before restarting treatment **(37,46)**. Otherwise, in case of severe root resorption or if root resorption is continued progressively, the treatment must be terminated and endodontic treatment with calcium hydroxide for the affected teeth should be considered **(25,37,46)**. Sometimes

prosthetic solutions to close spaces, interproximal reduction instead of extraction, and fixation of the resorbed teeth might also be considered **(25)** (strong recommendation).

6. After treatment, a follow-up radiographic assessment is required and caution should be paid during retention to avoid trauma from the occlusion especially with fixed retainers (conditional recommendation) **(25)**.

Limitations of the evidence

There are few (and sometimes complete lack of) RCTs and this means there is a lack of randomization of the participants, allocation concealment, and blinding **(36,37)**. Furthermore, some of the available clinical studies are not randomized, prospective, or representative to comprehensive orthodontic treatment **(25)**.

Many studies did not use strict inclusion and exclusion criteria, a control group for comparison with the intervention group or controlling of the confounding variables, a sample size calculation (power analysis), or a pre-treatment radiographic evaluation **(37)**. Additionally, heterogeneity among the methods of assessing OIIRR was present in many studies **(25,36,37)**. Hence, some recommendations above are only made conditionally.

Suggestion for future research

More evidence is required to determine the risk factors for patients susceptible to root resorption. Therefore, adequately designed RCTs with parallel groups, appropriate randomization, allocation concealment, masking for outcome assessment, and with an appropriate power calculation and a standardized method for the assessment of pre- and post-treatment root length/volume are required. Such RCTs could use premolar teeth that would be extracted and evaluated for OIIRR using scanning electron microscopy (SEM), transmission electron microscopy (TEM), confocal laser scanning microscopy (CLSM), or microcomputed tomography (μCT) **(37)**, or alternatively measuring OIIRR throughout orthodontic treatment. Genetic studies to identify patient susceptibility is also required to identify how these could affect the incidence and severity of OIIRR **(25)**.

Whenever it is ethically applicable, the effect of administration of fluoride, thyroxine, insulin, oestrogen, recombinant human growth hormone, and prednisolone on reducing OIIRR should be investigated.

CONCLUSIONS

1. The level of evidence regarding OIIRR is moderate and further high-quality RCTs and genetic studies are required.
2. According to the available evidence, the risk of OIIRR can be expected to be higher in the following situations: heavy and continuous forces with comprehensive fixed appliance treatment including intrusion (especially with anterior TADs), maxillary incisor torque and retraction (especially with extractions), treatment of severe malocclusions requiring complex mechanics, long duration of active treatment, and tooth-anchored expansion.
3. There is insufficient evidence to confirm the effect on OIIRR of other treatment- and patient-related factors. These factors include:
    - Appliances, such as aligners, removable appliances, functional appliances and tooth-and-tissue-anchored expanders.
    - Interventions, such as corticotomy, low-level laser therapy, low-intensity pulsed ultrasound, and mechanical vibration.
    - Single-phase as opposed to two-phase treatment.
    - Age and gender.
    - Unusual root morphology, history of trauma (especially with a sign of resorption), and endodontic treatment.
    - Genetic polymorphisms.
    - Systemic supplements, medications, hormones.

- Asthma/allergy.

4. Precautionary measures should be carefully considered when treating patients with high risk of OIIRR.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

FUNDING

None

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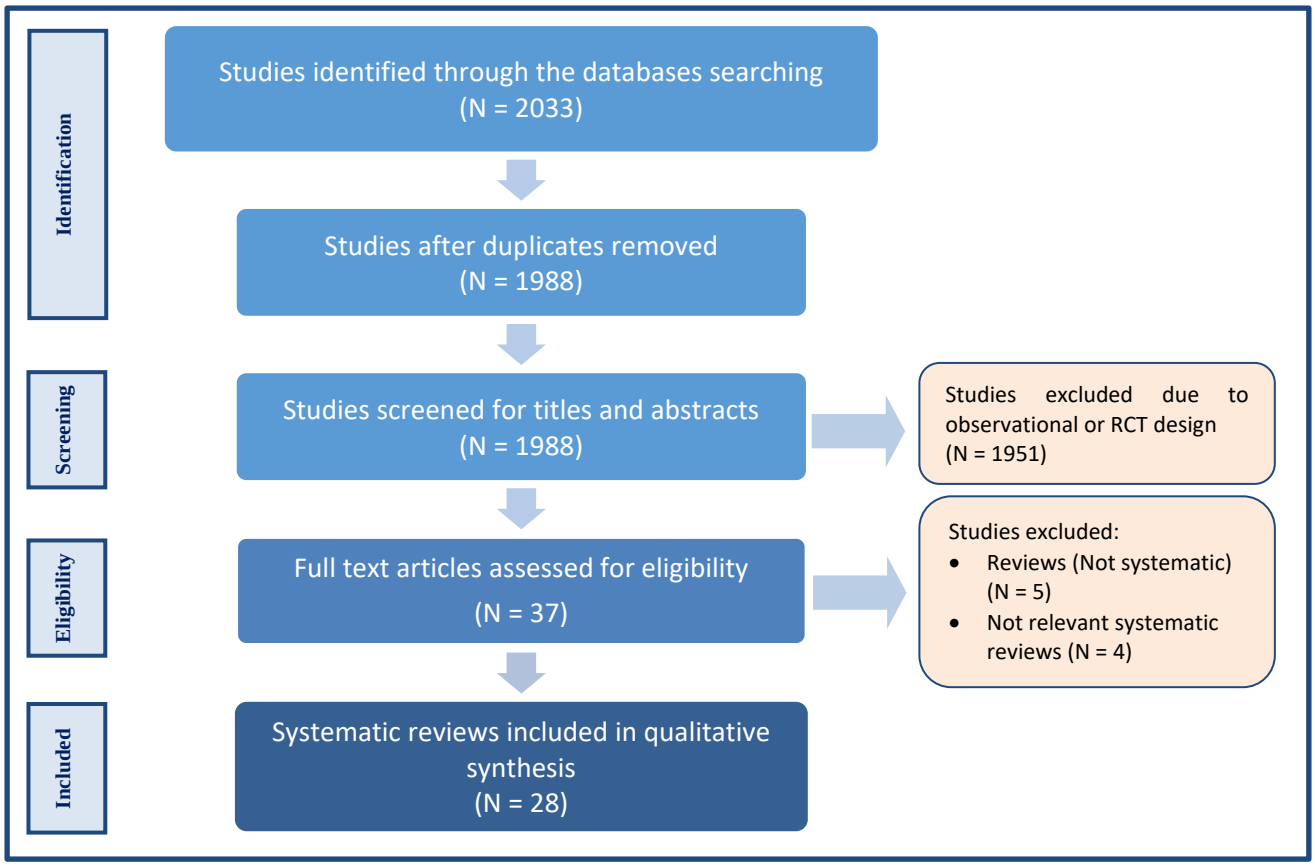

Figure 1: PRISMA flow diagram of the literature selection process

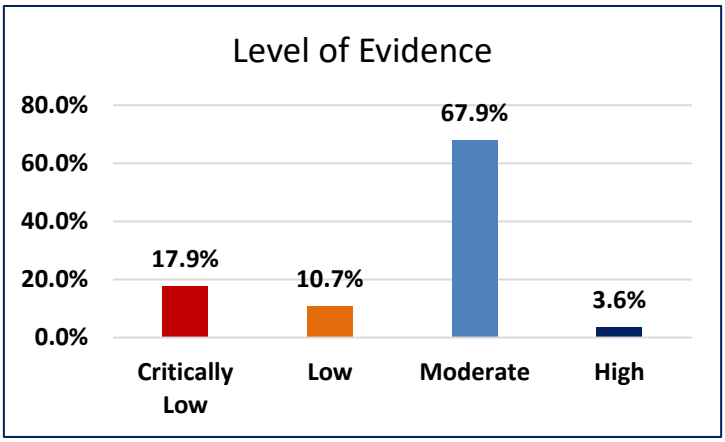

Figure 2: Level of evidence of the included systematic reviews according to AMSTAR 2 grades

Table 1: Systematic reviews that have assessed root resorption with orthodontic treatment

Author	Year	Study Design	No. of Studies	No. of Participants	Type of Studies	Period of Search	Journal	Objective	Quality of Evidence
Segal et al. (33)	2004	Meta-analysis	9 (8 for meta-analysis)	Not reported specifically	8 Retrospective studies 1 Prospective study	Not reported	Orthodontic & Craniofacial Research	To identify the possible treatment-related factors causing EARR	**Critically Low**
Weltman et al. (25)	2010	Systematic review	11 RCTs (12 articles)	652	RCTs	1950 to October 3, 2008	American Journal of Orthodontics & Dentofacial Orthopedics	Association of root resorption and fixed appliance orthodontic treatment	**Moderate**
Pejicic et al. (34)	2012	Systematic review	31 (although reported as 36. Some reported as duplicates of the same study)	6356	The majority of the studies are retrospectives	1929 to April, 2011	International Journal of Stomatology & Occlusion Medicine	The extent of apical root resorption with fixed appliance orthodontic treatment, and which teeth are most affected by apical root resorption	**Critically Low**
Forst et al. (35)	2014	Systematic review	3	43	2 NRCTs 1 Retrospective cohort study	Up to August 25, 2013	European Journal of Orthodontics	If jackscrew-based maxillary expansion therapies result in ERR	**Low**
Tieu et al. (36)	2014	Systematic review	8	354	1 RCT 8 Retrospective studies	1966 to July 20, 2013	Progress in Orthodontics	Evaluation of OIIRR during non-surgical orthodontic treatment of class II division 1 malocclusion (different types of appliances)	**Moderate**
Roscoe et al. (37)	2015	Systematic review	20 (21 articles)	514	10 RCTs 8 NRCTs 2 Cohort studies	Up to December 17, 2013	American Journal of Orthodontics & Dentofacial Orthopedics	Root resorption during orthodontic treatment and different force levels (fixed and aligner appliances)	**Moderate**
Elhaddaoui et al. (38)	2017	Systematic review	3	217	1 RCT 1 NRCT	Up to December, 2015	International Orthodontics	Comparing the incidence and severity of OIIRR caused by	**Critically Low**

Author	Year	Study Design	No. of Studies	No. of Participants	Type of Studies	Period of Search	Journal	Objective	Quality of Evidence
					1 Retrospective cohort study			aligners with that caused by fixed appliance	
Aldeeri et al. (39)	2018	Systematic review	2	87	1 RCT 1 Retrospective Cohort study	1980 to June, 2017	The Journal of Contemporary Dental Practice	Comparing OIIRR between clear aligners and fixed appliance	**Moderate**
Fang et al. (40)	2019	Systematic review and meta-analysis	11 (3 for meta-analysis)	1026	4 Cohort studies 1 Case-control study 6 Before and after studies	Up to December, 2018	Orthodontics and Craniofacial Research	Comparing OIIRR between clear aligners and fixed appliance	**Moderate**
Ghandi et al. (41)	2020	Systematic review and meta-analysis	16	523	4 Prospective studies 12 Retrospective studies	Up to December 31, 2019	European Journal of Orthodontics	Comparing OIIRR between clear aligners and fixed appliance	**Moderate**
De Brito et al. (42)	2016	Systematic review	6	892	3 Retrospective studies 3 Cohort studies	Up to December 13, 2014	Revista da Faculdade de Odontologia	Root resorption during orthodontic treatment	**Critically Low**
Vlasa et al. (43)	2016	Systematic review	23	Not reported	Not reported	1972 to March 31, 2016	Journal of Interdisciplinary Medicine	Correlation between OIIRR and orthodontic treatment (Removable or fixed appliances)	**Critically Low**
Yi et al. (44)	2016	Systematic review and meta-analysis	7 (5 for meta-analysis)	553	1 RCT 2 CCTs 4 Cohort studies	Up to April 10, 2016	BMC Oral Health	EARR with self-ligating or conventional brackets	**Moderate**
Deng et al. (45)	2018	Meta-analysis	12	247	12 NRCTs	Up to October, 2017	BMC Oral Health	Assessing OIIRR after orthodontic treatment	**Moderate**
Currell et al. (46)	2019	Systematic review	24 (25 articles)	1004	RCTs	Up to February, 2018	American Journal of Orthodontics & Dentofacial Orthopedics	Association between orthodontic tooth movement and EARR	**Moderate**

Author	Year	Study Design	No. of Studies	No. of Participants	Type of Studies	Period of Search	Journal	Objective	Quality of Evidence
Samandara et al. (28)	2019	Systematic review and meta-analysis	30 (33 articles) (27 for meta-analysis)	1219	6 RCTs 6 Prospective non-randomized studies 18 retrospective non-randomized studies	Up to January, 2017	European Journal of Orthodontics	Assessing OIIRR with orthodontic treatment (different types of appliances) and identifying factors associated with OIIRR	**High**
Michelogiannakis et al. (47)	2019	Systematic review	9	40 Human participants 164 Rats 16 Rabbits 14 Dogs	2 RCTs (Human) 7 Animal experiments	Up to and including September, 2018	Archives of Oral Biology	The influence of low-level laser therapy on OIIRR	**Moderate**
Lyu et al. (48)	2019	Systematic review	13	409	12 RCTs 1 CCT	Up to January 31, 2019	European Journal of Orthodontics	The effectiveness of vibrational force on orthodontic treatment	**Moderate**
Aminoshariae et al. (49)	2016	Systematic review	13	1623 + not reported number from one study	The majority of the studies are case-control	January 1990 to November, 2015	Angle Orthodontist	Association of genetic polymorphisms with EARR during orthodontic treatment	**Moderate**
Haugland et al. (27)	2018	Systematic review and meta-analysis	9 Human studies 36 Animal experiments	369 Human participants Not reported number of animals (mostly rats, 3 studies: dogs, mice, and rabbits)	9 Human studies: 4 RCTs 4 Cohorts 1 Case-control 36 Animal experiments (Clinical trials)	Up to October 9, 2017	European Journal of Orthodontics	Assess the effect of biologic factors and adjunctive therapies on OIIRR in both human subjects and animals	**Moderate**
Nowrin et al. (50)	2018	Systematic review and meta-analysis	17 (7 for meta-analysis)	2649	Case-control studies	Up to February 28, 2017	Korean Journal of Orthodontics	Association of genetic polymorphisms with EARR during orthodontic treatment	**Low**
Spoerri et al. (51)	2018	Systematic review and	13 (2 for meta-analysis)	677 Rats	Preclinical in-vivo	Up to October 5, 2017	Frontiers in Physiology	The effect of induced intrinsic/hormone-like molecules on ERR	**Moderate**

Author	Year	Study Design	No. of Studies	No. of Participants	Type of Studies	Period of Search	Journal	Objective	Quality of Evidence
		meta-analysis		32 Mice + not reported number of mice from one study	experimental animal studies			after orthodontic tooth movement in experimental animals	
Kaklamanos et al. (52)	2019	Systematic review	8 (only 3 of them related to root resorption	73	2 RCTs 1 Split mouth	Up to October 6 2018	European Journal of Orthodontics	The effect of medication administration on root resorption development in humans	**Moderate**
Makrygiannakis et al. (53)	2019	Systematic review	21	772 Rats	Animal experiments	Up to April, 2018	European Journal of Orthodontics	The effects of systemic medication on root resorption associated with orthodontic tooth movement	**Moderate**
Zymperdikas et al. (54)	2019	Systematic review	7	122	6 Case reports 1 Retrospective cohort study	Up to March, 2019	European Journal of Orthodontics	The effects of systematic bisphosphonate use in patients under orthodontic treatment	**Moderate**
Ioannidou-marathiotou et al. (55)	2013	Systematic review and meta-analysis	6 (4 for meta-analysis)	479 + 1 not calculated study	5 Retrospective CCTs 1 Prospective CCT	Up to January 11, 2012	Clinical Oral Investigations	The effect of orthodontic treatment on root resorption of endodontically treated teeth compared to vital teeth	**Low**
Walker et al. (56)	2013	Systematic review	4	175	Retrospective cohort studies	Up to July 11, 2012	European Journal of Orthodontics	The incidence of OIIRR in root-filled and vital teeth	**Moderate**
Alhadainy et al. (57)	2019	Meta-analysis	7	572	4 Retrospective CCTs 4 Prospective CCTs	Up to May, 2018	Journal of Endodontics	OIIRR of endodontically treated teeth	**Moderate**

RCT: Randomized controlled trial, CCT: Controlled clinical trial, NRCT: Non-randomized controlled trial

Table 2: A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) items

AMSTAR 2 Items	Meeting the criteria		
	Yes	**Partial Yes**	**No**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	23		5
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	12	2	14
3. Did the review authors explain their selection of the study designs for inclusion in the review?	23		5
4. Did the review authors use a comprehensive literature search strategy?	7	18	3
5. Did the review authors perform study selection in duplicate?	24		4
6. Did the review authors perform data extraction in duplicate?	22	1	5
7. Did the review authors provide a list of excluded studies and justify the exclusions?	3	12	13
8. Did the review authors describe the included studies in adequate detail?	3	18	7
9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	17	3	8
10. Did the review authors report on the sources of funding for the studies included in the review?	1		27
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	10		1
12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	9	1	1
13. Did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review?	23		5

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	14		14
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	7		4
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	23		5