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Systematic Review

# The effect of micro-osteoperforation on root resorption, pulp vitality, and biological changes of teeth subjected to orthodontic tooth movement: A systematic review study

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## ABSTRACT

**Background:** These days minimally invasive micro-osteoperforation (MOPs) has accelerated orthodontic tooth movement (OTM). However, there are some conflicting reports about their various impacts; hence, the present systematic review study aimed to evaluate the effect of MOP on root resorption, pulp vitality, and the biological changes of teeth subjected to OTM.

**Materials and Methods:** Search in electronic databases of English literature including PubMed, Scopus, Web of sciences, Cochrane, and Google scholar as well as a manual search was performed from 2013 to 2022. Most of the studies included in this article were randomized controlled trials.

**Results:** From the total number of 321 found articles, 31 duplicated and 268 irrelevant articles were excluded regarding the defined inclusion and exclusion criteria. Consequently, 22 articles were subjected to the quality assessment process, and finally, 18 articles were selected for the review phase. Root resorption during tooth movement using the MOP approach was reported only in one study. Besides, except for two animal studies, all of the relevant included articles showed that MOPs significantly increased the expression of some inflammatory biomarkers known to recruit osteoclast precursors and increase the number of osteoclast cells. On the other hand, two animal studies showed no differences in osteoclast counts by using MOPs in comparison to their control groups, which was consequently the result of biologic variability between animal and human and also probably the small sample sizes of these two studies.

**Conclusion:** In this systematic review, according to the adverse effects of MOP on root resorption, one study showed higher levels of root resorption among patients undergoing MOP. However, this outcome was due to the different methods used to evaluate the effect of MOPs on root resorption. Moreover, a high certainty of evidence supports that MOP causes biological changes and an elevation in cytokines, chemokines, and other biomarkers that stimulates osteoclasts differentiation which in turn accelerate OTM. There was no change in pulp vitality status based on available evidence.

**Key Words:** Biomarkers, flapless-osteoperforation, orthodontic tooth movement, pulp vitality, root resorption

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## INTRODUCTION

Extended orthodontic treatment time may result in numerous side effects including reduced patient cooperation and oral hygiene, increased dental caries, gingival recession, and root resorption. Therefore, many attempts have been made to accelerate tooth movement in orthodontic treatments.[1-7] Some methods of accelerating orthodontic tooth movement (OTM) are surgical techniques such as corticotomy,[8] micro-osteoperforation (MOPs), piezopuncture,[9,10] piezocision (PZC),[11,12] and modified corticotomy that was recently named "PAOO" and is defined as periodontally accelerated osteogenic orthodontics which can be used in most of the orthodontic treatments such as canine retraction.[13,14] Nonsurgical techniques include low-level laser therapy, vibration, electrical currents, and pharmacological processes.[15]

The most effective procedures are surgical techniques, but they are not commonly used due to their aggressiveness. Corticotomy is an acceptable method for accelerating tooth movement, and MOP is considered a less aggressive alternative approach for corticotomy. MOP is done by inserting a mini screw without releasing a flap;[16,17] this technique stimulates tooth movement by increasing the levels of cytokine expression and thereby local osteoporotic changes around the target teeth and induces the regional acceleratory phenomenon (RAP). RAP takes place when tissues regenerate locally in response to noxious stimuli in an intensified remodeling process that includes increased activity by osteoclasts, osteoblasts, and inflammatory markers.[18,19] In this regard, a simple noninvasive method is required for achieving these possibilities. In recent years, few components of gingival crevicular fluid (GCF) have been shown to be diagnostic biomarkers of active tissue destruction in periodontal disease; these components may also serve as diagnostic markers for biological responses in OTM.[20] Various studies have suggested that mechanical stimulants such as OTM may induce some inflammatory responses in periodontal tissues.[21] The cells can release adequate amounts of chemical mediators into GCF; therefore, the amount of these substances may increase in GCF during OTM.[22] In the terms of root resorption, Chan *et al*.[23] concluded that during buccal tipping force, maxillary first premolar subjected larger volumes of ortho-dontic root resorption craters, also in the study of Joseph *et al*.[24] after treating with MOP, over all root resorption was higher in a treated group in comparison to control group., whereas in the systematic review study of Dos Santos *et al*. in 2020.[25] They found that MOP did not have any effects on root resorption. In addition, in terms of the impact of MOP on pulp vitality, Joseph *et al*.[24] found that this nonaggressive treatment does not have side effect on pulp vitality of treated tooth.

As a result of above summary of literature, this systematic review aimed to evaluate the effect of MOP on root resorption, pulp vitality, and the histological changes in response to orthodontic force application following the surgical procedure of orthodontic treatment.

## MATERIALS AND METHODS

We carried out this systematic review study based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guidelines. Based on the PICOS model, the study was designed as follows: (P): patients and animals undergoing orthodontic treatment (I): MOPs (C): tooth movement without MOPs or other interventions, (O): root resorption, histological changes, and pulp vitality during treatment, and (S): systematic review.

### Search strategy

Five online databases, including PubMed, Scopus, Web of sciences, Cochrane, and Google scholar were searched limited to the English language up to December 2021 and by using the following keywords: ("Orthodontic*" OR "Tooth movement" OR "Orthodontic tooth movement" OR "Tooth displacement" OR "Orthodontic treatment" OR "Orthodontic therapy") AND ("minimally invasive" OR "micro-osteoperforations" OR "micro-perforations" OR "osteoperforations" OR "flapless osteoperforation") AND ("root resorption" OR " root shortening") AND ("histological changes" OR "Biological response") AND (Pulp vitality). WorldCat, OpenGrey, and ProQuest to obtain gray and unpublished articles. We also searched the reference list of the included studies to find any related articles. In case of missing data in the research work, an attempt was made to contact the corresponding author through E-mail.

### Inclusion criteria

(1) Studies in which patients received fixed orthodontic treatment and had teeth with normal roots (no internal or external resorption, severe curvature, or ankylosis) as well as animal studies (2) written in

the English language, (3) Studies in which MOP was the intervention and (4) studies with available full texts, and studies in which tooth extraction was done with the minimum time interval of 1 month between assessment phase and tooth extraction.

### Exclusion criteria

(1) Case reports and case series studies, (2) articles involving patients with a history of previous orthodontic treatment, systemic diseases, smoking, pregnancy, periodontal disease, and poor oral hygiene were excluded from the present study.

### Study selection

Two authors (N. M. and SH. B.) independently searched the abovementioned keywords in titles and abstracts of articles from the databases; in case of any disagreement, the third author (A. A. KH.) was consulted until a consensus was achieved. Search results were imported to EndNote software, and duplicate studies were eliminated. Then, two authors (N. M. and SH. B.) screened the titles and abstracts independently and removed irrelevant studies. Then, the full texts of the most relevant studies were retrieved and reviewed by these two authors.

### Risk of bias/quality assessment

We assessed the risk of bias/quality of the studies using the Newcastle–Ottawa scale (NOS) checklist. Tis scale allocates a 0–9 score to each study based on selection, comparability, and exposure/outcome.[26] Studies that scored 4 or below were considered of poor quality more information is in the Table 1.

### Data collection process

Two authors (N. M. and M. KF.) performed the data extraction independently and extracted the data of the selected studies. These data included the first author's names, publication year, study design and method, characteristics of participants, sample size, orthodontic aspects (malocclusion characteristics, biomechanics, and follow-up duration), statistical analysis, and prominent results.

## RESULTS

### Study selection

We found a total of 321 studies after a comprehensive search of the online databases, Grey literature, and manual searching of relevant journals. After removing duplicates, the titles and abstracts of the remaining 290 studies were screened separately by two reviewers. Afterward, 22 studies were excluded based on the inclusion and exclusion criteria and the PICOS model. Finally, 18 studies conducted by Khursheed Alam *et al*.,[27] Aboalnaga *et al*.,[28] Alqadasi *et al*.,[29] Khlef *et al*.,[30] Shahrin *et al*.,[31] Bansal *et al*.,[32] Chan *et al*.,[23] Parihar *et al*.,[34] Cheung *et al*.,[19] Kim *et al*.,[34] Lee *et al*.,[35] Alikhani *et al*.,[9] Cramer *et al*.,[36] Tsai *et al*.,[37] Pedraza *et al*.,[38] Sunny *et al*.,[39] and Kim *et al*.[40] were included in our quality assessment phase [Figure 1].

### Study characteristics

This systematic review included ten clinical studies and seven animal studies [Tables 2 and 3].

Clinical studies consisted of seven studies with split-mouth design, one micro-computed tomography

**Table 1: Risk of bias assessment of the studies based on the Newcastle–Ottawa Scale**

| Study | Selection (out of 4) | Comparability (out of 2) | Exposure/outcome (out of 3) | Total score (out of 9) |
|---|---|---|---|---|
| Khursheed Alam *et al*., 2018[27] | 4 | 2 | 3 | 9 |
| Chan *et al*., 2018[23] | 4 | 2 | 3 | 9 |
| Aboalnaga *et al*., 2019[28] | 3 | 2 | 3 | 8 |
| Alqadasi *et al*., 2019[29] | 3 | 2 | 3 | 8 |
| Bansal *et al*., 2019[32] | 3 | 2 | 3 | 8 |
| Khlef *et al*., 2020[30] | 3 | 2 | 2 | 7 |
| Shahrin *et al*., 2021[31] | 3 | 2 | 2 | 7 |
| Cheung *et al*., 2016 [19] | 3 | - | 3 | 6 |
| Parihar *et al*., 2020[33] | 4 | 2 | 3 | 9 |
| Kim.SG *et al*., 2021[34] | 3 | - | 3 | 6 |
| Lee *et al*,. 2018[35] | 3 | - | 3 | 6 |
| Alikhani *et al*,. 2013[9] | 4 | 2 | 3 | 9 |
| Cramer *et al*,. 2019[36] | 3 | - | 3 | 6 |
| Tsai *et al*,. 2016[37] | 3 | - | 3 | 6 |
| Pedraza *et al*., 2018[38] | 3 | - | 3 | 6 |
| Sunny *et al*.,. 2021[39] | 3 | 1 | 3 | 7 |
| Kim.J *et al*., 2019[40] | 3 | 2 | 3 | 8 |

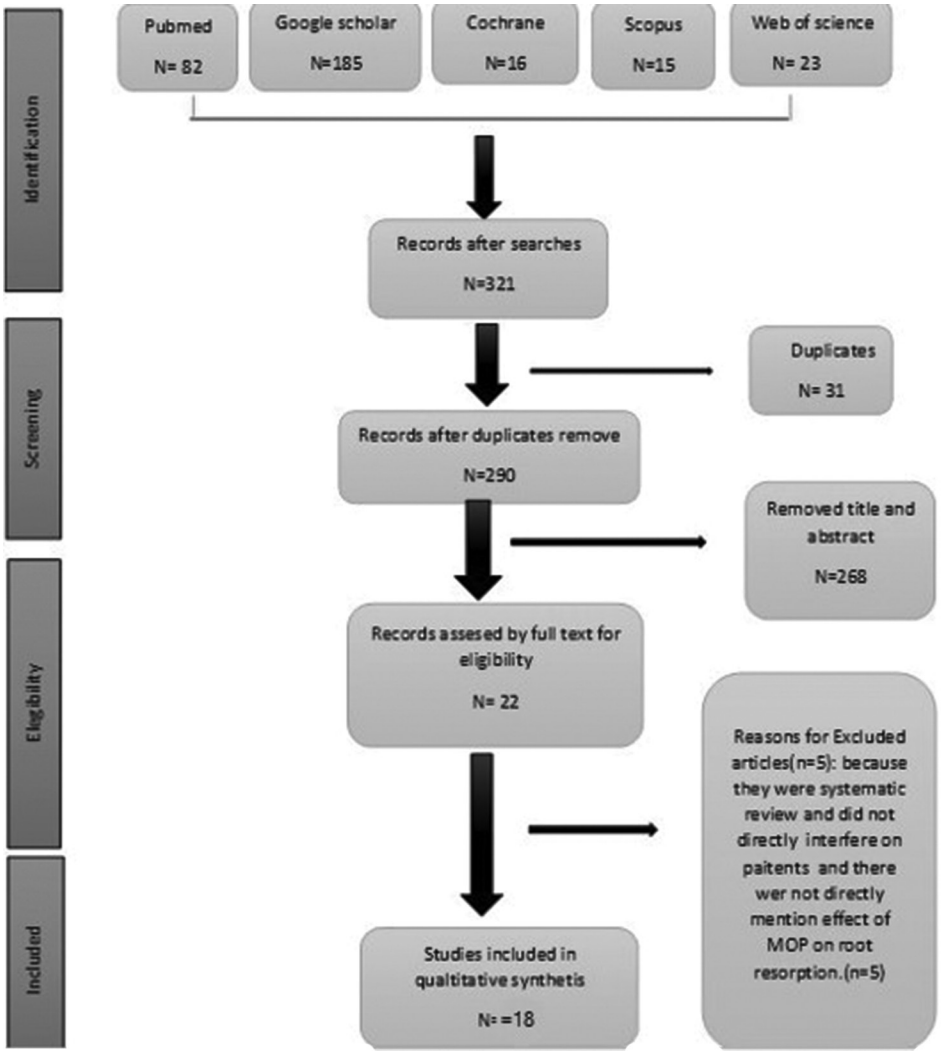


**Figure 1:** Flow diagram.

study, and two parallel-arm studies for qualitative synthesis. Moreover, the studies were all done from 2013 until 2022.

Of the total of seven animal studies, Cramer *et al*.[36] and Lee *et al*.[37] evaluated the second premolar retraction of beagle dogs after extraction of the third premolar in maxilla and mandible respectively. Kim J *et al*.[40] and Kim *et al*.[34] evaluated the traction between the incisor teeth and the first premolars to assess the effect of MOPs on the biological response and tooth movement in rabbits. Cheung *et al*.,[19] and Tsai *et al*.,[37] studied Sprague − Dawley rats which underwent traction forces between incisors and first molars, while Pedraza *et al*.[38] investigated Wistar rats.

Of the total of 10 clinical studies, there were 213 participants and the mean age of participants was between 16 and 45 years. Five studies investigated malocclusion class II/Div I,[9,27-30] Sharin *et al*.[31] investigated the crowding in the anterior maxilla, Bansal *et al*.[32] reported the crowding in the anterior of the mandible, and Chan *et al*.[23] investigated the patients with bimaxillary dentoalveolar protrusion.

For evaluation of tooth movement, most of the studies investigated the Maxillary canine retraction. At the same time, Banasal *et al*.[32] evaluated the mandibular anterior teeth movement, and Sharin *et al*.[31] analyzed the maxillary anterior teeth region.

The treatment plan in most studies was the extraction of the maxillary first premolar and canine retraction, but in Sharin *et al*.[31] and Banasal *et al*.[32] aligning the crowded teeth in the anterior region was planned for the samples.

For the MOP process, Sharin *et al*.,[31] Banasal *et al*.,[32] and Sunny *et al*.[39] inserted two mini-screws

**Table 2: Summery of included studies related to root resorption**

| Study | Study design | Number of patients included | Gender | Malocclusion | Type of tooth movement | Conclusion |
|---|---|---|---|---|---|---|
| Khursheed Alam *et al*., 2018[27] | RCT | 16 | - | Class II Div I Class II Div II | Canine retraction | Experimental PZC showed significant decreases in canine root length compared to both experimental MOP and control side after canine retraction |
| Chan *et al*., 2018[23] | A microcumputed tomography study | 20 | 8: Male 12: Female | Bimaxillary dentoalveolar protrusion | Canine retraction | MOP showed greater root resorption than control |
| Aboalnaga *et al*., 2019[28] | Split-mouth RCT | 18 | 0: Male 18: Female | Class II Div and Bimax I | Maxillary canine retraction | MOP did not increase nor decrease orthodontically induced root resorption |
| Alqadasi *et al*., 2019[29] | A three dimensional RCT | 8 | Both | Class II/Div I | Canine retraction | MOP didn't affect in anchorage loss, rotation, tipping, root resorption, plaque index, periodontal index, and pain perception |
| Bansal *et al*., 2019[32] | RCT | 30 | | Mandibular ant. crowdingg | Aligning | MOP didn't increase root resorption |
| Khlef *et al*., 2020[30] | A single -centered, RCT | 40 | | Class II/Div I | Maxillary enmass retraction | Neither technique (flapless and traditional corticotomies) caused any significant root resorption |
| Shahrin *et al*., 2021[31] | RCT | 30 | 5: Male 25: Female | Moderate crowding of the upper labial segment | Alignng tooth | MOP didn't exacerbate external apical root resorption |
| Cheung *et al*., 2016[19] | Animal study (sprague- dawley rats) | 6 | Male | | MOPs accelerated tooth movement without increased root resorption | MOPs accelerated tooth movement without increased root resorption |
| Kim *et al*., 2021[34] | Animal study (rabbit) | 24 | | | Tooth movement from the incisors to the first premolars | Microscopic examination of un decalcified samples revealed no root resorption |
| Parihar *et al*,. 2021[33] | Original article (RCT) | 16 | | Class II/Div I | Canine retraction | MOP accelerated tooth movement in the first 4 weeks and didn't have any effects on anchorage loss, tipping, vitality, and apical and lateral root resorption |

RCT: Randomized controlled trial, MOPs: Micro-osteoperforations, PZC: Piezocision

in the distal of the canine, while other studies inserted three mini-screws beside the considered tooth.

## Root resorption findings

Ten studies conducted by Alqadasi *et al*.,[29] Chan *et al*.,[23] Aboalnaga *et al*.,[28] Khursheed Alam *et al*.,[27] Shahrin *et al*.,[31] Bansal *et al*.,[32] Khalef *et al*.,[30] Parihar *et al*.,[33] Cheung *et al*.,[19] and Kim *et al*.,[34] had eligible findings concerning root resorption [Table 2].

### *Individual study results*

Chan *et al*.[23] evaluated root resorption of maxillary first premolars after treatment in the extra oral method. They stated that levels of root resorption in the roots' apical, middle, and cervical parts were the same. Furthermore, the amount of root resorption in mesial and distal regions was similar.

In most studies that investigated canine root resorption, no significant root resorption was found. However, Chan *et al*.[23] studied maxillary first premolars after treatment and reported significantly greater average amounts of root resorption than control teeth.

The included studies were inconsistent regarding their intervention methods, devices, and how they evaluated the outcome measure. Also, different jaws and different follow-up periods existed among the included studies. However, the studies were consistent concerning measuring and comparing the rate of canine retraction between the intervention and control groups for 1 month (4 weeks).

### *Animal study results*

Cheung *et al*.[19] and Kim *et al*.[34] both revealed accelerated tooth movement without increased risk for root resorption by using MOPs.

**Table 3: Summery of included studies related to biological changes**

| study | Study design | Number of population (human or animal) | conclusion |
|---|---|---|---|
| Cheung *et al*., 2016[19] | Animal study | Rat 6 | MOPs acted by inducing bone remodeling, H and E and TRAP analysis showed increased in osteoclast quantity and a decrease in bone volume and bone density |
| Kim *et al*., 2021[34] | Animal study | Rabbit 24 | MOP caused the TRAP-positive cell count was significantly increased between weeks 1 and 3, and increased number of osteoclast-like cells, especially at week 3 |
| Lee *et al*., 2018[35] | Original article (animal study) | 8 beagle dog | In MOP group the genes related to osteoclast differentiation and TNF signaling pathway were up-regulated and those associated with WNT signaling pathway and AMPK signaling pathway were down-regulated |
| Alikhani *et al*., 2013[9] | Split-mouth (RCT) | Adault 20 (Class II Div I) | MOP significantly increased the expression of cytokines and chemokines known to recruit osteoclast precursors and stimulate osteoclast differentiation was measured in gingival crevicular fluid using an antibody based protein assay |
| Cramer *et al*., 2019[36] | Split-mouth (animal study) | Beagle dog 7 | MOP showed no apparent differences in osteoblast, osteoclast or mineralization of bone near the teeth being moved |
| Tsai *et al*., 2016[37] | Original article (animal study) | 45–8 (week-old male sprague-dawley rats) | MOP increased bone remodeling and osteoclast activity for at least 2 weeks in rat |
| Pedraza *et al*., 2018[38] | Animal study | 40 (male wistar rats) | MOP led to more intense osteoclastic activity on the fourteenth day of tooth movement. |
| Sunny *et al*., 2021[39] | Original article | 18 patient (18–45 year old) | MOP increased the level of acid phosphatase noticed in the anterior segment whereas there was significant increase in the level of alkaline phosphatase noticed in both the anterior and posterior segment concluded that estimation of bone remodeling markers in GCF that is ALP and ACP levels serve as an indicator of the rate of remodeling of the tissues during tooth movement |
| Kim *et al*., 2019[40] | Animal study | 24 rabbit | MOP showed no significant differences in the TRAP-positive osteoclast count compared to both corticotomy groups and control |

MOPs: Micro-osteoperforation, GCF: Gingival crevicular fluid, ACP: Acid phosphatase, TRAP: Tartrate-resistant acid phosphatase, TNF: Tumor necrosis factor, ALP: Alkaline Phosphatase, AMPK: Adenosine Monophosphate-Activated Protein Kinase

## Biological changes findings

Nine studies conducted by Cheung *et al*.,[19] Kim *et al*.,[34] Lee *et al*.,[35] Alikhani *et al*.,[9] Cramer *et al*.,[36] Tsai *et al*.,[37] Pedraza *et al*.,[38] Sunny *et al*.,[39] and Kim *et al*.[40] were found with respect to this topic [Table 3].

### *Individual study results*

In the total of two individual studies,[9,39] 35 participants with the mean age of 18–45 years; underwent extraction of the maxillary first premolar and canine retraction. Both studies showed increased bone remodeling in the anterior segment than the posterior segment on applying the orthodontic force as well as using MOPs.

Both studies were compatible concerning their exclusion and inclusion criteria and the way of collecting GCF samples with filter-paper strips. However, the follow-up periods for collecting GCF samples, type of biological biomarkers, and the method of evaluating the samples were different in these two studies. Alikhani *et al*., found expression of cytokines and chemokines and stimulation of osteoclast differentiation in canine's GCF using an antibody-based protein assay.[9] Besides, Sunny *et al*. noticed a significant increase in the level of acid phosphatase in the anterior segment (canine) and a significant increase in the level of alkaline phosphatase in both the anterior and posterior segments (canine and first maxillary premolar).[39]

### *Animal study results*

Most animal studies revealed that MOPs induced bone remodeling by increasing average amounts of osteoclast using histological analysis.[19,34,37,38] While Kim J *et al*.[40] and Cramer *et al*.[36] found no significant differences in Osteoblast, Osteoclast, or mineralization of bone near the teeth being moved.

Another animal study conducted by Lee *et al*.[35] on atrophic alveolar ridge also corroborated these findings by performing RNA sequencing-based gene-enrichment analysis. They stated that using MOPs led to up-regulation of the genes related to osteoclast differentiation and TNF signaling pathway and down-regulation of those genes associated with WNT and AMPK signaling pathways.

*Pulp vitality findings*

In this term there are not enough study that evaluate the effect of MOP on pulp vitality just the study of Joseph *et al*.[24] revealed that There was no change in the pulp vitality status in both the experimental groups (MOP) and the control group.

## DISCUSSION

Since the introduction of the fixed orthodontic treatment, clinicians and researchers have tried to reduce the treatment time utilizing different methods and appliances with varying degrees of success.[41]

Surgical interventions have also been used to increase the rate of tooth movement, followed by a decrease in the treatment duration. Surgical methods such as osteotomy, corticotomy with or without bone graft, and less invasive techniques including piezocision, piezopuncture, and MOP have been used to stimulate the natural mechanisms of the bone remodeling which in turn increases the rate of tooth movement.[42]

Surgical noxious stimuli can increase the inflammatory mediators which temporarily increases bone metabolism and resorption. So, less invasive surgical methods such as corticision, PZC, piezopuncture, and MOP have been developed to address these problems.[43]

In this systematic review study, we found that MOPs increase the amount of canine retraction. This change is statistically significant and shows that MOP can be a valuable and effective method leading to an increased rate of tooth movement. These results are consistent with the findings of other studies and systematic reviews assessing the effects of PZC and other corticotomy methods on the rate of tooth movement.

Less invasive methods such as flapless corticotomies with PZC are painful and cause more root resorption in comparison to MOPs. However, these methods require special devices and usually demand intervention from another specialist. MOP is a minimally invasive intervention and can be performed by an orthodontist using appliances such as mini-screws. Hence, it can be more advantageous and less invasive for root resorption when compared to other treatment methods.[18]

There are a lot of factors that can initiate and induce root resorption during orthodontic treatment which are mentioned below. Individual susceptibility is the main factor determining root resorption, manifesting in both deciduous and permanent teeth. Historically, there has been appreciable variability among orthodontic patients regarding susceptibility to root resorption, which may be due to a systemic or innate predisposition to the occurrence of resorption. It is supposed that in case of increased susceptibility to root resorption, severe root resorption may occur without any evident reason.[44] Also, nutrition plays an essential role in this process. Becks has shown that root resorption in animals lacking calcium and vitamin D in their foods occurred to a higher degree.[44] The periodontal membrane becomes narrower and less vascularized and aplastic, the alveolar bone becomes denser, less vascularized, and the cementum becomes wider with age. Concerning these changes, adults represent higher susceptibility to root resorption.[44]

In a systematic review and meta-analysis study conducted by Shahabee *et al*.,[45] it was shown that the difference in the rate of canine retraction after performing the MOP was statistically significant but not very substantial clinically. Concerning the adverse effects of MOP, one study observed higher levels of root resorption among patients undergoing MOP. No other studies revealed similar results and negative consequences for MOP. MOP can be recommended after individual assessment of advantages and disadvantages for each patient.[45]

In a systematic review conducted by Patterson *et al*.[46] evaluating the effects of corticotomies, no adverse impact on the periodontium, root resorption, and tooth vitality was observed.

Agrawal *et al*.[47] in a case series study compared corticotomy with a mucoperiosteal flap to MOP concerning the buccal bone thickness before and after canine retraction. In both interventions, the thickness of the buccal bone was significantly increased, especially near the mid-root and coronal parts of the root. This systematic review showed that most articles did not find a significant relation between MOP and root resorption during tooth movement. Khursheed *et al*.[27] showed considerable root resorption in the experimental PZC side compared to the MOP side postoperatively after canine retraction. Furthermore, Chan *et al*.[23] demonstrated that MOP leads to higher levels of orthodontic root resorption when the maxillary first premolars are subjected to buccal tipping force. The periapical radiographs used to compare the length of roots were shown to be

significantly less accurate in detecting root resorption in comparison to MOP.[23]

Previous studies also have shown that the mechanism of orthodontic treatments ends up alveolar bone modeling. Hence, the rate-limiting step in OTM is considered bone resorption, which in turn is controlled by osteoclast activity.[48] Consequently, it is obvious that factors such as; chemokines and cytokines play a major role in the recruitment of osteoclast precursor cells and lead the differentiation of osteoclasts from their precursor cells into mature osteoclasts, respectively.[9,49,50]

Furthermore, a significant increase in the number and function of osteoclasts was found during alveolar corticotomy and nonsurgical interventions that accelerate tooth movement similar to MOPs, based on our systematic review and other studies.[9,19,34,35,37-39,48]

There is a significant correlation between the rate of inflammatory markers and Poor oral hygiene, periodontal disease, alveolar bone loss, systemic diseases, smoking, and consumption of anti-inflammatory medications.[9] The included studies in our systematic review had strict discipline and clear exclusion criteria to control these variables. Extraction is also another factor that can result in an elevation in the inflammatory markers which in turn may obscure the effects of MOPs; therefore, in our included studies, extraction was done at least 1 month before starting the fixed orthodontic treatment plan.

Although outcomes of parallel-arm studies on the effects of MOPs might be considered more reliable in comparison to split-mouth studies, Mohaghegh *et al*.[51] showed that the design of the study has no significant effect on the efficacy of MOPs. Besides, Alikhani *et al*.[9] suggested that notwithstanding the effect of MOPs on the tissues surrounding adjacent teeth, MOPs on one quadrant cannot increase the rate of OTM and inflammatory markers of the contralateral side when compared to the control group. This finding was consistent with the results of other parallel-arm study designs in both human and animal samples, conducted by Gulduren *et al*.[52] and Teixeira *et al*.,[53] respectively.

Alikhani *et al*.[9] evaluated the level of cytokines and chemokines of the human's GCF in a parallel-arm randomized controlled trial (RCT) design study and found that MOPs increase the levels of inflammatory markers such as CCL-2, CCL-3, CCL-5, IL-8, IL-1, TNF-a, and IL-6, 24 h after retraction, which consequently lead to osteoclastogenesis and accelerated OTM. IL-1 which is one of the main pro-inflammatory cytokines that is released during OTM was the only marker that was significantly higher 4 weeks postoperatively than its level before retraction; while the level of all other markers decreased over time. On the other hand, the findings of animal studies should be assessed with caution due to the biological variability between animals and humans; most of them were consistent with clinical studies on humans and showed a significant increase in the levels of inflammatory markers and osteoclasts while using MOPs.[19,34,35,37,38] Nevertheless, among the included studies, merely, two animal studies conducted by Kim and Cramer *et al*. were inconsistent with other animal studies and showed no differences in osteoclast counts by using MOPs in comparison to their control groups.[36,40]

Among the studies showing a significant increase in the levels of inflammatory markers and osteoclasts; these changes were found in different follow-up sessions. Kim *et al*.[34] revealed a considerable increase in the number of osteoclast-like cells at the 3rd week while Pedraza concluded more intense osteoclastic activity on the fourteenth day; without any evidence of accelerated OTM.[38] Furthermore, Tsai *et al*.[37] found increased bone remodeling, osteoclast activity, and induced faster OTM for at least 2 weeks in rats.

Cramer *et al*.,[36] in a split-mouth design study on 7 beagle dogs, showed no apparent differences between control and experimental groups in the number of osteoblasts, osteoclasts, or mineralization of bone near the maxillary second premolars that had been retracted for 7 weeks 1 month after 3rd premolar extraction, using H and E–staining and fluorescent analysis. However, in an almost similar study on 8 beagle dogs, Lee *et al*.[35] found an up-regulation in the genes related to osteoclast differentiation and TNF signaling 8 months after 3rd premolars extraction using RNA sequencing-based gene-enrichment analysis. Altogether, it seems that the small sample size in these two inconsistent studies makes it impossible to rule out the possibility of MOPs effect and further study may need to describe this effect more accurately.

Kim *et al*.[40] also found no significant differences in TRAP-positive osteoclast count between three flapped indentation corticotomy, flapless MOPs, and control groups in 48 mandibular quadrants of 24 rabbits undergoing connection of the first premolars

to the incisors. These inconsistent findings with human studies[9,39] might be due to the fact that bone metabolism in rabbits is three times faster than human beings and as a result a missed recording of the increase in TRAP-positive cells measurements 4 weeks postoperatively. Kim also suggested further studies including records from several time points, especially in the early stages, compensating this difference between rabbits and human beings.

In addition to chemokines and cytokines produced during the tooth movement phase, inflammation and cell necrosis lead to the production of the enzymes which consequently signifies osteoclastic and osteoblastic activities.[39] Among included studies, Sunny *et al*.[39] was the only study evaluating these enzymes from GCF samples of 15 patients before and 14 days after MOPs insertion undergoing canine retraction treatment plan after maxillary first premolar extraction. Significant elevation in the amounts of ACP was regarded as a biologic marker of bone destruction and osteoclastic activity in the anterior segment after MOPs insertion. Moreover, an elevated amount of ALP was considered a reliable marker of osteoblastic activity and bone deposition in both anterior and posterior segment. These findings generally indicate more bone remodeling in the movement unit (anterior segment in this study) than the anchorage unit (the posterior segment of this study) during retraction and the efficacy of MOPs on anchorage preservation. Hence, the bone remodeling markers can be considered a reliable way to assess the treatment progress.

It is clear that surgical procedure because of highly aggressive use of the blade and surgical mallet in corticision technique during tooth movement may cause some side effects such as bone fracture and loss of tooth vitality, but in MOP technique low loss of tooth vitality and pain were reported. However, more clinical trial studies regarding pulp vitality status of MOP treated tooth are required to obtain exact results.[53]

In summary, these results demonstrate that the clinician should consider all of the factors, the benefits, and the risks of the intervention before using MOP. These factors should mainly be assessed among patients with smaller extraction spaces and root distances. Since the beginning of the fixed orthodontic treatment, clinicians and researchers have tried to reduce treatment time utilizing different methods and appliances to varying degrees of success.[41]

### Limitation of this study

A major limitation that we encountered during this study was that the selection of articles only published in English; and therefore, some full-text articles related to the subject were not accessible because they were not indexed in the searched databases. The differences in the in terms of included study designs, methods of measuring the main outcome, and the intervention approaches can be regarded as the main limitation of this review.

### Recommendation for future studies

We suggest that more high-quality trials with more extended follow-up periods and accurate measuring methods be performed to study the effects of MOP on root resorption for more extended periods. Furthermore, it is recommended that conducting more studies evaluating the pulp vitality following MOP can be helpful.

## CONCLUSION

In this systematic review, according to the adverse effects on root resorption after MOP, one study showed higher amounts of root resorption among patients undergoing MOP. No other studies revealed similar outcomes and adverse effects for MOP.

Studies showed that MOP results in localized damage to the bone of the alveolar process, which initiates a localized bone remodeling by increasing the level of inflammatory biomarkers especially cytokines and chemokines known to recruit osteoclast precursors and stimulate osteoclast differentiation, also there was no change in the tooth pulp vitality status during the MOP treatment.

MOP can be recommended after careful evaluation of the advantages and disadvantages that can be offered to each patient.

### Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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### Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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