Facultad de Odontología

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Oral Biomarkers for Orthodontically Induced External Root Resorption

A Literature Review

UPDATE

Biomarcadores orales para reabsorción radicular externa inducida por ortodoncia

Una revisión de la literatura

Biomarcadores orais na reabsorção radicular externa induzida por ortodontia

Uma revisão da literatura

Abstract

» **Introduction.** Orthodontically induced external root resorption (OIERR) is a frequent and unpredictable complication. Radiographic methods have limited sensitivity; therefore, biomarkers in saliva and gingival crevicular fluid (GCF) may enable early, non-invasive detection.

» **Objective.** To analyze the current evidence on oral biomarkers associated with OIERR, emphasizing their potential for the early diagnosis of this condition.

» **Methods.** This narrative review was conducted in accordance with SANRA criteria. Searches were performed in PubMed, Scopus, Web of Science, Cochrane Library, and SciELO. Studies conducted in humans or animals that quantified biomarkers in saliva or GCF in the presence of orthodontically induced resorption compared with controls were included. Short communications, letters, and literature without original data were excluded. A manual reference search was also performed. A total of 28 studies were included.

» **Results.** The available evidence suggests the involvement of multiple oral fluid biomarkers in OIERR. Dentin-derived proteins, such as dentin sialoprotein (DSP), were increased in the GCF of teeth subjected to orthodontic forces with associated resorption. An increased RANKL/OPG ratio was observed in patients with OIERR, together with reduced levels of anti-resorptive cytokines. Bone remodeling enzymes, such as alkaline phosphatase, showed elevated levels under intense orthodontic forces.

» **Conclusions.** Dentin-derived proteins appear to be the most promising candidates for early detection and potential severity stratification, whereas bone and inflammatory mediators lack diagnostic specificity. Longitudinal studies are needed to validate cutoff points, assess multimarker panels, and standardize sampling and quantification methods.

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Keywords: External root resorption; Orthodontics; Biomarkers; Gingival crevicular fluid; Early diagnosis.

Resumen

» **Introducción.** La reabsorción radicular externa inducida por ortodoncia (RREO) es frecuente e impredecible. La radiografía tiene sensibilidad limitada; por ello, biomarcadores en saliva y en líquido crevicular gingival (LCG) podrían permitir detección no invasiva y temprana.

» **Objetivo.** Analizar la evidencia actual sobre biomarcadores orales asociados a la reabsorción radicular externa inducida por ortodoncia, enfatizando su potencial para el diagnóstico temprano de esta condición.

» **Métodos.** Revisión narrativa conforme a criterios SANRA. Búsquedas en PubMed, Scopus, Web of Science, Cochrane Library y SciELO. Se incluyeron estudios en humanos, y animales, que cuantificaran biomarcadores en saliva o en líquido crevicular gingival en presencia de reabsorción inducida por ortodoncia frente a controles; se excluyeron comunicaciones breves, cartas y literatura sin datos originales. Se añadió búsqueda manual. Se integraron 28 estudios.

» **Resultados.** La evidencia encontrada sugiere la participación de múltiples biomarcadores en fluidos orales asociados a la RREO. Proteínas dentinarias como la sialoproteína dentinaria aumentan su presencia en el LCG de dientes sometidos a fuerzas ortodónticas con RREO. Asimismo, se observó un incremento en el cociente RANKL/OPG en pacientes con RREO junto con una disminución de citoquinas antiresortivas. Enzimas de remodelación ósea, como la fosfatasa alcalina, muestran niveles elevados cuando se aplican fuerzas ortodónticas intensas.

» **Conclusiones.** Las proteínas dentinarias son las candidatas más prometedoras para detección precoz y posible estratificación de severidad, mientras que los mediadores óseos e inflamatorios carecen de especificidad diagnóstica. Se requieren estudios longitudinales que validen puntos de corte, evalúen paneles multimarcador y estandaricen muestreo y cuantificación.

Palabras clave: Reabsorción radicular externa; Ortodoncia; Biomarcadores; Líquido crevicular gingival; Diagnóstico precoz.

Resumo

» **Introdução.** A reabsorção radicular externa induzida por ortodontia (RREO) é uma complicação frequente e imprevisível. Os métodos radiográficos apresentam sensibilidade limitada; por isso, biomarcadores presentes na saliva e no fluido crevicular gengival (FCG) podem possibilitar a detecção precoce e não invasiva.

» **Objetivo.** Analisar criticamente as evidências atuais sobre biomarcadores orais associados à RREO, com ênfase no seu potencial diagnóstico precoce.

» **Métodos.** Revisão narrativa conforme os critérios SANRA. Realizaram-se buscas nas bases de dados PubMed, Scopus, Web of Science, Cochrane Library e SciELO. Foram incluídos estudos com humanos e animais que quantificaram biomarcadores na saliva ou no FCG na presença de reabsorção induzida por ortodontia em comparação com controles. Excluíram-se comunicações breves, cartas e literatura sem dados originais. Adicionou-se busca manual. Foram integrados 28 estudos.

» **Resultados.** As evidências sugerem o envolvimento de múltiplos biomarcadores em fluidos orais associados à RREO. Proteínas dentinárias como a sialoproteína dentinária apresentaram aumento no FCG de dentes submetidos a forças ortodônticas com RREO. Também foi observado um aumento na razão RANKL/OPG em pacientes com RREO, juntamente com uma diminuição de citocinas anti-reabsortivas. Enzimas relacionadas à remodelação óssea, como a fosfatase alcalina, mostraram níveis elevados sob forças ortodônticas intensas.

» **Conclusões.** As proteínas dentinárias são os biomarcadores mais promissores para detecção precoce e possível estratificação de severidade, enquanto mediadores ósseos e inflamatórios apresentam baixa especificidade diagnóstica. São necessários estudos longitudinais que validem pontos de corte, avaliem painéis multimarcadores e padronizem métodos de coleta e quantificação.

Palavras-chave: Reabsorção radicular externa; Ortodontia; Biomarcadores; Fluido gengival crevicular; Diagnóstico precoce.

Introduction

Orthodontic treatment has become increasingly common due to the high global prevalence of malocclusions, which affects approximately 56% of children and adolescents.[1] Although orthodontic treatment is effective in correcting dento-maxillofacial discrepancies, it may also be associated with certain complications. Among these, orthodontically induced external root resorption (OIERR) stands out as a pathological process in which the dental root undergoes progressive loss of dentin and cementum due to osteoclastic activity. External root resorption may have an inflammatory origin and is commonly classified according to its location and extent.[2] In the orthodontic context, OIERR is a common sequela: studies have reported that up to 73–90% of teeth show some degree of histological or radiographic OIERR, even if mild.[3] Fortunately, in most cases, root loss is minimal; however, in approximately 1–5% of cases, severe OIERR develops, defined as loss of more than one-third of root length, compromising the prognosis and stability of the tooth.[4–6]

Currently, detection of OIERR relies almost exclusively on imaging methods. These techniques allow resorption to be confirmed only after substantial destruction of root tissue has already occurred, thereby limiting early detection.[7] In addition, they provide static and retrospective information: they do not reveal whether the resorptive process is active or predict its progression, and their interpretation may be subjective and observer-dependent. Since timely interruption or modification of orthodontic mechanics may prevent further damage when a case prone to severe OIERR is identified early, there is a clinical need for more sensitive and objective complementary diagnostic methods. In this context, contemporary research has focused on exploring the role of molecular biomarkers.

A biomarker is defined as a measurable biological substance that serves as an indicator of a physiological or pathological process, or of the response to a therapeutic intervention.[8] In dentistry, oral biofluids such as saliva and gingival crevicular fluid (GCF) are accessible and non-invasive sources of biomarkers. GCF, in particular, provides a site-specific sample around individual teeth, reflecting local events in the periodontium of the affected tooth. Saliva, on the other hand, although it lacks anatomical specificity, provides a global but diluted view of the entire oral environment, allowing pathological processes to be detected more generally and serving as a useful tool for early screening of OIERR. During orthodontic tooth movement (OTM), an inflammatory microenvironment is triggered in the periodontium, activating alveolar bone remodeling and, as a collateral effect, potentially inducing external root resorption. This microenvironment leads to the release of numerous cytokines, enzymes, and matrix proteins from adjacent bone and dentin tissues.[9] The central hypothesis is that these biomolecules, once they reach detectable concentrations in saliva or GCF, could act as early indicators of OIERR, even before radiographic evidence is present.

In recent years, multiple studies[3,10–23] have investigated various salivary and crevicular biomarkers associated with OIERR. These include mediators of bone remodeling, inflammatory mediators, and components of the dentin matrix and cementum that are released as root tissue degrades. However, not all of them have the specificity or feasibility required for eventual clinical use.

Based on the above, this narrative review aimed to analyze current evidence on oral biomarkers associated with OIERR, emphasizing their potential for the early diagnosis of this condition. It further aimed to classify relevant biomarkers associated with OIERR according to their pathophysiological origin, analyze the specificity of each biomarker for OIERR together with its potential clinical utility and feasibility of detection using accessible methods, and identify gaps in the evidence in order to propose guidelines for future studies that clinically validate the biomarkers with the greatest potential.

Methodology of the narrative review

A narrative review of the literature was conducted, justified by the broad and heterogeneous nature of the topic. Unlike a systematic review, this approach allows findings from diverse clinical studies to be integrated with basic science evidence, providing a comprehensive and critical perspective. Nevertheless, the Scale for the Assessment of Narrative Review Articles (SANRA)[24] guidelines were followed to strengthen rigor in the search process and presentation of results.

Information sources

A literature search was performed in the PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and SciELO databases. In addition, clinical trial registries were consulted, including ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), and the ISRCTN registry. A manual reference search was conducted based on key articles. The last search was performed in August 2025.

Search strategy

Controlled terms (MeSH/DeCS) and free-text keywords related to the topic were used and combined with Boolean operators (AND, OR). An example of a PubMed search equation was: “External apical root resorption” AND “orthodontics” AND (“biomarkers” OR “gingival crevicular fluid” OR “saliva”). Publications in English and Spanish were considered, with no date restrictions, in order to include both still-relevant classic literature and recent studies.

Selection criteria

In vivo studies analyzing the presence or concentration of biomarkers in GCF or saliva in the context of OIERR were included. Both clinical studies in humans and

studies in animal or ex vivo models were considered when they provided relevant information. Systematic reviews published in recent years were also included. Merely descriptive reports without quantitative data, short communications, letters to the editor, and secondary literature without a comprehensive analysis of the information were excluded. The information of interest included biomarker concentrations in GCF or saliva, measured in pg/mL, ng/mL, or units of enzymatic activity; mean differences between groups (OIERR vs. non-OIERR); correlation of biomarker levels with OIERR severity, such as millimetric grades; and reported diagnostic properties (sensitivity, specificity, and cutoff points).

Selection and extraction process

After the initial search, duplicates were removed, and two reviewers independently screened titles and abstracts to exclude clearly irrelevant studies. Full texts of potentially eligible records were then obtained, and the inclusion and exclusion criteria were applied. The key data mentioned above were extracted from each source, with particular attention to mean numerical values and the statistical significance of the differences found (**Figure 1**).

Synthesis of the available evidence

The evidence is presented below, grouped according to the biological nature of the biomarkers studied in OIERR.

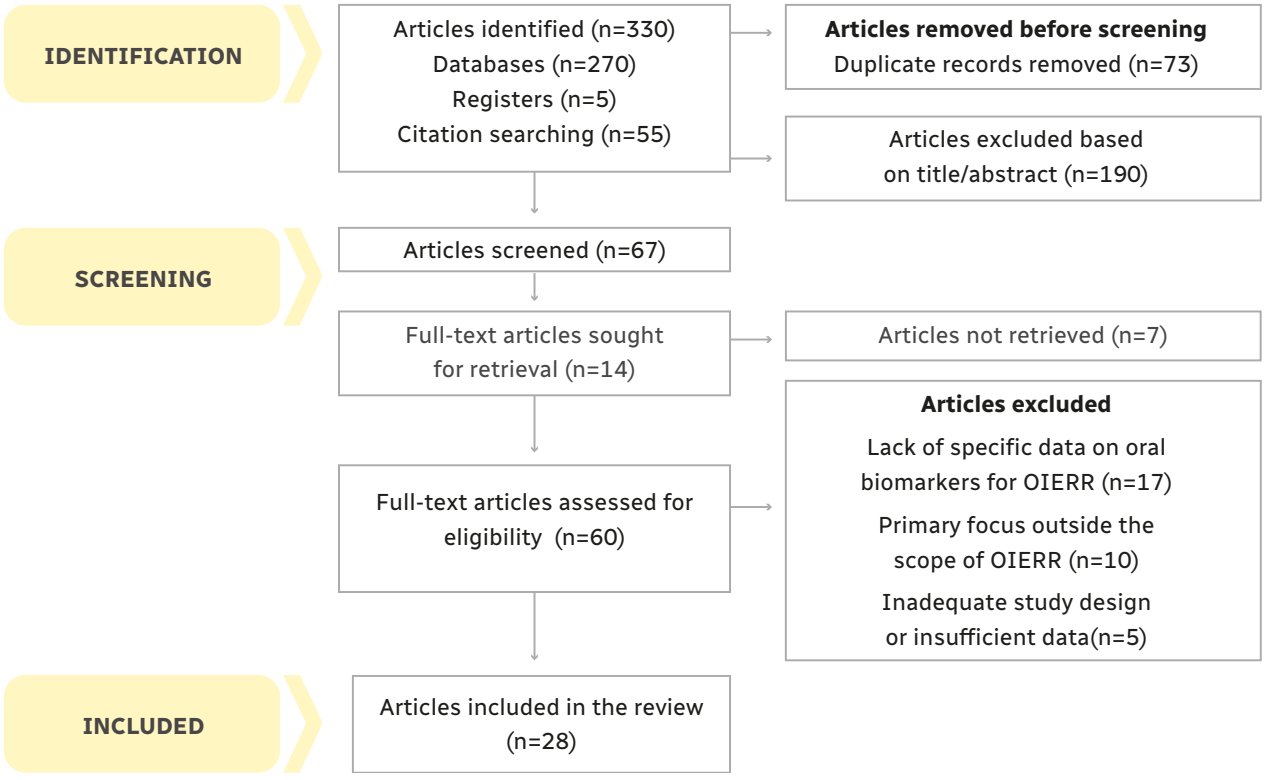


Figure 1. Flow diagram - Study identification process

Bone biomarkers associated with OIERR

Orthodontic tooth movement triggers remodeling of the alveolar bone; therefore, several bone mediators have been investigated as potential indirect indicators of OIERR. Among the most widely studied are the RANKL/OPG system, osteopontin, and proteins related to bone resorption.

RANKL/Osteoprotegerin

Receptor activator of nuclear factor kappa-B ligand (RANKL) is a key cytokine that stimulates osteoclast differentiation and activation by binding to its receptor, RANK, thereby promoting bone resorption. Osteoprotegerin (OPG), in contrast, is a decoy receptor that binds to RANKL and prevents its interaction with RANK, acting as an inhibitor of osteoclastogenesis.[10] A RANKL/OPG balance shifted toward RANKL favors bone resorption. Orthodontic studies have shown that force application causes an increase in RANKL and a decrease in OPG in GCF during the early stages of tooth movement.[10] Since OIERR shares resorptive mechanisms with bone remodeling, this axis has been investigated in patients with root resorption. One study showed that RANKL concentration in GCF was significantly elevated in subjects with moderate and severe OIERR compared with controls consisting of patients who had not yet started orthodontic treatment and had no radiographically detectable evidence of OIERR.[11] However, these authors noted that this elevation could reflect alveolar bone remodeling inherent to orthodontic treatment rather than root resorption per se. Along the same lines, it has recently been confirmed that the RANKL/OPG ratio tends to be higher in teeth with OIERR than in controls, supporting its association with resorptive activity.[3] Nevertheless, because the RANKL/OPG system is ubiquitous in bone remodeling processes, its specific diagnostic value for OIERR is limited; elevated RANKL levels may indicate active bone remodeling due to orthodontic treatment, even when the root itself is not affected.

Osteopontin

Osteopontin (OPN) is a bone matrix glycoprotein produced by osteoblasts and other cell types, with roles in cell adhesion and osteoclast regulation. In patients undergoing orthodontic treatment with radiographic evidence of moderate to severe OIERR, elevated OPN levels have been detected in GCF. When these levels were compared with those of patients not undergoing orthodontic treatment and without evidence of OIERR, statistically significant differences were found. Moreover, the authors noted that this protein probably originated from the adjacent alveolar bone undergoing remodeling rather than from the specific area of root resorption.[11] This again points to an issue of specificity: OPN may increase in response to any osteoclastic activation in bone and not exclusively due to root dentin resorption. Therefore, although osteopontin may reflect an active osteo-

clastic microenvironment, it cannot determine whether the resorptive activity originates from alveolar bone remodeling or from damage to the dental root.

Dentin matrix protein-1

Although its name suggests a dentin origin, dentin matrix protein-1 (DMP-1) is a non-collagenous phosphoglycoprotein found in both dentin and bone tissue. It participates in mineralization and is expressed by odontoblasts and osteocytes. Balducci et al. detected elevated DMP-1 levels in the GCF of patients with OIERR compared with controls without orthodontic treatment or evidence of OIERR, with a statistically significant difference.[20] This would initially suggest that DMP-1 may serve as a marker of dentin resorption. However, when stratifying by severity, they found no significant differences between moderate and severe OIERR, suggesting that, once the process has begun, DMP-1 release may become saturated or may originate from additional sources. Indeed, it has been argued that the detected DMP-1 may originate mainly from remodeling alveolar bone rather than exclusively from root dentin.[12] Thus, given the presence of DMP-1 in bone tissues, it would be inappropriate to consider it a specific marker of OIERR. In summary, further studies are needed involving orthodontically treated control groups without evidence of OIERR to determine whether elevated DMP-1 in GCF is specifically due to root resorption or represents an epiphenomenon of concomitant bone remodeling.

Consequently, bone-derived markers lack specificity, since any active orthodontic tooth movement involving alveolar remodeling could increase their levels, regardless of whether pathological root resorption is present. Although these markers may confirm the presence of osteoclastic activity or treatment-associated bone loss, they do not allow OIERR to be reliably diagnosed.

Inflammatory biomarkers associated with OIERR

The process of induced root resorption is closely linked to local inflammation of the periodontal ligament in response to orthodontic force. Numerous pro-inflammatory cytokines involved in the immune response and remodeling have been investigated in this context.[13]

Pro-inflammatory interleukins

IL-1β and IL-6 are classic cytokines released by periodontal cells during the response to orthodontic pressure. Studies have reported increased IL-1β levels in gingival crevicular fluid (GCF) from teeth with OIERR.[13] However, the evidence regarding its role in the OIERR process remains limited. Regarding IL-6, Kunii et al.[14] demonstrated that its concentrations in GCF were significantly higher in patients with severe OIERR than in patients undergoing orthodontic treatment without evidence of OIERR, and that they further correlated with the magnitude and duration of the applied force. IL-6 is a potent stimulator of

osteoclastogenesis, and its sustained elevation may promote resorption.[14,25] In animal models, it has been associated with the progression of mechanically induced root resorption.[26]

Overall, pro-inflammatory cytokines tend to increase in the environment of a tooth subjected to orthodontic force, particularly when active OIERR is present. However, a critical point is that these interleukins also increase simply as a result of the periodontal inflammation that accompanies orthodontic tooth movement, even when root resorption is minimal or physiological. For example, IL-6 rises within a few days of starting orthodontic treatment in virtually all patients, as part of the normal response of the periodontal ligament.[15,16] Therefore, as with bone markers, further studies are needed to determine whether elevated IL-1β or IL-6 levels in GCF can distinguish between significant pathological OIERR and adaptive alveolar remodeling alone. This greatly limits their usefulness as specific diagnostic biomarkers for OIERR, since they could generate false positives in patients without clinically relevant root damage.

Anti-inflammatory interleukins

The body also releases anti-inflammatory mediators to counteract the resorptive process. One of these is the IL-1 receptor antagonist (IL-1ra), which blocks IL-1 receptors and thereby reduces the inflammatory cascade. In one study, IL-1ra levels in GCF were significantly lower in patients with induced OIERR, with a mean of approximately 320 pg/mL, than in controls without orthodontic treatment, who showed levels of approximately 658 pg/mL.[17] This difference suggests that the presence of OIERR is associated with a decrease in IL-1ra, probably due to consumption or an imbalance favoring active IL-1 in the microenvironment. In fact, Mandour et al.[17] proposed an IL-1ra value of ≤432 pg/mL as a cutoff indicative of active resorption, with 80% sensitivity and specificity in their cohort. However, it is important to note that the decrease in IL-1ra could be a general phenomenon of orthodontic tooth movement, since the application of orthodontic force inevitably generates some local inflammation, such as hyalinization of the periodontal ligament, which in itself reduces IL-1ra compared with the healthy state. Therefore, low IL-1ra levels could occur in any patient undergoing orthodontic treatment, even if they do not develop significant OIERR, especially given the nonspecific origin of IL-1ra with respect to dentin.[17]

In summary, the anti-inflammatory markers discussed tend to be reduced when active resorption is present;(17,18) however, specificity remains an issue. The decrease in IL-1ra accompanies orthodontic treatment in general and is not exclusive to OIERR, so its value in isolation is debatable. Thus, studies are needed to compare IL-1ra concentrations in GCF between orthodontically treated patients with OIERR and patients undergoing the same treatment without OIERR, in order to determine whether the levels of this anti-inflammatory interleukin change

specifically due to the presence of OIERR while maintaining the bone remodeling conditions inherent to treatment.

Dentin matrix biomarkers associated with OIERR

This group comprises proteins that are exclusive to, or predominant in, dentin and the pulp complex and that may be released into the external environment when root tissue resorption occurs. Since OIERR involves the destruction of mineralized dentin, the detection of its organic components in GCF or saliva has been proposed as the most direct way to specifically identify this lesion.[12,13,17,21,27]

Dentin sialophosphoprotein

Dentin sialophosphoprotein (DSPP) is the main non-collagenous protein of dentin and is synthesized by odontoblasts. It is a proprotein that undergoes post-translational cleavage into at least two major fragments: dentin sialoprotein (DSP) and dentin phosphoprotein (DPP), in addition to other minor peptides.[19] These dentin matrix proteins play roles in mineralization during root formation and, under normal conditions, remain trapped within dentin.[19,28] Their presence in GCF would indicate disruption of the dentin matrix—that is, root resorption—which makes them highly specific candidates for OIERR detection.[17,27]

Mandour et al.[17] evaluated DSPP in the GCF of incisors with OIERR versus orthodontically untreated controls without resorption, finding markedly elevated DSPP levels in the orthodontic group: 30.1 ± 9.6 pg/mL versus 1.6 ± 1.0 pg/mL in controls ($p<0.001$). They also included a group of children with physiological resorption, who showed even higher concentrations (~39 pg/mL), demonstrating that DSPP is released during any process of active dentin resorption, whether pathological or physiological. Moreover, this study calculated a DSPP cutoff point of ≥7.33 pg/mL in GCF to detect the presence of root resorption with 100% sensitivity and specificity in its sample, positioning DSPP as an excellent diagnostic candidate.

Another recent study validated a rapid immunochromatographic test kit for DSPP and found that it effectively distinguished among healthy patients without orthodontic treatment or OIERR, patients with moderate OIERR, and patients with severe OIERR.[27] It is worth noting that, according to the survey included in the study, GCF sampling was considered simple and safe by clinical orthodontists, suggesting the feasibility of implementing a DSPP test in practice. Overall, the evidence indicates that DSPP is the most specific biomarker currently identified for OIERR: it originates only from affected dentin tissue, and detection methods are already under development. Elevated DSPP levels indicate the presence of resorption and are detectable even in early stages.

Dentin phosphoprotein

Dentin phosphoprotein (DPP) constitutes the highly phosphorylated C-terminal segment of DSPP and is rich in aspartic acid residues, which confer a high affinity

for calcium. DPP is essential for mineral nucleation in dentin.[19] Under physiological conditions, it remains integrated into the dentin matrix; however, during OIERR, it is released and diffuses into GCF.[13] Several studies have confirmed that DPP levels in GCF are significantly higher in teeth with OIERR than in controls. For example, Mah and Prasad[12,19] reported mean values of 9.3 ± 4.7 µg/mL in teeth with OIERR versus 5.1 ± 4.1 µg/mL in controls, a statistically significant difference. In addition, DPP has shown some correlation with resorption severity: Balducci et al.[20] found sufficiently distinct DPP variations between moderate and severe resorption to allow the degree of resorption to be distinguished through its measurement.

Kapoor et al.,[3] in a review, also identified a significant positive correlation between the degree of OIERR and DPP levels in oral fluids. These data suggest that DPP could be used not only to detect the presence of resorption, but also to estimate its severity, with higher concentrations indicating more severe resorption. However, an important consideration is that DPP is not entirely specific: Kereshanan et al.[21] detected DPP in GCF from teeth undergoing physiological resorption and also at baseline levels in permanent teeth undergoing orthodontic treatment without radiographic evidence of OIERR. This implies that small amounts of DPP may be released during remodeling of dental tissues. Therefore, establishing reference thresholds for DPP has been proposed in order to differentiate pathological resorption from physiological variations. Mona et al.[13] recommend further research to determine clear cutoff values, since the presence of DPP at baseline could affect the interpretation of a diagnostic test.

In summary, DPP is a highly sensitive marker of resorption and has the potential to correlate with severity; however, its specificity should be interpreted with caution. It is likely to be more useful as part of a combined panel, together with DSPP or other biomarkers, or when increases are assessed relative to an individual baseline level. This approach would help distinguish normal DPP concentrations in oral fluids associated with physiological processes from DPP concentrations suggestive of ongoing OIERR.

Dentin sialoprotein

Dentin sialoprotein (DSP) corresponds to the N-terminal fragment of DSPP and is a dentin-specific glycoprotein. It has been studied less extensively than DPP, but it has also been detected in GCF in the context of resorption. Kereshanan et al.[21] identified DSP in GCF both during physiological root resorption and in permanent teeth undergoing orthodontic movement, but not in teeth without orthodontic treatment and without evidence of OIERR. An increase in DSP concentration was observed in the presence of root resorption compared with virtually undetectable levels in teeth not undergoing orthodontic treatment and without OIERR. In addition, Balducci et al.[20] reported significant differences in DSP levels between cases of moderate and severe OIERR, suggesting that DSP may also reflect the severity of the process. However, the specificity of DSP has been questioned based on certain

molecular findings: the gene encoding DSPP, and therefore DSP, is also expressed in osteoblasts and other hard tissues. Qin et al.[22] demonstrated DSPP expression in bone, indicating that small amounts of DSP could originate from normal bone remodeling. This is consistent with the detection of DSP in GCF from orthodontically treated controls without OIERR, possibly released from alveolar bone during physiological remodeling. However, other authors argue that DSP is more specific to dentin than DPP itself. Immunohistochemical studies have located DSP predominantly within odontoblasts and associated it with predentin, dentin, and pulp, while ruling out its significant presence in bone, cartilage, or cementum.[28] According to this view, DSP detected in orthodontic controls without OIERR would not originate from bone, but rather from developing dentin or from rapidly repaired physiological resorption.[21] Thus, its potential baseline presence implies that DSP alone could yield false-positive results.

Discussion

This narrative review critically analyzed several biomarkers in saliva and GCF that have been proposed for the complementary diagnosis of OIERR. Overall, the findings confirm that, although a wide range of molecules change their levels during orthodontic treatment and OIERR, only a minority meet the ideal characteristics of a clinically useful biomarker: high specificity for the pathological process under study, a consistent difference between affected and unaffected individuals, and the ability to indicate severity.

On the one hand, relatively nonspecific biomarkers have been identified that are indeed altered by tooth movement but do not adequately distinguish when such movement has caused pathological root resorption. This group includes bone mediators and inflammatory cytokines. Numerous studies have demonstrated significant variations in the concentrations of RANKL, OPG, DMP-1, IL-1, IL-6, and IL-1ra when comparing treatment groups with control groups. However, the main disadvantage of these markers lies in their low specificity. For example, as George et al. noted, the increase in OPN and RANKL appears to be more closely associated with bone remodeling induced by orthodontic force than with root damage itself, since this increase could originate from adjacent bone tissue undergoing remodeling.[11] This makes it difficult to establish a clear causal relationship between OIERR and the concentrations of these biomarkers, as an orthodontist might observe elevations in RANKL/OPG in virtually all patients undergoing active orthodontic forces, regardless of whether they develop severe OIERR.

Likewise, although pro-inflammatory interleukins may be involved in the cascade leading to OIERR, an increase in cytokines such as IL-6 in GCF primarily reflects the localized inflammation produced by tooth movement itself. Therefore, although these cytokines play a fundamental role in orthodontic tissue remodeling, it is not appropriate to consider them specific biomarkers of OIERR because of their

nonspecificity.[15,16] Conversely, in the case of the anti-inflammatory interleukins discussed, a decrease in IL-1ra would be expected where inflammation is present; therefore, it is not a specific indicator of OIERR, but rather an indication that the area is undergoing active remodeling.(17) However, studies comparing orthodontically treated patients with OIERR versus orthodontically treated controls without OIERR are essential to determine whether variations in the levels of these biomarkers can establish statistically significant differences between the two groups.

On the other hand, specific dentin matrix biomarkers emerge as the most promising candidates. The accumulated evidence—from the early studies by Balducci et al.[20] and George et al.[11] to the more recent studies by Mandour et al.,[17] Huang et al.,[23] and Tan et al.[27]—demonstrates fairly consistent, statistically significant increases in these markers in the presence of OIERR. Taken together, these studies support their usefulness in determining the presence of active root resorption. However, nuances and debates remain regarding their use in predicting severity and their absolute specificity.

Regarding DPP, although it is clear that detectable baseline levels may interfere with a clinical test,[12,19] most studies agree that its levels increase substantially in OIERR. Some authors, such as Mona et al.,[13] emphasize the need to define physiological reference values for DPP in order to avoid confusion with pathological values. On the other hand, Balducci et al.[20] reported sufficiently large variations in DPP levels between patients with moderate and severe OIERR to distinguish the degree of resorption by measuring this biomarker. Similarly, Kapoor et al.[10] described a significant positive correlation between the degree of resorption and DPP levels in oral fluids, reinforcing the hypothesis that this biomarker may be used as a predictor of resorption severity. Taken together, the studies suggest that DPP is a highly sensitive biomarker for any resorptive process and has the potential to indicate severity, but it requires calibration, such as cutoff points, to improve its specificity.

With regard to DSPP, the evidence provided by Mandour et al.[17] and Tan et al.[27] strongly demonstrated marked variations in its levels in patients with OIERR. This biomarker has even been validated in point-of-care tests due to its high specificity and abundance in dentin, which facilitates detection using simple methods. The results of these studies[27] showed agreement between a lateral flow assay and ELISA in detecting elevated DSPP in cases of OIERR, while also indicating good acceptance among clinicians. This positions DSPP as the leading marker in terms of applicability: in the near future, test strips could become available for GCF sampling to determine whether DSPP exceeds the threshold indicative of resorption. In conclusion, DSPP already meets many of the criteria of a good clinical biomarker: it is specific, clearly distinguishable from controls, reliably measurable, and non-invasive. Its main limitation is that, to date, it has been correlated with the presence or absence of OIERR, but it remains unclear whether its absolute level can distinguish between moderate and severe resorption.

With regard to DSP, the literature shows significant increases in patients with OIERR. Kereshanan et al.(21) found DSP in situations of physiological and pathological resorption, but it was practically absent under normal conditions. However, the findings of Qin et al.(22) raised a warning signal by demonstrating that the DSPP gene is expressed in bone-forming cells, which could explain small amounts of DSP in the GCF of controls due to osteoblastic activity. The subsequent review by Kapoor et al.[3] nuanced this interpretation by indicating that DSP is found mainly in dentin and pulp and only minimally in bone, attributing the DSP detected in controls without OIERR to release from immature growing apices. Thus, the question of DSP specificity remains incompletely resolved.

Limitations of current evidence

Most of the included studies have small sample sizes and heterogeneous designs, making direct comparison difficult. There is also heterogeneity in how OIERR is defined and measured: some studies use linear measurements on periapical radiographs, others use Malmgren grades, and some include only maxillary incisors. This affects the correlation with biomarkers. In addition, there are variations in GCF sampling techniques and quantification methods, which may influence detection sensitivity. Another limitation is that some studies did not adequately control for confounding factors, such as gingival inflammation or incipient periodontitis, which could increase baseline levels of several markers.

In another area, the literature on OIERR suggests that many previous studies did not include a control group of patients undergoing orthodontic treatment without developing resorption, which constitutes an important methodological limitation. This omission hinders the interpretation of the reported biomarkers, as it prevents determining with certainty whether their expression is a consequence of orthodontic movement per se or of the pathological process of root resorption. In the absence of an orthodontic control group without OIERR, any increase in certain biomarkers could simply be due to physiological bone remodeling induced by orthodontic forces, rather than exclusively reflecting pathological root damage.

The lack of a control group consisting of orthodontic patients without OIERR compromises the internal validity of the available studies, as it fails to adequately control for the effect of tooth movement as a confounding factor. It also limits the diagnostic specificity of the proposed biomarkers, since it remains unclear whether they truly distinguish pathological resorption from the biological changes typical of any orthodontic treatment. To address this limitation, it is crucial that future studies include this type of control group. Only then will it be possible to determine with greater certainty which biomarkers are specifically associated with the pathological process of OIERR and which are part of the normal orthodontic response, thereby strengthening the validity of the evidence and the clinical utility of these biomarkers.

Finally, no research to date has established a standardized clinical protocol for using biomarkers in daily orthodontic practice. For example, the best time for sample collection remains unknown, as does how to interpret a positive result in the absence of visible radiographic changes: should the clinician immediately reduce the force upon detecting an elevated biomarker? To address this issue, longitudinal studies will likely be necessary, in which patients are monitored throughout orthodontic treatment with serial biomarker measurements and these findings are correlated with the subsequent appearance of radiographic OIERR in order to determine their true predictive value.

Conclusions

Salivary and crevicular biomarkers represent a promising approach for improving the detection and monitoring of OIERR, providing real-time information on resorptive activity in a non-invasive manner. Although they do not yet replace radiographic assessment, they may complement it in the near future by allowing clinicians to objectively identify teeth at risk before clinically significant root loss occurs. This would contribute to safer, more personalized orthodontic treatments based on each patient's individual biology. Achieving this goal will depend on continued research focused on the most specific markers and on refining the clinical validity of the diagnostic tests derived from them.

References

1. De Ridder L, Aleksieva A, Willems G, Declerck D, Cadenas de Llano-Pérula M. Prevalence of orthodontic malocclusions in healthy children and adolescents: A systematic review. Int J Environ Res Public Health [Internet]. 2022;19(12):7446. DOI:10.3390/ijerph19127446

2. Patel S, Foschi F, Mannocci F, Patel K. External cervical resorption: a three-dimensional classification. Int Endod J [Internet]. 2018;51(2):206–14. DOI: 10.1111/iej.12824

3. Kapoor P, Chowdhry A, Bagga DK, Bhargava D. Biomarkers in external apical root resorption: An evidence-based scoping review in biofluids. Rambam Maimonides Med J. 2022;13(4):e0027. DOI: 10.5041/RMMJ.10482

4. Killiany DM. Root resorption caused by orthodontic treatment: an evidence-based review of literature. Semin Orthod. 1999;5(2):128–33. DOI: 10.1016/s1073-8746(99)80032-2

5. Linge L, Linge BO. Patient characteristics and treatment variables associated with apical root resorption during orthodontic treatment. Am J Orthod Dentofacial Orthop. 1991;99(1):35–43. DOI: 10.1016/S0889-5406(05)81678-6

6. Mirabella AD, Artun J. Prevalence and severity of apical root resorption of maxillary anterior teeth in adult orthodontic patients. Eur J Orthod. 1995;17(2):93–9. DOI: 10.1093/ejo/17.2.93

7. Villaman-Santacruz H, Torres-Rosas R, Acevedo-Mascarúa AE, Argueta-Figueroa L. Root resorption factors associated with orthodontic treatment with fixed appliances: A systematic review and meta-analysis. Dent Med Probl. 2022;59(3):437–50. DOI: 10.17219/dmp/145369

8. Atkinson AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, et al. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89–95. DOI: 10.1067/mcp.2001.113989

9. Hartsfield JK Jr, Everett ET, Al-Qawasmi RA. Genetic factors in external apical root resorption and orthodontic treatment. Crit Rev Oral Biol Med . 2004;15(2):115–22.

10. Kapoor P, Kharbanda OP, Monga N, Miglani R, Kapila S. Effect of orthodontic forces on cytokine and receptor levels in gingival crevicular fluid: a systematic review. Prog Orthod. 2014;15(1):65. DOI: 10.1186/s40510-014-0065-6

11. George A, Evans CA. Detection of root resorption using dentin and bone markers. Orthod Craniofac Res. 2009;12(3):229–35. DOI: 10.1111/j.1601-6343.2009.01457.x

12. Mah J, Prasad N. Dentine phosphoproteins in gingival crevicular fluid during root resorption. Eur J Orthod. 2004;26(1):25–30. DOI: 10.1093/ejo/26.1.25

13. Mona M, Abbasi Z, Kobeissy F, Chahbandar A, Pileggi R. A Bioinformatics Systems Biology Analysis of the Current Oral Proteomic Biomarkers and Implications for Diagnosis and Treatment of External Root Resorption. Int J Mol Sci. 2021 Mar 20;22(6):3181. DOI: 10.3390/ijms22063181

14. Kunii R, Yamaguchi M, Tanimoto Y, Asano M, Yamada K, Goseki T, et al. Role of interleukin-6 in orthodontically induced inflammatory root resorption in humans. Korean J Orthod. 2013;43(6):294–301.

15. Uematsu S, Mogi M, Deguchi T. Interleukin (IL)-1 beta, IL-6, tumor necrosis factor-alpha, epidermal growth factor, and beta 2-microglobulin levels are elevated in gingival crevicular fluid during human orthodontic tooth movement. J Dent Res [Internet]. 1996;75(1):562–7. DOI: 10.1177/00220345960750010801

16. Ren Y, Hazemeijer H, de Haan B, Qu N, de Vos P. Cytokine profiles in crevicular fluid during orthodontic tooth movement of short and long durations. J Periodontol [Internet]. 2007;78(3):453–8. DOI: 10.1902/jop.2007.060261

17. Mandour KAA, Tawfeek MA, Montasser MA. Expression of biological markers in gingival crevicular fluid of teeth with orthodontically induced root resorption. J Orofac Orthop. 2021;82(5):313–20. DOI: 10.1007/s00056-020-00267-x

18. Ahuja R, Almuzian M, Khan A, Pascovici D, Dalci O, Darendeliler MA. A preliminary investigation of short-term cytokine expression in gingival crevicular fluid secondary to high-level orthodontic forces and the associated root resorption: case series analytical study. Prog Orthod. 2017;18(1):23. DOI: 10.1186/s40510-017-0177-x

19. Prasad M, Butler WT, Qin C. Dentin sialophosphoprotein in biomineralization. Connect Tissue Res [Internet]. 2010;51(5):404–17. DOI: 10.3109/03008200903329789

20. Balducci L, Ramachandran A, Hao J, Narayanan K, Evans C, George A. Biological markers for evaluation of root resorption. Arch Oral Biol. 2007;52(3):203–8. DOI: 10.1016/j.archoralbio.2006.08.018

21. Kereshanan S, Stephenson P, Waddington R. Identification of dentine sialoprotein in gingival crevicular fluid during physiological root resorption and orthodontic tooth movement. Eur J Orthod. 2008;30(3):307–14. DOI: 10.1093/ejo/cjn024

22. Qin C, Brunn JC, Cadena E, Ridall A, Tsujigiwa H, Nagatsuka H, et al. The expression of dentin sialophosphoprotein gene in bone. J Dent Res. 2002;81(6):392–4. DOI: 10.1177/154405910208100607

23. Huang GY, Choi SH, Jung HD, Kim HS, Hwang CJ, Lee KJ. Tissue-specific biomarkers in gingival crevicular fluid are correlated with external root resorption caused by constant mechanical load: an in vivo study. Clin Oral Investig. 2021;25(11):6321–33. DOI: 10.1007/s00784-021-03932-6

24. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4(1):5. DOI: 10.1186/s41073-019-0064-8

25. Kikuta J, Yamaguchi M, Shimizu M, Yoshino T, Kasai K. Notch signaling induces root resorption via RANKL and IL-6 from hPDL cells. J Dent Res. 2015;94(1):140–7. DOI: 10.1177/0022034514555364

26. Hayashi N, Yamaguchi M, Nakajima R, Utsunomiya T, Yamamoto H, Kasai K. T-helper 17 cells mediate the osteo/odontoclastogenesis induced by excessive orthodontic forces: T-helper 17 cells induce osteo/odontoclastogenesis. Oral Dis. 2012;18(4):375–88. DOI: 10.1111/j.1601-0825.2011.01886.x

27. Tan JHS, Yazid F, Kasim NA, Ariffin SHZ, Wahab RMA. A newly developed kit for dental apical root resorption detection: efficacy and acceptability. BMC Oral Health. 2024;24(1):298. DOI: 10.1186/s12903-024-04056-5

28. Bronckers AL, Farach-Carson MC, Van Waveren E, Butler WT. Immunolocalization of osteopontin, osteocalcin, and dentin sialoprotein during dental root formation and early cementogenesis in the rat. J Bone Miner Res. 1994;9(6):833–41. DOI: 10.1002/jbmr.5650090609

Data availability

The dataset supporting the results of this study is published within the article.

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Authors' Contributions and Collaboration Statement

Full name of authors	Academic collaboration													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
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3. Formal Analysis
4. Conceptualization
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