Detection of oral biomarkers as a diagnostic tool for orthodontically induced inflammatory root resorption: a literature review

Detección de biomarcadores orales como herramienta de diagnóstico para la reabsorción radicular inflamatoria inducida ortodónticamente: una revisión de la literatura

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ABSTRACT

Orthodontically induced inflammatory root resorption (OIIRR) is one of the most common complications of orthodontic treatment. Historically, only radiographic methods were available, while offering ease of use and accessibility, many limitations exist. Problems of technique, standardization, limited points of view and radiation exposure remain. Resorption can only be detected after a significant portion of the root has been lost (60% to 70% mineralized tissue). Moreover, these methods are static and cannot indicate if the process of root resorption has arrested or is ongoing. Recently, oral fluids have been used as a tool for the diagnosis and monitoring of oral and systemic diseases through the detection of biomarkers. The purpose of this review is to describe the scientific evidence related to the prevalence, etiology, the traditional diagnostic methods and the advances in the detection of oral biomarkers through molecular biology for this pathology.

KEY WORDS: Root resorption, biomarkers, saliva, gingival crevicular fluid, diagnosis, orthodontics.

RESUMEN

La reabsorción radicular inflamatoria inducida ortodónticamente (RRIIO) es una de las complicaciones más comunes del tratamiento de Ortodoncia. Históricamente, solo estaban disponibles los medios radiográficos para detectarla, sin embargo, requieren de exposición a radiaciones ionizantes potencialmente dañinas, la técnica radiográfica es sensible, detecta la reabsorción después de que se ha perdido una porción significativa de la raíz (60% al 70% del tejido mineralizado) y no proporciona información sobre su actividad. Recientemente, los fluidos orales vienen siendo utilizados como herramienta para el diagnóstico y monitoreo de enfermedades orales y sistémicas mediante la detección de biomarcadores. El propósito de esta revisión es describir la evidencia científica relacionada con la prevalencia y etiología, los métodos diagnósticos tradicionales y los avances en la detección de biomarcadores orales mediante biología molecular.

PALABRAS CLAVE: Reabsorción radicular, biomarcadores, saliva, líquido del surco gingival, diagnóstico, ortodoncia.

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INTRODUCTION

Orthodontically induced inflammatory root resorption (OIIRR) is an unavoidable, unwanted, yet unexplained, consequence of orthodontic treatment. The incidence of OIIRR has been reported to be greater than 90% in histological studies, while radiographic techniques report an incidence of 73%. However, most of the time, the loss of root structure is minimal and it is not clinically significant. Severe root resorption, defined as root loss greater than 4 mm or loss of a third of the original length, is only observed in 1-5% of teeth (1).

Root resorption is a physiological or pathological process of multifactorial etiology, which consists of an eventual and/or permanent loss of mineralized tissues (dentin and/or cementum) of the dental roots due to a mainly odontoclastic action, wherein the resorbed root portion is replaced with normal bone. In permanent dentition, root resorption is pathological and can be reversible or irreversible depending on the capacity of the cementoblasts to reconstitute the root. During orthodontic movement, forces are transmitted from the tooth to the periodontal ligament and it is thus that the areas of compression of the ligament generate the activation of osteoclastic cells that cause bone resorption. Areas of tension promote osteoblast differentiation and bone apposition. The imbalance between the amount of resorption and bone apposition combined with the loss of some protective characteristics of the cementum, contribute to the resorption of root areas. Root resorption can be compensated by the replacement of cement, generating the repair of damaged structures (2).

The assessment of biologic markers for disease detection is a novel diagnostic method. A biomarker is a biological substance that can be measured quantitatively, playing an important role determining the onset, progression and treatment of certain diseases. It also helps to predict patient susceptibility to a certain type of disease. From a diagnostic standpoint, using them for the early detection of oral diseases such as root resorptions among others has generated a huge interest in the dental field. Biomarkers are present in different body fluids such as saliva, GCF (gingival crevicular fluid), blood, or urine (3), but for this literature review, we will focus on biomarkers detected in oral fluids. There are currently no specific validated oral biomarkers that allow the early diagnosis of OIIRR, an area of study that should be explored and researched more. This diagnostic approach has excellent potential as it can prevent unnecessary invasive procedures, like

X-ray radiographs, and also has a promising future use in patients' routine dental care and can eventually have a significant impact on the overall health care system. The ideal goal of this line of research is developing a rapid chair-side test to spot specific biomarkers that predict the patient's susceptibility, diagnose and monitor OIIRR during treatment. The purpose of this review is to collect scientific evidence to describe the traditional diagnostic methods, the type of samples used for the detection of oral biomarkers and the identification of those that could serve as potential diagnostic tools for OIIRR.

OIIRR diagnostic methods

Radiographic Methods

Historically, only radiographic means were available to detect OIIRR. This was problematic as it requires exposure to potentially harmful ionizing radiation, the technique is sensitive and can only detect resorption after a significant portion of the root (60% to 70% of the mineralized tissue) has been lost (4). Likewise, it cannot provide information on whether it is active (5). Regarding the radiographic type, periapical are superior to accurately detecting the magnitude of root resorption, however, panoramic radiographs have certain advantages such as lower exposure to the radiation (as they are usually used for orthodontic treatment diagnosis and control), shorter clinical time and provide an overview of all the structures. Several correction formulas have been developed to account for differences caused by enlargement in panoramic radiographs, including the calculation of root lengths adjusted as a function of a crown length that is a constant, and the use of the crown-to-root ratio instead of the root length to measure changes. A study by Brezniak et al. found that the three-formula rule used by Linge and Linge is the most precise, so they modified it by using the median of the cement enamel junction because it is less affected by the angular changes between the tooth and the radiographic film (6).

Molecular biology

The concept of "molecular diagnosis" is a term that includes molecular biology techniques for the benefit of human health, detecting and/or quantifying specific genetic sequences of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins. This dynamic area in constant development has revolutionized clinical diagnostics. The specific detection and quantification of biomarkers on a sample have shown a significant impact in all areas of health,

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and dentistry has not been the exception. (7) Today, with the technology available, samples obtained from oral fluids allow the identification of different biological markers through different procedures like Enzyme-Linked Immunosorbent Assay (ELISA), Western Blot, Cytometric Bead Arrays (CBA), two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (2DE-SDS-PAGE) followed by mass spectrometry (MS), polymerase chain reaction (PCR), high-performance liquid chromatography (HPLC), spectrophotometry, among others.

Types of oral samples for the study of biomarkers

Biomarkers are used to objectively measure normal biological processes, pathogenic processes, or responses to a therapeutic intervention. Additionally, biomarker screening can detect susceptibility to a specific disease. With the recent advances in highly sensitive assays, whole saliva (WS) and GCF appear to be potential fluids that may contain important biomarkers with applications in dentistry and medicine (8). A great advantage of biomarker assays is their ability to detect changes before clinical signs or symptoms become obvious. For example, dentin and cementum biomarkers can be utilized to diagnose OIIRR before radiographic signs are noticed (9,10).

Saliva is an acidic biological fluid (pH: 6–7) that plays a crucial role in many oral functions. For this reason, some of the advantages to use it as a biofluid are the quick, easy, inexpensive, and non-invasive collection. It is uncomplicated to store; the sample does not clot and can reflect the current physiological state of an individual. Since there is no need to use needles for sample collection, it is more comfortable and also reduces the anxiety levels of patients. One of the pointed disadvantages of using saliva as a diagnostic tool was the lack of adequate cost-effective technology. However, recent publications show that this obstacle will be removed soon. It has been reported that saliva could be used as a diagnostic tool to monitor a disease if it meets the criteria for the easy and non-invasive collection, has validated and definitive biomarkers for a specific disease, and if existing technologies are capable of detecting its biomarkers (11). Therefore, it is important to use only one type of collection technique when performing studies as salivary flow rate can be affected by the degree of hydration of the subject and olfactory stimulation and also has a circadian rhythm with peak flow in the afternoon in this lies the importance to control these variables when collecting the samples (12).

Alternatively, GCF was first described in 1899 as a fluid that emerges between the surface of the tooth and the epithelial integument. It is an excellent source for assaying specific dental biomarkers of oral conditions due to its ability to be site-specific which is why multiple techniques have been used to collect it (8). The traditional method entails the use of absorbent filter paper strips that are inserted just at the entrance of the crevice, to the base of the pocket, until minimum resistance is felt. The advantages of this technique include being quick and easy to use, the ability to apply it to individual sites, and causing minimal trauma when used correctly. The amount of GCF collected may be measured by various means; however, the most common and accurate method is the electronic method that measures the amount of GCF collected on paper strips by using an electronic transducer. The method is based on the fact that the flow of electronic current is affected by the wetness of the paper strip and thus provides a digital readout (13).

Potential Biomarkers for OIIRR

Several proteins have been evaluated as possible biomarkers for OIIRR. In Table 1, the identified potential oral biomarkers along with the associated type of sample and processing method in the research studies cited are presented.

A study by Mah and Prasad compared the concentration of dentin phosphoproteins released in GCF during resorption. The results of the ELISA assay showed that the highest levels were found in patients with resorbed deciduous molars, followed by those with mild OIIRR (group of orthodontic patients), and the lowest levels were found in the controls (non-treated). It was concluded that root resorption can be studied using an immunological technique and that it can provide a quantitative measurement of phosphoproteins in GCF (14).

Another study, carried out by Balducci *et al*., aimed to identify and quantify extracellular matrix proteins, dentin matrix acid phosphoprotein 1 (DMP-1), dentin phosphoprotein (DPP), and dentin sialoprotein (DSP) in the GCF of orthodontic patients. The ELISA results showed that the concentration of DMP-1 and DPP were higher in the GCF of orthodontic patients with evidence of OIIRR in comparison to the controls. It was also found that the concentration of DSP in GCF was higher in patients who presented severe resorption compared to those who presented in its mild form, but this difference did not exist for DMP-1 (9).

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Table 1. Identified potential oral biomarkers for OIIRR diagnosis in articles cited.

Times	Year	Biomarker	Type of sample	Sample Processing
Mah and Prasad (14)	2004	Dentin phosphoproteins (DPP)	GCF	ELISA
Balducci *et al.* (9)	2007	Dentin matrix protein 1(DMP1), dentin phosphophoryn (PP), dentin sialoprotein (DSP)	GCF	(SDS-PAGE), Western Blot, indirect ELISA
Kereshanan *et al.* (15)	2008	Dentine sialoprotein (DSP)	GCF	Western Blot
George and Evans (5)	2009	OPN, OPG, RANKL	GCF	SDS-PAGE, Western Blot, ELISA
Shah *et al.* (4)	2014	Dentine sialoprotein (DSP)	GCF	ELISA, Spectrophotometry
Kaczor-Urbanowiccz *et al.* (16)	2017	Fetuin-A, p21-ARC	Saliva	SDS-PAGE, quantitative mass spectrometry (qMS), Western Blot
Yashin *et al.* (17)	2017	*Saliva:* IL-7, IL-10, IL-12p70, IL-4, interferon-gamma (IFN-γ). *Blood:* Procollagen type I N-terminal peptide (P1NP) and osteocalcin	Saliva, blood	ELISA
Ahuja *et al.* (18)	2017	TNF-α, IL-7, recombinant human granulocyte macrophage colony-stimulating factor (GM-CFS)	GCF	Multiplex bead immunoassay
Zhou *et al.* (19)	2017	Butyrate, alpha-linolenic acid, alpha-glucose, urea, fumarate, formate, guanosine, purie,etc.	Saliva	NMR
Holt (20)	2018	DMP1, DPP	Saliva	ELISA
Mohd Nasri *et al.* (21)	2020	Protein S100A9, J Chain (IGJ), Heat shock 70 kDa protein 1A (HSPA1A), Ig heavy variable 4–34 (IGHV4–34), Thymidine phosphorylase (TYMP), and Vitronectin (VTN)	GCF	LC-MS
Mandour *et al.* (22)	2020	IL-1ra, DSPP	GCF	ELISA
Ghaleb *et al.* (23)	2021	DPP	GCF	ELISA
Huang *et al.* (24)	2021	CEMP-1, DPP, CTX-I,	GCF	ELISA

Kereshanan *et al.* fulfilled a research to quantify the concentration of DMP-1 and dentin sialoprotein, released in the GCF during physiological and orthodontic induced root resorption. The samples were analyzed using an immunoassay (Western Blot). Dentin sialoprotein was elevated at sites that were undergoing physiological resorption compared to non-resorbed controls ($p<0.05$). The results highlight the potential to measure this protein in the GCF as a biomarker to monitor root resorption (15).

In the University of Illinois a group of researchers tested the hypothesis that during root resorption, organic matrix proteins and cytokines from the surrounding bone and dentin are released into the gingival sulcus. For this purpose, GCF was collected and subsequently analyzed using Western Blot and ELISA techniques. The proteins studied were osteopontin (OPN), osteoprotegerin (OPG), and nuclear receptor activator ligand kβ (RANKL). Preliminary results confirm the presence of matrix proteins and cytokines in the GCF of subjects with root resorption. Furthermore, OPG was present locally in excessive amounts over RANKL and the increase in RANKL/OPG proportion in the study groups could be correlated with increased bone resorption activity during orthodontic tooth movement (5).

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In 2014, Shah *et al*. used the ELISA technique combined with electrochemistry and ELISA combined with spectrophotometry to measure the biochemical marker of dentin sialophosphoprotein (DSPP) in the GCF of orthodontic patients (treated for 8-12 months). The results showed that ELISA combined with electrochemistry is a reliable and sensitive method to detect dentin sialophosphoprotein in gingival crevicular fluid (4).

In 2017, Kaczor-Urbanowiccz *et al*. executed a project to discover the diagnostic potential of protein biomarkers for the detection of OIIRR in saliva. Unstimulated saliva was collected from 72 individuals: 48 with OIIRR and 24 non-treated. The evaluation of the periapical radiographs of the upper incisors was performed before and 9 months after the brackets bonding. High abundance protein concentration was determined followed by two-dimensional gel electrophoresis and quantitative mass spectrometry. Finally, to initially validate the results of the quantitative mass spectrometry, a Western Blot test was performed. The importance of new salivary proteomics methodologies for the detection of OIIRR biomarkers was demonstrated. The results of the study propose a series of pathogenic mechanisms for this type of reabsorption, which differs between young and adult patients. In young individuals, they were associated with dynamic and acute processes while in adults they were associated with a slower phenomenon; demonstrating the importance of division by age group. Finally, the primary validation using the Western Blot test of the two candidate biomarkers (p21-ARC and fetuin-A) showed similar trends in quantitative mass spectrometry, which supports the reliability of the latter test. These two proteins were selected as biomarker candidates due to their association with inflammation, hard tissue resorption, and orthodontic tooth movement (16).

That same year, Yashin *et al*. conducted a study to identify biochemical markers in blood and saliva that may be correlated with the trend of extensive OIIRR and to use these markers to predict patients susceptible to orthodontic treatment. It was found that patients with moderate to severe OIIRR showed a significant increase in salivary cytokines, including concentrations of interleukin IL-7, IL-10, IL-12p70, and interferon-gamma (IFN-γ), as well as a significant decrease at the IL-4 level. According to the results saliva could be a more valuable way of measuring changes in cytokine expression than blood secondary to orthodontic treatment (17).

Ahuja *et al.,* using a split-mouth model, studied the changes in cytokine profile in the GCF secondary to heavy forces during orthodontic treatment and compare the cytokine expression between participants showing severe and mild root resorption. For this aim, eight patients with maxillary first premolar extractions as part of their treatment plan were recruited in this study. The teeth on the tested side received 225g of controlled buccal tipping force for 28 days, while the contralateral teeth act as a control. GCF was collected from teeth in both sides before application of force and 3 h, 1 day, 3 days, 7 days, and 28 days after loading the application. Afterwards, samples were analyzed with multiplex bead immunoassay to determine the cytokine levels. A statistically significant temporal increase was found in the tested side teeth for tumor necrosis factor-alpha (TNF-α) at 3 h and 28 days (p = 0.01). Interleukin 7 (IL-7) significantly peaked on the 28th day. Comparing cytokine profile for participants with severe and mild root resorption (>0.35 and <0.15 mm, respectively), the levels of granulocyte-macrophage colony-stimulating factor was significantly greater in low root resorption cases (p < 0.05). The amount of root resorption which craters on mesial, distal surfaces, and middle third region were significant in the tested side teeth (p < 0.05). It was concluded that IL-7 and TNF-α (pro-resorptive cytokine) increased significantly secondary to a high level of the orthodontic force application. High levels of granulocyte-macrophage colony-stimulating factor (anti-resorptive cytokine) were detected in mild root resorption cases secondary to high-level orthodontic force application (18).

Zhou *et al.* aimed to identify salivary metabolic products using unbiased metabolic profiling in order to discover biomarkers that may indicate OIIRR. Unstimulated saliva samples were analyzed from 19 healthy orthodontic patients with OIIRR (n=8) and with non-resorption (n=11). Metabolite profiling was performed using 1H Nuclear Magnetic Resonance (NMR) spectroscopy. A total of 187 metabolites were found in saliva samples. The effective separation capacity of 1H NMR-based metabolomics suggested the potential feasibility of clinical application in monitoring periodontal and apical conditions in orthodontic patients during treatment and making early diagnosis of this pathology. Metabolites detected in this study need further validation to identify exact biomarkers of OIIRR (19).

In 2018, Holt evaluated changes in the levels of DMP-1 and dentin phosphoprotein (DPP) in

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saliva during orthodontic treatment, as well as their relationship with root resorption. The concentration of DMP-1 and DPP was higher in all evaluation periods during orthodontic treatment compared to baseline values; the only exception was at four months for PPD. Elevation of DMP-1 levels in saliva had a positive association with the average amount of incisor root resorption. Subjects who lost more than 10% of root length in any of the teeth had the highest saliva concentrations of DMP-1 during treatment. This study suggests that the level of DMP-1 in saliva can be considered as a biomarker of root resorption during orthodontic treatment potentially useful in clinics (20).

Because OIIRR is an iatrogenic effect and cannot be examined regularly due to the harmful effects of sequential doses of radiation, Mohd Nasri *et al.* compared protein abundance (PA) of pre-treatment and during orthodontic treatment to determine potential early markers for root resorption. Ten subjects who had fixed appliances were recruited for this study. GCF was obtained using periopaper strips at pre-treatment (T0), 1 month (T1), 3 months (T3), and 6 months (T6) of orthodontic treatment. Periapical radiographs of the upper permanent central incisors were taken at T0 and T6 to measure the amount of root resorption. Identification of changes in PA was performed using liquid chromatography-tandem mass spectrometry (LC-MS). Findings showed that all ten subjects had mild root resorption, with an average resorption length of 0.56 ± 0.30 mm. A total of 186 proteins were found to be commonly present at T0, T1, T3, and T6. There were significant changes in the abundance of 16 proteins (student's t-test, $p \leq 0.05$). The increased PA of S100A9, immunoglobulin J chain, heat shock protein 1A, immunoglobulin heavy variable 4–34, and vitronectin at T1 suggested a response to stress that involved inflammation during the early phase of orthodontic treatment. On the other hand, the increased PA of thymidine phosphorylase at T3 suggested growth promotion and, angiogenic and chemotactic activities. The identified proteins can be potential early markers for root resorption based on the increase in their respective PA and predicted roles during the early phase of orthodontic treatment (21).

Later, in 2020, Mandour *et al.* directed a study to investigate interleukin-1 receptor antagonist (IL-1ra) and DSPP levels in GCF as potential biomarkers for OIIRR using ELISA. Levels of IL-1ra and DSPP detected in the orthodontic (evidence of resorption 1-3 mm) and pediatric groups (evidence of physiologic root resorption) indicate a possible association with OIIRR. The results suggest that efforts to develop tests for screening, diagnosis and monitoring of this pathology should continue (22).

Recently, Ghaleb *et al.* evaluated and compared the extent of possible root resorption using dentin phosphoprotein levels GCF fluid between controlled continuous and intermittent orthodontic force groups. For this purpose, a sample of 16 maxillary first premolars from 8 patients requiring bilateral extractions was recruited. A buccally directed continuous force of 150 g, reactivated after 28 days, was applied to the upper first premolar on one side for 8 weeks. On the contralateral first premolar, a buccally directed intermittent force (21 days on, 7 days off) of the same magnitude was applied for the same period. GCF samples were collected at the beginning of the study, 1st, 3rd, 4th, and 5th week, and at the end of the study. Dentin phosphoprotein levels showed a higher concentration in the continuous force group than the intermittent force group in weeks 4 and 8 of sample collection; where the differences were statistically significant, no harm was observed. Dentin phosphoprotein was found to be a useful early biomarker to detect and monitor OIIRR, showing that the application of an intermittent orthodontic force caused less root resorption (23).

Finally, in 2021, Huang et al. investigated the association of changes in cementum protein-1 (CEMP-1), dentin phosphoprotein (DPP), and c-terminal cross-linked telopeptide of type I collagen (CTX-I) levels in GCF under constant load with external root resorption volume and amount of tooth movement. GCF samples were obtained from premolars at T0, T1 (1 day), T2 (1 week), T3 (2 weeks), T4 (4 weeks), and T5 (8 weeks) under constant 100-gm buccal tipping force. Opposite premolars were used as controls. Teeth were extracted at T5, followed by quantification of external root resorption volume and histological analysis. In the test group, T5/T0 ratios of CEMP-1 and DPP levels, differential CEMP-1 levels between T5 and T0, and differential DPP levels between T2 and T0 correlated positively with root resorption volume. CEMP-1 levels at T0 and T3 correlated negatively with root resorption volume, and CTX-I levels at T5 correlated positively with the amount of tooth movement. Alterations in CEMP-1 and DPP levels in human GCF at specific timepoints during orthodontic treatment may be associated with different degrees of external root resorption (24).

CONCLUSION

To date, molecular diagnostic kits for OIIRR detection have not been developed. There is no consensus of these proteins as validated biomarkers. Further investigations with a larger sample size and using more sensitive kits, if produced in the future, will be beneficial to overcome the shortcomings of the studies (23).

The methods used in the analysed studies were not homogeneous regarding the timing of sampling, the type of sample, the processing method, thus hindering the possibility of a clear comparison of the results. In addition, the lack of homogeneity in the results may depend on the numerous biomarkers and/or the genetic variations. Standardisation in the method may influence the outcome of future studies (25). The upcoming field will depend on further validation of specific biomarkers and their incorporation into state-of-the-art assays that are reliable, sensitive, specific, and cost-effective for broad implementation in clinical practice (26).

Several challenges must be addressed to ensure accurate and quality diagnoses. Furthermore, it is important to inform and train the medical team and health professionals about this type of techniques, to promote the development of multidisciplinary teams that in the future may design, implement, standardize, control and interpret these helpful diagnostic tools.

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