Review Article

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A Review of Biomarkers in Gingival Crevicular Fluid for Root Resorption

Garepally Sravani[1*] Anisha N Prasad[2] Manoj GS[3] Tahseen Sultana[4]

[1]Senior Lecturer, Department of Orthodontics and Dentofacial Orthopaedics, Sri Balaji Dental College and Hospital, Yenkapally, Telangana State, India.

[2]Senior Lecturer, Department of Orthodontics and Dentofacial Orthopaedics, Sri Balaji Dental College and Hospital, Yenkapally, Telangana State, India.

[3]Private Practitioner, KSA.

[4]Private Practitioner, Hyderabad, India.

ABSTRACT

Background: The incidence of root resorption has received much importance in recent times. Previously radiographic evaluation was the only method of detection. But repeated exposure to radiographs has significant side effects. With the advent of newer methods of investigation, evaluation of biomarkers in gingival crevicular fluid is proving to be a promising method for detection of root resorption. A wide array of markers have been reported which can help in non-invasive detection and monitoring of root resorption.

Keywords: Root resorption, biomarkers in gingival crevicular fluid, orthodontic tooth movement.

INTRODUCTION

Root resorption is a fairly common phenomenon following orthodontic treatment. Ketcham[1] first demonstrated radiographic evidence of changes in the shapes of tooth roots before and after orthodontic treatment. He showed that root resorption was a common and occasionally severe consequence of orthodontic treatment. Minor loss of root length (<2mm) has no clinical consequence. Brezniak and Wasserstein[2,3] gave the term "*Orthodontically Induced Inflammatory Root Resorption*" (OIIRR). However, early detection for those at risk may minimize chances of inadvertent damage during the course of treatment.

Currently, subtle radiographic changes are used to detect development of root resorption but these require frequent radiation exposure and may not entirely reliable. Problems of technique standardization and limited point of view exist. Moreover, about 60-70% of the mineralized tissue is lost prior to radiographic detection[4, 5]. The development of biochemical approaches will allow for discovery of non-invasive and predictive approaches for monitoring the status of roots before, during and after treatment. Once the marker molecules specific to root resorption are identified, the means to monitor their presence in GCF should make this approach viable.

Oral fluids like saliva and gingival crevicular fluid (GCF) are easily collectible and serve as a warehouse of information regarding the oral and general health conditions. With the advent of the 21st century, much of the research efforts have been directed towards identifying markers that can assess and improve tooth movement. Krishnan and Davidovitch[6] classified the identified markers into three main types

1. Metabolic products of paradental remodeling
2. Inflammatory mediators and patient response modifiers
3. Patient derived enzymes and enzyme response modifiers

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***Correspondence Dr. Garepally Sravani.**

Department of Orthodontics and Dentofacial Orthopaedics, Sree Balaji Dental College and Hospital, Chennai, Tamil Nadu, India.

Email: Not Disclosed

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With respect to orthodontic therapy although GCF and saliva are expected to have similar constituents, concentrations of the constituents are higher in GCF. GCF was acknowledged greater than a hundred years ago and has an inherent advantage that it is closer to site of activity of paradental tissue remodeling. In healthy gingival crevice, GCF is a transudate of interstitial fluid and in inflamed or stimulated conditions; it is an exudate reflective of serum concentration of metabolites. Recent studies to evaluate orthodontic tooth movement and root resorption have used GCF due to its non-invasive nature and ease of repetitive sampling using platinum loops, micro pipettes, filter paper strips and gingival washings.

OBJECTIVES

The objective of this review was to identify and evaluate the effectiveness of various biomarkers applicable for assessing root resorption in orthodontics to enable prediction and minimization of this adverse effect.

MATERIALS AND METHODS

Type of participants: Patients undergoing orthodontic treatment

Intervention: Collection of GCF at various intervals

Comparison: Levels of the various biomarkers identified in GCF in relation to root resorption

Outcome: Prediction and minimization of root resorption.

Focused question: The following research question was constructed: "What are the biomarkers useful for early detection of root resorption from gingival crevicular fluid?"

SELECTION CRITERIA

This review included of studies on: (1) prospective clinical trials, (2) human studies, (3) studies assessing root resorption using biomarkers, (4) tooth movement via coil springs and wires, (5) physiologically resorbing teeth. Case reports, reviews and letters to the editor were excluded.

SEARCH METHODOLOGY

An electronic search was conducted via PubMed/Medline, for articles in English, using the Medical Subject Headings (MeSH) terms "Gingival crevicular fluid, Biomarkers of tooth movement, Biomarkers of root resorption, Root resorption in orthodontics. Similar search was conducted via Google Scholar, Scopus and Hindawi.

STUDY SELECTION

Preliminary screening consisted of a total of 25 articles, of which 18 articles were selected. Initially the articles were screened for title and abstract for relevance. Following that a full text screening was done. The duplicate articles were eliminated and finally a total of 16 articles were included in the study.

GENERAL OUTCOME OF SELECTED STUDIES

From the studies that met the selection criteria, it was observed that there was a statistically significant increase in the concentration of biomarkers like Interleukin-6,7 (IL-6,7), Tumor necrosis factor-alpha (TNF-alpha), Alkaline phosphatase (ALP), Tartarate resistant acid phosphatase (TRAP), Dentin sialoprotein (DSP), dentin phosphophoryn (PP), dentine phosphoproteins (DPP), Osteoprotegerin (OPG), Receptor Activated Nuclear factor-Kappa Ligand (RANKL) and decrease in Interleukin-1 Receptor Antagonist (IL-1 RA) levels in the GCF collected from resorbing teeth.

DISCUSSION

Dentin breakdown products:

In an attempt to develop a more sensitive and specific test to diagnose and monitor OIIRR, Mah and Prasad [11] were one of the first to investigate biomarkers associated with OIIRR.These authors targeted dentine phosphoproteins (DPP) as local organic matrix proteins released into the GCF during resorption of dentine. They recruited three groups of teeth: (1) untreated healthy permanent central incisors (control), (2) mildly resorbed permanent central incisors under active orthodontic treatment, and (3) deciduous second premolars with half their roots resorbed. By showing that DPP levels in GCF were higher in the deciduous group (P=0.001) and mildly resorbed in the treated group (P=0.046) than in the control

group. Other dentine breakdown products have also been identified as possible suitable biomarkers of OIIRR. Balducci et al[12] in their cross-sectional study reported that dentin phosphophoryn (PP) and dentin sialoprotein were found in statistically higher amounts in severe OIIRR than in mild OIRR. PP and DSP were also found in small amounts in GCF of untreated control patients, but in lower levels.

Kereshanan et al[13] also reported elevated levels of DSP at 12 weeks after starting orthodontic therapy. The findings of dentine breakdown products in the controls support the findings that tooth roots undergo physiological remodeling and turnover with baseline root resorption.

Proteins:

Rody Jr et al[14] utilized a new proteomic technology that combines mass spectrometry and liquid chromatography to profile a panel of over 2000 proteins in the GCF collected from resorbing deciduous molars and non-resorbing permanent molars. There was significant characteristic up-regulation and down-regulation of proteins in deciduous teeth with root resorption.

OPG/RANK/RANKL system:

The OPG/RANK/RANKL system has an established role in the process of physiological root resorption of deciduous teeth as mentioned by Shiotani et al[15]. RANK and RANKL are both expressed by odontoclasts that resorb deciduous roots and OPG suppresses the RANKL induced activation of odontoclasts. Hence it was suggested that the RANKL: OPG ratio may contribute to the process of root resorption.

Yamaguchi et al[16] reported that compressed periodontal ligament cells obtained from cells with severe root resorption produced increased amount of RANKL and upregulated osteoclastogenesis. Nishijma et al[17] using an in vitro model demonstrated that compression force significantly increased secretion of RANKL and decreased secretion of OPG in human PDL cells in a time and force magnitude dependent manner. Similarly, Tyrovala et al[18] found that on application of force during orthodontic tooth movement, the compressed periodontal ligament upregulated osteoclastogenesis due to increase in RANKL and decrease in OPG levels.

George and Evans[19] conducted a cross-sectional study to show that both the concentration of RANKL and the RANKL:OPG ratio in GCF of mild and severe OIRR patients were significantly higher than in negative untreated controls implicating RANKL as possible biomarker for OIRR.

However, because the regulatory role of the OPG/RANK/RANKL system is common for both odontoclasts and osteoclasts more evidence is required to demonstrate how RANKL concentrations and RANKL:OPG ratio in GCF can be differentially interpreted to indicate bone remodeling rate during OTM or OIRR.

Cytokines:

Cytokines are innately linked to cellular processes of hyalinization; bone resorption and root resorption during OTM. Cytokines were sub-classified into two main groups: pro-resorptive and anti-resorptive. Pro-resorptive cytokines include interleukin-1, IL-2, IL-6, IL-7, IL-8 and TNF. TNF-α and IL-1β directly induce osteoclastogenesis and promote osteoclast function. Similarly, IL-6 acts synergistically, with IL-1 and TNF-α to promote osteoclast function. IL-7 works indirectly through the induction of TNF-α, while IL-8 enhances RANKL expression; both increase osteoclast generation and activate osteoclasts. On the other hand, anti-resorptive cytokines such as IL-4, IL-10, IL-13, interferon gamma (IFN-γ) and Granulocyte macrophage colony-stimulating factor (GM-CSF) suppress and inhibit bone resorption.[20]

Kurihara et al[21] reported that IL-6 stimulates formation of early osteoclast precursors. Moreover, Adebanjo et al[22] reported that IL-6 activates mature osteoclasts. Yamaguchi et al[23] reported the release of IL-6 protein is increased in a time and magnitude dependent manner. Yamomoto et al[24] reported that hydrostatic pressure induces IL-6 production while Lee et al[25] reported that a continuous static compressive force (1.76g/cm^2) induces IL-6 gene expression.

Zhang et al reported that compressive force induces IL-17 expression and its receptor in osteoblast like cells and induces differentiation and function of

osteoclasts via prostaglandin. Adamopoulos et al reported that IL-17 regulates RANKL expression leading to increased sensitivity to RANKL signaling, osteoclast differentiation and bone loss.[26]

CONCLUSION

However, the search for a single biomarker for OIRR in GCF may have a low probability for success as it requires the individual separation, identification and testing of each biomarker. It is also difficult to develop antibodies against dentine breakdown products for immunoassay because dentine proteins are heavily phosphorylated making them less antigenic and less reactive with antibodies. Further longitudinal studies are essential to evaluate the diagnostic potential of these biomarkers.

CONFLICT OF INTEREST

No potential academic conflict of interest relevant to the above article was reported.

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