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Review Article

A systematic review on the correlation of expression of dentin sialophosphoprotein and orthodontic root resorption: An update on current evidence

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Abstract

Objectives: Orthodontic root resorption is a significant concern during orthodontic treatment, and can range from mild (0.4-1.5mm) to severe root resorption (>4mm). Recent studies have suggested that Dentin Sialo phosphoprotein (DSPP) may also be associated with the development and progress of orthodontic root resorption. The current systematic review's objective is to investigate the data currently available about the quantification of DSPP in patients who have orthodontic root resorption.
Materials and Methods: Using both manual and computer databases, a thorough literature search was carried out to find pertinent papers. Primary research studies that explored the association between DSPP expression and orthodontic root resorption in human subjects had been included in the inclusion criteria. The extraction of data and quality appraisal were performed according to established guidelines. A qualitative synthesis of the findings was performed due to variations in study designs and methodologies.
Results: During the initial search, 1192 records were found in total. After the screening procedure, thirty-three papers were chosen for full-text review. Both exclusion and inclusion criteria were used, and twelve studies were ultimately included in this systematic review. Study design, sample size, measuring techniques, and outcome measures varied between the research. DSPP expression and root resorption may be positively correlated, according to some research, although other investigations produced contradictory or equivocal findings.
Conclusions: This systematic review draws attention to the discrepancies in the literature that currently exist on the association between orthodontic root resorption and dentin sialophosphoprotein expression. Methodological differences and limitations across the studies contribute to the inconsistency in findings. The role of DSPP as a predictive marker for root resorption in orthodontic treatment has to be clarified by more studies using bigger sample sizes and standard methods.

Keywords: Dentin phosphoprotein, Dentin sialoprotein, Dentin Sialophosphoprotein, Gingival crevicular fluid, Root resorption, Systematic review

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1. Introduction

External root resorption is one adverse consequence of orthodontic treatment.[1] Based on radiographic methods, the incidence of orthodontic root resorption in teeth which have received orthodontic treatment is 73%, but histological studies have demonstrated an incidence of over 90%.[2,3] The degree of root resorption that occurs during orthodontic treatment can vary from mild (0.4-1.5mm) to severe (≥4mm).[3-5] Between 1 and 5% of people have severe root resorption, which can have serious clinical repercussions, such as a decreased crown-to-root ratio that may compromise the dentition's longevity.[3,6] Orthodontic root resorption (ORR) has multiple underlying causes that are still poorly understood.[7] The degree of resorption appears to be influenced by treatment duration, force (continuous vs. intermittent forces) and the direction of tooth movement.[8]

At present, radiographic imaging is the primary approach used for arriving at a clinical evaluation of root resorption. This is problematic because it only identifies ORR after a considerable amount of the root has been removed, is dependent on technique, involves exposure to possibly damaging ionizing radiation and cannot provide information about the persistence of root resorption.[9] In terms of radiographic images, periapical radiographs are better than

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panoramic radiographs at precisely determining the extent of root resorption; nevertheless, panoramic radiographs offer benefits over periapical radiographs, such as better visualization and reduced radiation exposure.[10] Since ORR can be addressed after the orthodontic force stops, early identification is essential.[11] Consequently, a sensitive and reliable approach for early root resorption identification and monitoring of its progress during the orthodontic treatment course must be developed.

Recent research has examined the use of Gingival Crevicular Fluid to collect and analyze protein biomarkers, as it offers several benefits, including non-invasiveness, ease of use and earlier determination of severity of resorptive activity.[12–14] The quest for biomarkers was aided by the detection of dentinal proteins in gingival crevicular fluid, as the by-products of orthodontic root resorption.[15-16] Dentin sialo phosphoprotein (DSPP) is one of the most ubiquitous proteins that are not collagen-based and is extremely dentin-specific. Earlier immunohistochemical studies have shown that the only tissues or cells that contain DSPP are odontoblasts, dentin and predentin; enamel, bone, muscle, and cartilage do not.[17-19] However, other biomarkers, such us those for inflammation or bone remodelling, may be less specific to ORR since their expression may be impacted by systemic inflammation or bone metabolic abnormalities.[15,20,21,22] The gold standard technique for identifying a variety of target molecules with the aid of certain antibodies is the enzyme-linked immunosorbent assay (ELISA), which may be utilized to measure the level of biomarkers in gingival crevicular fluid (GCF).[23]

The research question was formatted as- Does the expression of dentin sialo phosphoprotein (DSPP) correlate with the occurrence and severity of orthodontic root resorption? The results of this review are intended to offer an analysis of the data pertaining to dentin sialo phosphoprotein and resorption of roots during orthodontic tooth movement by evaluating the quality of evidence supporting the relationship and the risk of bias.

2. Objectives

Examining the most recent data on the quantification of DSPP in patients with external root resorption was the foremost intent of this systematic review.

3. Materials and Methods

The nature of this investigation precluded the need for ethical clearance. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used in the preparation of this systematic review (**Figure 1**).[20]

3.1. Protocol and registration

With reference number CRD42023434228, the study protocol for this systematic review was pre-registered at the International Prospective Register of Systematic Reviews database (PROSPERO).

3.2. Eligibility criteria

The criteria for eligibility were established using the PICOS (Population, Intervention, Comparison, Outcome, and Study design) model. (**Table 1** and **Table 2**).

3.3. Information sources and search strategy

A thorough search of the literature was conducted for relevant articles investigating orthodontic root resorption published up to October 31, 2024, to identify articles considering the inclusion criteria. This could be achieved utilizing digital databases including PubMed, Science Direct, Wiley Library and Cochrane Library (**Table 3**). PROSPERO was used to look for any ongoing systematic reviews, and in order to gather a wider range of evidence, OpenGrey (www.opengrey.eu) and Google Scholar were used to conduct a grey literature search for unpublished papers, theses, and conference proceedings. Only English-language publications were included. The list of references of the included studies and pertinent reviews were manually searched to retrieve any literature that might not have been identified by the computerized search.

An amalgamation of the Boolean operators AND/OR and MeSH/non-MeSH terms was employed to select relevant research. For the search strategy, the algorithm selected was: (root resorption OR external root resorption) AND (Dentin sialo phosphoprotein OR Dentin sialoprotein OR Dentin phosphoprotein OR DSPP OR DSP OR DPP) AND (orthodontic tooth movement OR tooth movement).

3.4. Data extraction

A data collection sheet was prepared using the Cochrane Consumers and Communication Review Group's data extraction template. The second review author (PP) verified the data that the lead author (VA) had taken out of the included papers. The third author (AG) settled any disputes about the listed studies.

Relevant information was taken out of the included studies, including study characteristics, sample size, methodology, DSPP assessment methods, and key findings using a standardized form (**Table 4**). The Cochrane risk of Bias tool was used for assessing the included studies' risk of bias and methodological quality.

4. Results

4.1. Study selection

Using database searches, 1192 studies had been detected. 33 articles were evaluated for eligibility after duplicates were eliminated and titles and abstracts were screened. Twelve of these studies were included in this systematic review after meeting the inclusion criteria. (**Figure 1**)

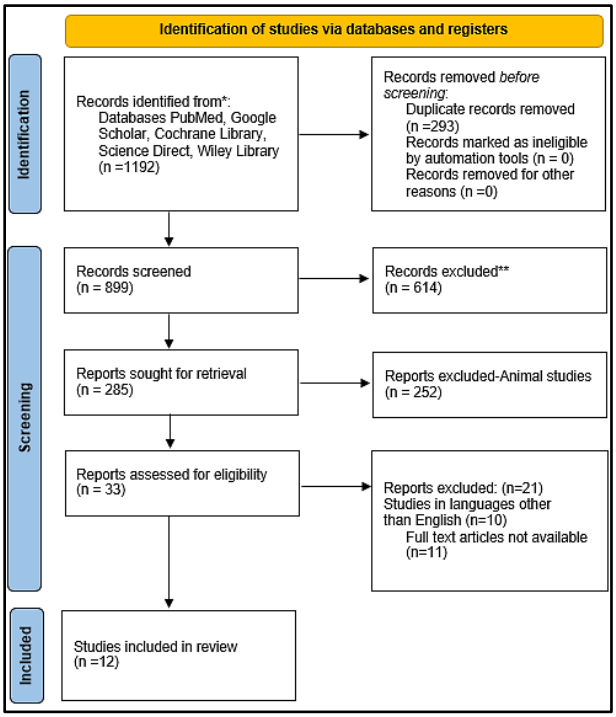

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature review.

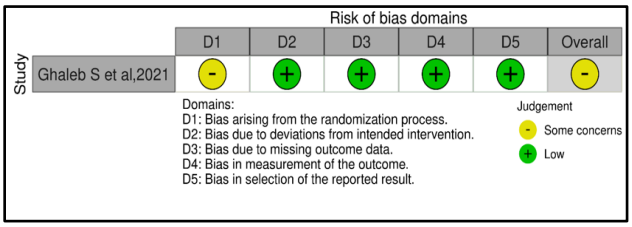

Figure 2: Rob 2 tool

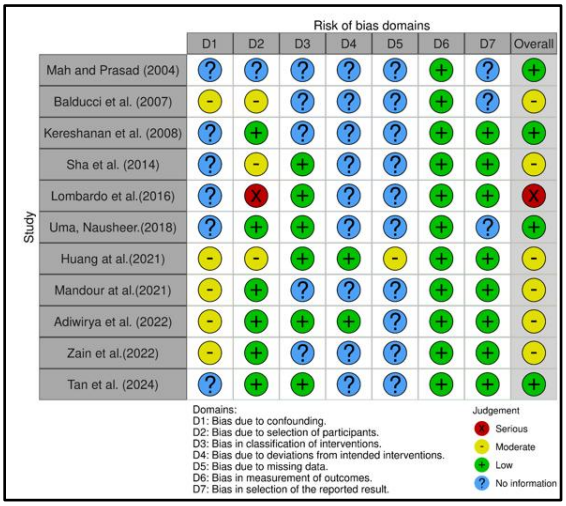

Figure 3: ROBINS I tool

Table 1: Inclusion criteria

Criteria	Description
Population	Studies involving human participants undergoing orthodontic procedures at any age
Intervention	Studies that evaluate the role of dentin sialophosphoprotein (DSPP) in orthodontic root resorption
Comparison	Any kind of orthodontic therapy at a different point in time or untreated controls
Outcome	Quantification of DSPP in patients undergoing fixed orthodontic treatment
Study design	Included both experimental and observational studies, such as randomized controlled trials, cross-sectional studies, case-control studies and prospective or retrospective cohort studies
Publication date	Studies published between 2000 and October 31, 2024, were included

Table 2: Exclusion criteria

Criteria	Description
Animal studies	Studies conducted on animal models or in vitro studies
Irrelevant studies	Studies that do not specifically explore the relationship between DSPP and orthodontic root resorption
Review articles and commentaries	Systematic reviews, meta-analyses, opinion pieces, and editorials. However, review articles were used for reference mining
Case reports and case series	Excluded individual case reports or case series without a control group
Studies with insufficient data	Studies with insufficient information to appraise the association between DSPP and orthodontic root resorption
Duplicate studies	Duplicate studies or multiple publications of the same study

Table 3: List of search engines

S. No	Search Engine	Results
1	Pubmed	11
2	Google scholar	898
3	Cochrane Library	2
4	Science Direct	186
5	Wiley Library	95

Table 4: Characteristics of the studies included in the systematic review

Author	Design	Objective	Experimental Subjects/Teeth (No./Age/Sex)	Control Group	Biomarkers Studied	Technique	Outcomes	Conclusions
Mah J, Prasad N. Eur J Orthod (2004)[15]	Cross-sectional study	To identify difference in the levels of DPP between 3 groups of 20 patients each.	Grp 1: Mx central incisor (n=20) with 1–3 mm RR; 13F, 7M; 12–16 y Grp 2: 10 second molars (n=20); 15F, 5M; 9–12 y	Mx central incisors (n=20) of untreated pts, 12F, 8M, 12–16 y	DPP	Periopaper, ELISA	Levels of DPP: greatest in resorbing 10 molar (11.7±4.1 μg/mg) followed by orthodontically treated tooth (9.3±4.7 μg/mg) and least in controls (5.4±4.1 μg/mg); NS between resorption Groups	DPP can be detected in exfoliating primary teeth and orthodontically-treated teeth
Balducci L et al. Archives of Oral Biology. (2007)[22]	Cross-sectional study	To identify and quantify DMP1, PP, DSP in the gingival crevicular fluid of subjects undergoing orthodontic treatment.	20 pts with mild RR (≤2 mm) (11F, 9M, 14–40 y), 20 pts with severe RR (>2 mm) (15F, 5M, 15–44 y)	20 pts (13F, 7M, 12–34 y); no RR/orthodontic Tx	DMP1, PP, DSP	Periopaper (mesial and distal of Mx central and lateral incisors), SDS–PAGE, stained western blot, ELISA	ELISA showed Sig. ↑ of DMP1, PP, DSP in RR vs control groups and of PP and DSP in severe RR vs mild RR Groups	DMP1, DSP, and PP in GCF proved a biomarker for RR in orthodontic Tx
Kereshanan S et al. Eur J Orthod (2008)[22]	Prospective cohort study	To identify and quantify dentin sialoprotein (DSP), released into GCF during physiological root resorption and orthodontic tooth movement.	Grp 1: 50 second deciduous molars (9–14 y) (advanced coronal RR [n=33] and apical minimal RR Grp [n=17]) Grp 2: 20 pts (11–15 y), T0=pre-fixed Tx, T1=12 mo post start of Tx	Control: 20 pts (10–15 y) erupted second premolars with no RR	DSP	Micropipettes, slot blot immunoassay	DSP levels: greater in physiological RR than non-resorbing teeth, DSP levels NS between coronal RR and apical RR; DSP levels Sig. higher in T1 compared to T0	DSP in GCF proved a biomarker of root resorption
Sha H et al. Am J Orthod Dentofacial Orthop. 2014[21]	Comparative study	To compare ELISA combined with electrochemistry and ELISA combined with spectrophotomet	20 pts (12F, 8M, 13–24 y), 8–12 months of orthodontic Tx	Same pts for both methods (ELISA with spectrophotometry and electrochemical detection)	Dentine sialophosphoprotein	Filter paper strip (mesial/distal sites of left and right Mx central	DSPP detection with spectrophotometric ELISA 10 times greater than with electrochemical detection. DSPP conc	DSPP can be sensitively and accurately detected in root resorption

		ry to measure DSPP in gingival crevicular fluid of orthodontic patients (treated for 8-12 months).				incisors), ELISA	range NS between methods	
Uma HL, Nausheer A.2018[25]	Prospective cohort study	To identify the role of DSPP in root resorption during orthodontic intrusion using three piece base arch.	10 experimental subjects before intrusion and 2 months after intrusion. Age: 16-22 years.	10 control subjects with no history of orthodontic treatment	dentine sialophospho protein	GCF was collected using microcapillary tube from permanent maxillary central and lateral incisors using ELISA method.	Highly significant increase in DSPP levels after 2 months of intrusion. Low levels of DSPP were detected in control subjects.	DSPP can be considered as a biomarker for root resorption
Lombardo et al. 2016,[23]	Comparative study	To compare two different methods of analysing DSP in the gingival crevicular fluid (GCF): the conventional ELISA and DSP antibody-coated magnetic micro-beads	6 pts (5F, 1M), average age 14 y, 12 wks orthodontic Tx	Same pts for both methods (conventional ELISA vs DSP antibody-coated magnetic micro-beads prior to ELISA)	DSP	Mesial and Ds sites of Mx central and lateral incisors, sterile paper strips	Sig. diff between standard ELISA and micro-beads for DSP evaluation in early RR evaluation; results of micro-bead approach are more uniform and highly sensitive	Modified micro-bead approach is more reliable for early detection of RR for DSP evaluation
Ghaleb S et al. Prog Orthod.2021 [26]	Single-blind, split-mouth, randomized controlled trial	To evaluate and compare the extent of root resorption using DPP levels in gingival crevicular fluid between controlled	16 maxillary first premolars from 8 patients (5F, 3M, 13–18 y). A buccally directed continuous force of 150 g, reactivated after 28 days, was applied to the upper	Split-mouth trial- 8 premolars in 8 patients on one quadrant. On the contralateral first premolar, a buccally	Dentin phosphoprotein	Filter paper strips at pre, 1st, 3rd, 4th, 5th and 8th week to quantify and compare dentin phosphoprot	Dentin phosphoprotein levels showed a higher concentration in the continuous force group than the intermittent force group in week 4 and 8 of sample collection- statistically significant differences.	Dentin phosphoprotein was found to be a useful early biomarker to detect and monitor root resorption, showing that the

		continuous and intermittent orthodontic force groups.	first premolar on one side for 8 weeks.	irected intermittent force (21 days on, 7 days of) of the same magnitude was applied for the same period.		ein levels in both groups using ELISA.		application of an intermittent orthodontic force caused less root resorption than a continuous force.
Mandour KAA et al. J Orofac Orthop. 2021[24]	Cross-sectional study	To investigate interleukin-1 receptor antagonist (IL-1ra) and dentin sialophosphoprotein (DSPP) levels in gingival crevicular fluid (GCF) as potential biomarkers for orthodontically induced root resorption using ELISA	74 subjects- 3 groups: 2 treatment, 1 control. Group 1 orthodontic patients(n= 25) 1-3 mm root resorption of a maxillary central incisor mean age- 15.6 ± 2.5, Group 2 pediatric group- (n= 24) physiologic root resorption of a lower second primary molar mean age- 9 ± 1	Control (n= 25)-mean age- 18.2 ± 6.8.subjects who had no orthodontic treatment and showed no radiographic evidence of root resorption.	Dentin sialophosphoprotein (DSPP)	Endodontic paper points and ELISA.	DSPP levels were 1.6 ± 1.0, 30.1 ± 9.6, and 39.2 ± 3.3 pg/ml for the control, orthodontic, and pediatric groups, respectively. Sensitivity and specificity of DSPP for the diagnosis of OIRR showed 100% reliability and a cutoff value of ≥7.33 pg/ml.	The levels of IL-1ra and DSPP detected in the orthodontic and pediatric groups indicate a possible association with OIRR.
Huang GY et al. Clin Oral Investig. 2021[27]	Prospective cohort study	To investigate the association of changes in CEMP-1, DPP, and CTX-I levels in human gingival crevicular fluid (GCF) under constant load	11 healthy adult patients (mean age, 23.5 years [range, 18.3–37.7]; 4M, 7F. 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	Cementum protein-1 (CEMP-1), dentine phosphoprotein (DPP), and c-terminal cross-linked telopeptide of type I collagen (CTX-I)	Periopaper 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 and ELISA.	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. CTX-I levels at T5 correlated positively	Changes in the levels of tissue-specific biomarkers in GCF may facilitate early detection of external root resorption during orthodontic tooth movement.

							with the amount of tooth movement	
Kusumah Adiwirya MS et al. J Orthod Sci. 2022[40]	Prospective cohort study	To evaluate differences in concentration of DSP in gingival crevicular fluid relating to orthodontically induced inflammatory root resorption (OIIRR) at the initial stage of orthodontic treatment using self-ligating and conventional preadjusted brackets.	18 patients- three groups of equal size. 2 experimental groups received non-extraction orthodontic treatment using passive self-ligating or conventional preadjusted bracket.	Control group included patients without orthodontic treatment.	DSP	GCF was collected from five proximal sites of maxillary anterior teeth at intervals: pre-treatment (T0), and at three and 12 weeks after initiation of treatment (T1 and T2).ELISA	There were no significant differences in DSP levels within both experimental groups and the control group during T0-T1-T2 ($P \geq 0.05$). A significant difference of DSP concentration was found between the conventional preadjusted bracket and the control group at T2 ($P = 0.038$). However, it was thought to be clinically insignificant.	No significant difference in DSP concentration at the initial stage of orthodontic treatment with either self-ligating or conventional preadjusted bracket.
Mohd Zain MN et al. BMC Oral Health. 2022[14]	Clinical trial-Cross-sectional study	To compare DSPP detection using the univariate and multivariate analysis in predicting classification level of root resorption	30 patients in 3 group classified as normal, mild (n = 5), and severe groups of OIIRR (n = 11). The GCF samples- upper permanent central incisors in the normal and mild group while the upper primary second molars in the severe group.	Permanent central incisors of untreated subjects in the normal control group (n = 14)	Dentine sialophospho protein	Periopaper. ELISA utilizing univariate and multivariate analysis.	Multivariate analysis technique using partial least square-discriminate analysis has successfully improved in classification prediction for the normal and mild group at 0.88% accuracy and was able to predict normal and mild tooth resorption classes better than the univariate analysis.	Multivariate analysis helps to predict an early detection of tooth resorption complimenting the sensitivity of the univariate analysis.
Tan et al. BMC Oral Health (2024)[11]	Cross-sectional study	To determine the efficacy of a newly developed kit in DSPP detection and	Group RM consisted of 15 patients who were ongoing active orthodontic treatments with fixed appliances	Control (RO) 15 untreated patients who have not started orthodontic treatment and	Dentine sialophospho protein (DSPP)	Efficacy of a newly developed kit in dentine sialophospho protein (DSPP)	The DSPP concentrations measured using ELISA were the highest in the RS group (6.33±0.85 ng/mL) followed by RM group	The new kit was validated to detect the colour intensities of different severity of root resorptions. Most

		compare it with enzyme-linked immunosorbent assay (ELISA).	and radiographic evidence of mild root resorption of central incisors (< 2 mm)Mean age- 24.07 ± 2.71; group RS consisted of 15 paediatric patients (8–11 years old) with the primary second molars undergoing active physiological root resorption and radiographic evidence of severe root resorption (≥ 2 mm)	with no radiographic evidence of root resorption (central incisors). Mean age- 22.07 ± 8.30		detection and compare it with ELISA	(3.77±0.36 ng/mL) and the RO group had the lowest concentration (2.23±0.55 ng/mL). The new kit portrayed similar results as the ELISA.	of the responses to the survey were positive towards the new kit for being a safer and simpler method to detect apical root resorption.

A total of 12 studies were included in this systematic review, encompassing cross-sectional, prospective cohort, comparative, and clinical trial designs. These studies evaluated the association between dentin sialoprotein (DSP), dentin phosphoprotein (DPP), dentin sialophosphoprotein (DSPP), and the severity of orthodontic root resorption (ORR). Biomarker levels in gingival crevicular fluid (GCF) were quantified using methods such as enzyme-linked immunosorbent assay (ELISA), Western blot, and modified detection techniques. Sample sizes ranged from 6 to 74 participants, covering diverse age groups and orthodontic interventions.

This systematic review aimed to compare and analyze the existing evidence on the relationship between root resorption and the presence of specific biomarkers in GCF. Collectively, the studies highlight the potential of DSPP, DSP, and DPP as reliable biomarkers for the detection and monitoring of root resorption during orthodontic treatment. A summary of the main features of the included studies is presented in **Table 4.** The studies varied considerably in their design, sample size, methodology, and follow-up duration.

DSP consistently emerged as a promising biomarker. Kereshanan S et al.[21] found significantly higher DSP levels in resorbing primary molars compared to controls. Balducci L et al.[22] established a correlation between DSP concentration and root resorption severity. These findings are corroborated by Lombardo L et al.[23] who found that DSP detection using antibody-coated magnetic microbeads enhanced sensitivity. Mandour KAA et al.[24] reported significantly elevated DSPP levels in orthodontic and pediatric resorption cases compared to controls.

Uma HL and Nausheer A[25] investigated DSPP levels during orthodontic intrusion using a three-piece base arch and their results indicated that DSPP was upregulated during intrusion and may serve as a biomarker for root resorption in such mechanics.

DPP also exhibited strong potential as a biomarker. Mah J and Prasad N[15] observed the highest DPP levels in exfoliating primary teeth, followed by teeth undergoing orthodontic treatment, and the lowest in controls. Ghaleb S et al.[26] further demonstrated that continuous orthodontic force leads to higher DPP levels and larger resorption craters compared to intermittent force, highlighting the influence of force type on root resorption.

The use of multiple biomarkers might enhance diagnostic accuracy. Huang GY et al.[27] found positive correlation between root resorption volume and changes in CEMP-1 and DPP levels. This suggests that incorporating multiple tissue-specific biomarkers could give a more thorough evaluation of root resorption.

Progress toward clinical applicability was seen in the work of Tan JHS et al. (2024),[11] who validated a newly developed kit for DSPP detection, demonstrating its efficacy in differentiating root resorption severity and its positive acceptance among orthodontists. This finding emphasizes the potential for translating laboratory research into clinically applicable diagnostic solutions.

4.2. Risk of bias/ Quality assessment of selected Studies

A pair of observers (VA and PP) independently evaluated the included studies' quality using the Cochrane Collaboration risk of bias tool. Overall, the studies exhibit varying degrees of risk of bias. The Cochrane Handbook for Systematic Reviews of Interventions for Randomized Controlled Trials describes the Risk-of-bias VISualization (ROBVIS) (RoB 2).[28] The assessment covered five different areas of bias: A) bias resulting from the randomization process; B) bias resulting from a departure from the intended intervention; C) bias resulting from missing outcome data; D) bias in outcome measurement; E) bias in the selection of the reported result. Three risk categories—low, moderate and high risk—were employed to categorise the included studies. (**Figure 2** and **Figure 3**). The randomized controlled trial (Ghaleb S et al)[26] has some advantages in controlling for confounding factors through randomization, but they also have limitations related to blinding and sample size.

The ROBINS-I technique was utilized to assess the risk of bias among the observational studies as low, moderate, serious or critical.[29] Six studies showed a moderate risk of bias, although the other five had a substantial risk of bias, according to the assessment's overall results, which are displayed in **Figure 3**.

The observational studies generally have higher risks of bias due to potential confounding factors and limitations in participant selection and comparability. These constraints should be mindfully taken when analysing the findings and drawing conclusions about the relationship between GCF biomarkers and root resorption. In light of the variability of the methods, outcomes assessed in each study, and statistical approaches employed, meta-analysis was not carried out.

5. Discussion

Orthodontic root resorption is the most frequent and least desirable side effect of orthodontic treatment and is observed in 20% to 100% of orthodontic patients.[30] Severe cases, characterized by resorption exceeding 5 mm or up to one-fourth of the root length, are rare and occur in only 1% to 5% of patients.[31] Early observation of root resorption has been shown to predict more severe resorption with ongoing orthodontic treatment. Hence, precise identification of minor progressive root resorption in the initial stages of orthodontic treatment is essential to prevent more severe resorption in individuals who are vulnerable to it.[32] Although uncommon, more severe root resorption linked to orthodontic therapy can have serious clinical repercussions, including premature tooth loss and a reduced crown-to-root ratio which can cause

mobility of teeth. Consequently, it is critical to determine patients who are more likely to experience significant external root resorption so that the treatment plan can be altered.[32,33]

Currently, the gold standard for diagnosing and evaluating mineralized tissue resorption is cone-beam computed tomography.[34] However, the hazards posed by elevated radiation have led medical professionals to advise against its use for routine purposes in healthy patients. Basically, without a screening method, the frequently silent characteristic of root resorption can go undetected.

GCF analysis offers a non-invasive, safe, and sensitive way to identify individuals who are at elevated risk for root resorption, forecast their subsequent clinical course and prognosis, and optimize their treatment.[35] A plethora of research has been done in this field and candidate biomarkers have been suitably identified. The studies had the disadvantages of being animal studies, cross-sectional studies or studies with a duration of maximum six months. The outcome of these studies has proved certain biomarkers like Dentin sialoprotein to be associated with root resorption.[36]

The DSPP gene (located at 4q21) encodes dentin sialophosphoprotein (DSPP), which is processed by proteases into three distinct protein products: dentin phosphoprotein (DPP), dentin glycoprotein (DGP) and dentin sialoprotein (DSP).[37] Furthermore, it was observed by Yuan G et al[38] in 2017 that MMP-9 plays a crucial role in tooth development, and during dentinogenesis; DSP is a target of MMP-9. These proteins serve as key biomarkers, which is why this systematic review focuses on the relevant published literature pertaining to them.

6. Summary of Evidence

The objective of this literature review was to identify the influence and levels of dentin sialophosphoprotein (DSPP) in patients undergoing comprehensive orthodontic treatment. Despite great efforts to gather knowledge about this subject matter, the findings should be critically assessed. This is primarily due to the methodological quality of the studies and the limited number of relevant publications. There was one randomized controlled trial, while the other studies were observational, including both prospective and cross-sectional studies.

The effects of dentin sialoprotein and dentin phosphoprotein were examined in seven articles, while dentin sialophosphoprotein (DSPP) was specifically studied in five articles. The small sample sizes and short follow-up periods of the individual studies limit the ability to reliably estimate long-term effects. The overall quality of the non-randomized controlled trials (Non-RCTs) was moderate, necessitating careful interpretation of outcomes due to the high risk of bias. A thorough assessment of the diagnostic potential of gingival crevicular fluid (GCF) biomarkers for the early detection of root resorption (ORR) was not possible due to the significant heterogeneity among the studies. Nevertheless, the insights summarized provide a solid framework for starting reliable clinical trials in this vital area.

1192 papers were chosen for this systematic review using MeSH keywords and few hand-picked articles. Twelve publications were ultimately taken into consideration for this systematic review after thorough assessment utilizing inclusion and exclusion criteria to evaluate the impact of dentin sialophosphoprotein/Dentin sialoprotein/Dentin phosphoprotein as a biomarker for assessing orthodontic root resorption. Each study investigated the presence/level of DSPP/DSP/DPP found in gingival crevicular fluid (GCF) and done by ELISA.

6.1. Dentin phosphoprotein and dentin sialoprotein

The studies by Mah J and Prasad N, Balducci L et al, Mohd Zain MN et al, Tan et al. and Mandour KAA et al were cross-sectional studies.[11,15,22,24,39] The only randomized control trial was conducted by Ghaleb S et al.[26] Prospective studies were carried out by Huang GY et al, Kereshanan S et al and Adiwirya et al.[21,27,40]

Dentinal proteins are considered the best markers for diagnosing root resorption since areas of the cementum often undergo repair during orthodontic movement and thus are not strong indicators of root structure loss. Dentin, however, may not repair larger defects, particularly at the apex, making its loss a significant contributor to root structure loss.[41] Mah J and Prasad N[15] assessed the concentration of DPP in the GCF of 3 groups of patients- a control group, patients undergoing orthodontic treatment and subjects with physiologic root resorption of the second molars. The findings demonstrated a statistically significant difference between the orthodontic group and the control group, as well as between the control group and the group with physiologic root resorption. However, there was no discernible difference between the orthodontic group and the group with physiologic root resorption. The comparison of the three groups revealed that the group with physiologic resorption of the second molars had the highest concentration of DPP. Similar findings were also obtained by Balducci L et al.[22]: the group with severe root resorption had the highest DPP concentrations, followed by the group with mild resorption and the control group, which had the lowest concentrations. Other than that, the appearance of DPP in the control groups was somewhat unexpected and was obviously harder to explain because these teeth apparently were not structurally altered. Balducci L et al.[22] and Mah J and Prasad N[15] claim that the ELISA technique's sensitivity is the most likely justification. Other explanations, such as the fact that dentin is not a homogeneous tissue and that its protein components alter with age, are not precluded even though these studies had a moderate risk of bias. In conclusion, as DPP is primarily an organic, non-collagenous component of dentin, it may be a great biomarker of root resorption and is probably more

suggestive of the irreversible loss of root structure than cementum proteins.

Balducci L et al.[22] and Kereshanan S et al.[21], evaluated dentin sialoprotein. The concentration of this cytokine was significantly higher in the severe and mild root resorption groups than in the control group, according to the first study. Particularly in cases of severe root resorption, the peak is higher. The study by Kereshanan S et al.[21] however, compares the DSP concentrations in individuals receiving orthodontic treatment with those whose second primary molars are experiencing physiological root resorption. A statistically significant difference was seen between the study groups and the control group. Researchers have recognized the use of physiological root resorption as an appropriate model to investigate pathological root resorption, based on multiple investigations on dentin resorption. It is understood that the actual biochemical mechanism that occurs is essentially the same, even though the initiation method may vary.

In order to assess the degree of root resorption utilizing dentin phosphoprotein (DPP) levels in gingival crevicular fluid (GCF) under continuous versus intermittent orthodontic forces, Ghaleb S et al.[26] carried out a two-arm parallel split-mouth trial in 2021. The study involved eight patients needing bilateral upper first premolar extractions, totaling 16 premolars. For eight weeks, one premolar was subjected to a constant 150 g buccally directed force that was reactivated after 28 days. For the same amount of time, the contralateral premolar was subjected to an intermittent force of identical magnitude (21 days on, 7 days off). To quantify DPP levels, GCF samples were taken at the beginning, as well as during weeks 1, 3, 4, 5, and 8. At weeks 4 and 8, the continuous force group's DPP concentrations were considerably higher than those of the intermittent force group. The study observed that intermittent orthodontic force results in less root resorption than continuous force, and that DPP is a useful diagnostic biomarker for recognizing and tracking root resorption.

The studies by Huang GY et al.[27] and Adiwirya MSK et al.40[40] both explored biomarkers in GCF in relation to orthodontic root resorption during treatment, but with different focuses and methodologies. Huang's study[27] investigated the relationship between dentine phosphoprotein (DPP) levels and external root resorption under a constant orthodontic force, involving 11 participants and observed a positive correlation between levels of DPP at specific time points and volume of root resorption. In contrast, Adiwirya MSK et al.[40] examined dentin sialoprotein (DSP) levels in 18 patients using conventional and self-ligating brackets, and found no significant differences in DSP concentrations within groups over time, although a clinically insignificant difference was noted between the conventional bracket group and the control group at 12 weeks. Both studies highlight the complexity of identifying reliable biomarkers for orthodontic root resorption, emphasizing the need for further research with larger sample sizes and varied orthodontic protocols.

6.2. Dentin sialophosphoprotein

Dentin sialophosphoprotein (DSPP) was measured in the gingival crevicular fluid of orthodontic patients receiving treatment for eight to twelve months in 2014 by Sha H et al.[42] using ELISA in conjunction with spectrophotometry and electrochemistry. They found no significant difference between the methods but noted that electrochemistry had a lower detection limit, making it a reliable and sensitive method for detecting DSPP. In 2020, DSPP levels in GCF were evaluated by Mandour KAA et al.[24] as possible indicators of orthodontic root resorption. The study included 74 participants divided into orthodontic, pediatric, and control groups. DSPP readings were significantly greater in the pediatric and orthodontic groups when compared to the control group, suggesting DSPP as a potential biomarker for orthodontic root resorption. In 2022, Mohd Zain MN et al.[39] compared univariate and multivariate analysis techniques for detecting DSPP to predict root resorption levels. They found that multivariate analysis provided improved classification accuracy for detecting root resorption, enhancing early detection. Finally, in 2024, JHS Tan et al.[11] evaluated a new kit for detecting DSPP against ELISA. Their study involved 45 participants categorized by root resorption severity. The new kit showed high sensitivity and specificity, comparable to ELISA, and was well-received by orthodontists for being a convenient method for detecting apical root resorption.

7. Limitations

The studies' findings consistently support the potential of DSPP and its components as biomarkers for root resorption. Higher levels of these biomarkers are generally associated with active root resorption, and some studies demonstrate the ability to differentiate between resorption severity and force types. However, the studies also acknowledge limitations, such as variations in methodologies, potential influencing factors, and the need for further validation to establish baseline values and refine clinical applications. Additionally, the focus on published studies might introduce publication bias.

8. Conclusion

This systematic review demonstrates the potential of dentin proteins (DSP, DPP and DSPP) as biomarkers for monitoring orthodontically-induced root resorption. Based on the existing research, there is insufficient evidence to make robust recommendations for dentin proteins (DSP, DPP and DSPP) as biomarkers for monitoring orthodontically-induced root resorption, as the quality of evidence was low. Despite the advancements in detection methods, such as the use of ELISA combined with electrochemistry and multivariate analysis techniques, the studies exhibited significant heterogeneity in methodologies, sample sizes, and follow-up

durations. This variability limits the ability to perform quantitative synthesis and draw definitive conclusions. However, the evidence suggests that continuous monitoring of DSPP levels could provide valuable insights into the onset and progression of orthodontically-induced root resorption, guiding more effective management strategies in orthodontic practice. Future research with larger, well-designed clinical trials is essential to validate these findings and establish standardized protocols for using DSPP as a biomarker in clinical settings. The development of new diagnostic kits that are both accurate and user-friendly also holds promise for improving early detection and treatment outcomes for patients undergoing orthodontic treatment.

9. Source of Funding

None.

10. Conflict of Interest

None.

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