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CALPROTECTIN AS AN EMERGING INFLAMMATORY BIOMARKER IN PERIODONTITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Calprotectin is a neutrophil-derived inflammatory protein implicated in several chronic inflammatory diseases, including periodontitis. Its potential role as a biomarker for periodontal disease has gained increasing attention.
Aim: To systematically review the available evidence on the association between calprotectin and periodontal disease and evaluate its diagnostic and therapeutic significance.
Methods: A systematic search of PubMed, Scopus, Web of Science, and Google Scholar was conducted according to PRISMA guidelines. Fourteen human studies published between January 2016 and May 2026 assessing calprotectin levels in saliva, gingival crevicular fluid (GCF), serum, or blood in relation to periodontal disease was included.
Results: All included studies reported elevated calprotectin levels in periodontitis patients compared with healthy controls. Calprotectin concentration increased in periodontitis and showed positive correlations with clinical periodontal parameters, including probing pocket depth, clinical attachment loss, and bleeding on probing. Salivary calprotectin demonstrated good diagnostic performance, with reported ROC/AUC values ranging from 0.86 to 0.894. Additionally, calprotectin levels were associated with key periodontal pathogens and were significantly reduced following nonsurgical periodontal therapy in most intervention studies.
Conclusion: Current evidence suggests that calprotectin is a promising biomarker for the diagnosis, assessment of disease severity, and monitoring of treatment outcomes in periodontal disease.

INTRODUCTION

Periodontal disease is a chronic multifactorial inflammatory disorder characterized by the progressive destruction of the tooth-supporting tissues, including the gingiva, periodontal ligament, cementum, and alveolar bone. It develops as a consequence of a dysbiotic subgingival biofilm interacting with a susceptible host immune response. Although clinical parameters such as probing pocket depth (PPD), clinical attachment loss (CAL), bleeding on probing (BOP), and radiographic bone loss remain the gold standard for diagnosis, these measures primarily reflect past tissue destruction rather than current disease activity [1]. The search for reliable biomarkers capable of detecting active periodontal inflammation, predicting disease progression, and monitoring therapeutic outcomes has gained considerable attention in recent years. Among the numerous inflammatory biomarkers investigated, calprotectin has emerged as a promising candidate [2].

Calprotectin, also known as myeloid-related protein-8/14 (MRP-8/14) or S100A8/S100A9, is a heterodimeric calcium-binding protein predominantly expressed in neutrophils, monocytes, macrophages,

and epithelial cells. It accounts for approximately 60% of the soluble cytosolic protein content of neutrophils and is released during inflammatory responses [3]. Calprotectin functions as a damage-associated molecular pattern (DAMP) molecule and exerts its biological effects through activation of Toll-like receptor-4 (TLR4) and the receptor for advanced glycation end products (RAGE), thereby amplifying inflammatory signaling pathways [4].

Several studies have demonstrated elevated levels of calprotectin in saliva, gingival crevicular fluid (GCF), serum, and gingival tissues of individuals with periodontal disease [5]. Furthermore, reductions in calprotectin levels following nonsurgical periodontal therapy suggest its potential utility as a biomarker of treatment response [6]. Given the increasing number of studies evaluating calprotectin in periodontal disease, a comprehensive synthesis of the available evidence is warranted. Therefore, the aim of this systematic review was to evaluate the association between calprotectin and periodontal disease and to assess its diagnostic, prognostic, and therapeutic significance.

MATERIALS AND METHODS

Protocol and Registration: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [7] (PRISMA 2020) guidelines. The review protocol was registered with the International Prospective Register of Systematic Reviews (CRD420261414039).

Focused Question

According to the PICO framework:

Population (P): Individuals with gingivitis or periodontitis

Intervention/Exposure (I): Assessment of calprotectin (S100A8/S100A9; MRP-8/14) levels in biological samples

Comparison (C): Periodontally healthy individuals and after periodontal therapy

Outcome (O): Evaluation of differences in calprotectin levels between periodontal health and disease, assessment of the correlation between calprotectin concentrations and clinical periodontal parameters, determination of the diagnostic accuracy of calprotectin as a periodontal biomarker, and analysis of changes in calprotectin levels following periodontal therapy.

Information Sources and Search Strategy

A comprehensive electronic literature search was conducted using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases from January 2016 to May 2026 to identify relevant studies evaluating calprotectin in periodontal disease. The search strategy was developed using a combination of Medical Subject Headings (MeSH) terms, keywords, and Boolean operators. The following search terms were used: ("Calprotectin" OR "S100A8" OR "S100A9" OR "MRP8" OR "MRP14" OR "MRP-8/14") AND ("Periodontitis" OR "Periodontal Disease" OR "Periodontal Inflammation" OR "Gingivitis") AND ("Saliva" OR "Gingival Crevicular Fluid" OR "Serum" OR "Biomarker"). The search was supplemented by manual screening of reference lists from eligible articles to identify additional relevant studies.

Eligibility Criteria: Studies were considered eligible for inclusion if they were human clinical investigations, including cross-sectional, case-control, cohort, longitudinal, and clinical intervention studies that evaluated calprotectin, MRP-8/14, S100A8, or S100A9 in relation to periodontal disease. Only articles published in the English language were included. Studies were excluded if they were animal or in vitro investigations, narrative reviews, systematic reviews, case reports, conference abstracts, or lacked relevant periodontal clinical data necessary for evaluating the association between calprotectin and periodontal disease.

Data extraction and synthesis

Data extraction and synthesis were conducted systematically for all included studies. Data were extracted independently by two reviewers using a standardized form that captured information on the author and year of publication, study design, study population, sample size, periodontal disease classification, biological sample analyzed, biomarker evaluated, laboratory assessment method, and principal findings. Any disagreements were resolved through discussion and consensus. A qualitative narrative synthesis was undertaken to summarize and compare the evidence concerning calprotectin levels in periodontal health and disease, their association with clinical periodontal parameters, diagnostic accuracy, and changes following periodontal therapy.

RESULTS

Study Screening and Selection

The study screening and selection process was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA) guidelines. A total of 330 records were initially identified through database searching and manual screening, of which 67 duplicates were removed. After title and abstract screening, 223 records were excluded, and 40 full-text articles were assessed for eligibility. Following full-text evaluation, 26 articles were excluded, resulting in 14 studies being included in the qualitative synthesis .Figure 1 shows PRISMA Flow chart figure 01.

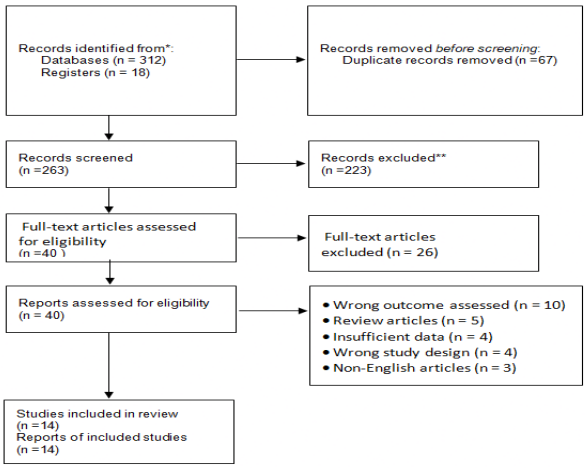

Figure 01: PRISMA Flow of Study Selection

Table 01 and 02 summarizes the characteristics and key findings of the studies included in this systematic review. The studies evaluated calprotectin and its related proteins (S100A8, S100A9, and MRP-8/14) in various biological samples, including saliva, gingival crevicular fluid, serum, and blood. Most studies reported significantly elevated calprotectin levels in individuals with periodontal disease compared with healthy controls. Furthermore, calprotectin levels were positively associated with clinical periodontal parameters, demonstrated promising diagnostic performance, and generally decreased following nonsurgical periodontal therapy, highlighting its potential as a biomarker for periodontal disease diagnosis and treatment monitoring.

Table 01: Characteristics and Key Findings of Included Studies (2016–2020)

Author (Year)	Study Design	Population	Sample Type	Method	Key Findings
Haririan et al. (2016)	Cross-sectional	100 patients (periodontitis, healthy controls)	Saliva, Serum	ELISA	↑ Salivary and serum calprotectin in periodontitis
Lira-Junior et al. (2017)	Cross-sectional	40 patients (aggressive periodontitis, gingiviti, healthy control)	Saliva, Serum	ELISA	↑ Serum calprotectin in aggressive periodontitis
Kajiura et al. (2017)	Cross-sectional	34 patients (periodontitis)	GCF	ELISA	↑ GCF calprotectin at inflamed periodontal sites
Shin et al. (2019)	Proteomic study	207 patients (periodontitis)	Saliva	Proteomics + ELISA	↑ Salivary calprotectin
Holmström et al. (2019)	Cross-sectional	436 patients (periodontitis)	Saliva	ELISA	↑ Salivary calprotectin
Karna et al. (2019)	Cross-sectional	326 patients (periodontitis)	Saliva	ELISA	↑ Salivary calprotectin in periodontitis;
Nemec et al. (2020)	Longitudinal	15 (orthodontic patients with periodontis)	Saliva	ELISA	↑ Salivary calprotectin and associated with periodontal pathogens

Table 02: Characteristics and Key Findings of Included Studies (2021–2026)

Author (Year)	Study Design	Population	Sample Type	Method	Key Findings
Kim et al. (2021)	Cross-sectional	149 patients (periodontitis)	Saliva, Blood, GCF	ELISA	↑ Calprotectin in periodontitis
Aadhithiyan et al. (2023)	Clinical intervention	20 patients (aggressive periodontitis)	GCF, Serum	ELISA	↓ Calprotectin after scaling and root planing

Menon et al. (2024)	Interventional	40 patients (healthy and periodontitis)	GCF, Saliva, Serum	ELISA	↓ Calprotectin after nonsurgical periodontal therapy
Popoca-Hernández et al. (2024)	Quasi-experimental	30 women with rheumatoid arthritis and periodontitis	Saliva, Serum	ELISA	↓ Calprotectin after nonsurgical periodontal therapy
Bayırlı et al. (2025)	Cross-sectional	165 patients (periodontitis)	Saliva	ELISA	↑ Calprotectin in periodontitis
George et al. (2025)	Longitudinal	10 patients (Stage III/IV periodontitis)	GCF, Saliva	ELISA	↔ No significant change in calprotectin after NSPT
Kajiura et al. (2026)	Cross-sectional	93 patients (periodontitis)	Saliva	LATIA	↑ Calprotectin in periodontitis

Table 03: Risk of Bias Assessment

Study	Selection Bias	Comparability Bias	Outcome Assessment Bias	Overall Methodological Quality
Haririan et al. (2016)	Low Risk	Low Risk	Low Risk	High
Lira-Junior et al. (2017)	Low Risk	Low Risk	Low Risk	High
Kajiura et al. (2017)	Low Risk	Low Risk	Low Risk	High
Shin et al. (2019)	Low Risk	Moderate Risk	Low Risk	High
Holmström et al. (2019)	Low Risk	Low Risk	Low Risk	High
Karna et al. (2019)	Low Risk	Moderate Risk	Low Risk	Moderate–High
Nemec et al. (2020)	Moderate Risk	Moderate Risk	Low Risk	Moderate
Kim et al. (2021)	Low Risk	Low Risk	Low Risk	High
Aadhithiyan et al. (2023)	Moderate Risk	Low Risk	Low Risk	Moderate–High
Menon et al. (2024)	Low Risk	Low Risk	Low Risk	High
Popoca-Hernández et al. (2024)	Moderate Risk	Low Risk	Low Risk	Moderate–High
Bayırlı et al. (2025)	Low Risk	Low Risk	Low Risk	High
George et al. (2025)	Moderate Risk	Low Risk	Low Risk	Moderate–High
Kajiura et al. (2026)	Low Risk	Low Risk	Low Risk	High

Risk of Bias Assessment

The methodological quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) [8], whereas intervention studies were evaluated using the Joanna Briggs Institute Critical Appraisal Tool**.** Table 2 shows risk of bias assessment. The studies were evaluated across three domains: selection bias, comparability bias, and outcome assessment bias. Selection bias assessed the adequacy of participant selection and representativeness of the study population, comparability bias evaluated the control of potential confounding factors, and outcome assessment bias examined the validity and reliability of biomarker measurement and outcome reporting. Each domain was classified as having low, moderate, or high risk of bias. Overall study quality was subsequently categorized as high, moderate-high, or moderate. Most included studies demonstrated a low risk of bias and high methodological quality, indicating reliable and consistent evidence regarding the association between

calprotectin and periodontal disease. Moderate risk was observed primarily in longitudinal and interventional studies due to smaller sample sizes, potential confounding variables, and limitations in study design.

DISCUSSION

Calprotectin (CLP) is highly expressed in several chronic inflammatory disorders, including inflammatory bowel disease [9], chronic bronchitis [10], rheumatoid arthritis [11], diabetes mellitus [12], and psoriasis [13]. Owing to its strong association with inflammatory activity, CLP has emerged as a reliable biomarker for assessing inflammatory responses and monitoring the effectiveness of anti-inflammatory therapies [14]. In recent years, considerable attention has been directed toward understanding its role in the pathogenesis of periodontal disease (PD) [15]. Increasing evidence supports the involvement of calprotectin (CLP) in the pathogenesis of PD, with altered CLP levels consistently reported in periodontitis individuals [16]. CLP and its subunits have been identified in various oral samples, including dental calculus, gingival crevicular fluid (GCF), and saliva. Several cross-sectional studies have demonstrated significantly elevated CLP concentrations in GCF, with S100A8 levels reported to be up to 20 times higher in patients with PD compared with periodontally healthy individuals[17]. Furthermore, CLP levels have shown positive correlations with inflammatory mediators such as prostaglandin E_2, interleukin-1β (IL-1β), collagenase, and aspartate aminotransferase [18, 19], as well as with key clinical periodontal parameters including bleeding on probing (BOP), probing pocket depth (PPD), and gingival index (GI) [20] [21].These findings suggest that CLP reflects both the inflammatory burden and clinical severity of periodontal disease, supporting its potential utility as a biomarker for disease assessment and monitoring.

The present systematic review evaluated 14 studies investigating calprotectin (S100A8/S100A9; MRP-8/14) in periodontal disease. Calprotectin is consistently elevated in periodontal inflammation, correlates with clinical disease severity, reflects microbial dysbiosis, and reduced levels following successful periodontal therapy. These findings support the growing recognition of calprotectin as a promising biomarker for periodontal diagnosis and treatment monitoring.

Haririan et al., [22] provided one of the strongest evidence supporting the diagnostic potential of calprotectin. Their study demonstrated significantly higher salivary and serum MRP-8/14 levels in periodontitis patients than in healthy controls. Notably, salivary MRP-8/14 achieved a receiver operating characteristic value of 0.86, indicating excellent diagnostic accuracy. Furthermore, calprotectin levels correlated positively with clinical periodontal parameters and the periodontal pathogen Treponema denticola. Lira-Junior et al., [23] who investigated serum and salivary calprotectin levels in individuals with aggressive periodontitis, gingivitis, and periodontal health. Their findings demonstrated significantly elevated serum calprotectin concentrations in aggressive periodontitis patients. Kajiura et al., [24] examined gingival crevicular fluid (GCF) calprotectin concentrations in periodontitis patients. They observed significantly higher calprotectin levels at inflamed periodontal sites compared with healthy sites within the same individuals. Unlike serum biomarkers, GCF biomarkers reflect site-specific periodontal activity. Therefore, this study provided strong evidence that calprotectin directly mirrors local periodontal inflammation and may serve as a sensitive indicator of active periodontal lesions.

Shin et al., [25] represented a major advancement in biomarker discovery. Using proteomic analysis followed by Enzyme Linked Immunosorbant Assay (ELISA) validation, the investigators identified S100A8 and S100A9 among the most significant proteins associated with periodontitis strengthening biological significance of calprotectin in periodontal disease. Holmström et al., [26] evaluated salivary S100A8/A9 concentrations in a large cohort of 436 participants. Their study demonstrated significant associations between calprotectin levels and bleeding on probing, periodontal pocket depth, and overall inflammatory burden. The study confirmed that calprotectin concentrations increase proportionally with disease severity, supporting its potential utility as a quantitative marker of periodontal inflammation. Karna et al., [27] evaluated salivary S100A8 and S100A9 in 326 Korean adults. They reported significantly elevated S100A8 concentrations in periodontitis patients and demonstrated moderate screening capability.

Nemec et al., [28] extended the understanding of calprotectin beyond traditional periodontal disease by evaluating salivary MRP-8/14 levels during orthodontic maxillary expansion therapy. The investigators observed increased calprotectin concentrations accompanied by increased Tannerella forsythia and Treponema denticola levels. Although the participants were not periodontitis patients, the study demonstrated the sensitivity of calprotectin to inflammatory changes within the oral cavity. These findings suggest that calprotectin may serve as a general indicator of oral inflammatory responses. Kim et al., [29], compared salivary, blood, and GCF biomarkers and identified salivary S100A8 as the best-performing marker for screening established periodontitis. The study also highlighted the feasibility of developing chair side salivary tests for periodontal screening.

Aadhithiyan et al., [30] investigated the effect of scaling and root planing on serum and GCF calprotectin levels in aggressive periodontitis patients. Elevated baseline concentrations were observed in both biological samples and significant reductions occurred following periodontal therapy. These findings provide evidence

that calprotectin is not merely associated with disease presence but also responds dynamically to therapeutic intervention. Therefore, calprotectin may function as a treatment-monitoring biomarker. Menon et al., [31] further strengthened this evidence by evaluating calprotectin levels in saliva, GCF, and serum simultaneously. Their study demonstrated significant reductions in all three biological compartments following nonsurgical periodontal therapy. This comprehensive approach showed that successful periodontal treatment can reduce both local and systemic inflammatory burdens. Such findings support the concept that periodontal therapy may exert beneficial systemic effects through modulation of inflammatory mediators such as calprotectin. Popoca-Hernández et al., [32] examined women with rheumatoid arthritis and periodontitis, a population characterized by chronic systemic inflammation. Following nonsurgical periodontal therapy, significant reductions in serum calprotectin concentrations were observed. This finding is particularly noteworthy because calprotectin is already recognized as a biomarker of rheumatoid arthritis activity. The study therefore suggests that periodontal treatment may contribute to improved systemic inflammatory control in medically compromised individuals.

Bayırlı et al., [33] evaluated salivary calprotectin concentrations in healthy individuals, gingivitis patients, and periodontitis patients. Their results demonstrated a clear stepwise increase in calprotectin levels across the disease spectrum.The observed correlation with periodontal clinical parameters further support its utility in assessing disease activity. George et al., [34] investigated longitudinal changes in calprotectin among patients with Stage III and Stage IV periodontitis and reduced calprotectin following treatment. Kajiura et al., [35] demonstrated excellent diagnostic performance of salivary calprotectin, with an AUC of 0.894, sensitivity of 91%, and specificity of 73% using rapid latex agglutination turbidimetric immunoassay (LATIA)

The present 14 studies demonstrated remarkable consistency with elevated calprotectin concentrations observed in saliva, gingival crevicular fluid, and serum of periodontitis patients. Positive correlations with probing pocket depth, clinical attachment loss, bleeding on probing, and microbial burden were consistently reported. Intervention studies further demonstrated reductions following periodontal therapy, supporting the utility of calprotectin as a dynamic biomarker of disease activity.

Despite these encouraging findings, several limitations remain. Most studies were cross-sectional, preventing causal inference. Variability in periodontal classification systems, laboratory assays, and sample collection protocols contributed to methodological heterogeneity. In addition, standardized diagnostic thresholds have not yet been established. Future multicenter longitudinal studies are necessary to determine optimal cutoff values and evaluate the predictive value of calprotectin for disease progression and recurrence.

Future research should focus on strengthening the clinical applicability of calprotectin as a periodontal biomarker by establishing standardized cutoff values in saliva and gingival crevicular fluid (GCF) for disease diagnosis and monitoring. The development of rapid point-of-care diagnostic kits incorporating calprotectin could facilitate chairside assessment of periodontal inflammation.

CONCLUSION

Calprotectin is a sensitive inflammatory biomarker that reflects both local periodontal inflammation and systemic inflammatory burden. Its presence in saliva, serum, and gingival crevicular fluid provides a non-invasive approach for disease detection and monitoring. The strong correlation between calprotectin levels and periodontal clinical parameters highlights its potential role in precision periodontal diagnostics and personalized patient management.

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CONFLICT OF INTEREST

NIL

INFORMED CONSENT

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Prospero Registration

AUTHOR CONTRIBUTION

RISHITHA PENUMAKA: Data collection, analysis, and manuscript drafting.

NAGENDRA BABU SURABHI: Conceptualization, supervision, and critical revision of the manuscript.

MANASWINI MUPANENI: Data interpretation and literature review.

NAGA JYOTHI CHADALVADA Methodology and validation.

DEEPA ANUMALA: Data curation and visualization.

HIMA SILPA CHERUKULA: Review, editing, and final approval of the manuscript.

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