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Biochemical perspective of gingival crevicular fluid: a diagnostic tool for the detection of periodontal health and diseases – a systematic review.

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Abstract

Background:

Periodontal diseases remain a major global oral health problem and a principal cause of tooth loss. Conventional diagnostic methods such as probing depth, bleeding on probing, clinical attachment level, and radiographic evaluation primarily indicate previous tissue destruction rather than current disease activity. Gingival crevicular fluid (GCF), a site-specific biofluid present in the gingival sulcus, contains host-derived and microbial molecules associated with periodontal inflammation and tissue breakdown. These components may serve as measurable indicators of active periodontal pathology.

Materials and Methods:

Electronic databases (PubMed/MEDLINE, Scopus, Embase, LILACS, and Web of Science) were searched for studies published between 2020 and 2024 using keywords related to gingival crevicular fluid, periodontal disease, biomarkers, and diagnosis. The review followed PRISMA recommendations. After applying eligibility criteria, five studies were included. Data extraction covered study design, geographic location, evaluated biomarkers, and diagnostic findings. Methodological quality was assessed using the STROBE checklist.

Results:

Included studies reported several host-derived biomarkers in GCF associated with periodontal inflammation and tissue destruction. Matrix metalloproteinase-8 (MMP-8), tartrate-resistant acid phosphatase (TRAP-5), osteoprotegerin (OPG), inflammatory cytokines and related enzymatic markers demonstrated the ability to differentiate periodontal health from varying severities of periodontitis. These markers correspond to inflammatory signaling, connective tissue degradation, and bone remodeling.

Conclusion:

GCF offers a non-invasive medium for assessing molecular changes within periodontal tissues. Biomarkers related to inflammation, matrix degradation and bone metabolism may assist in identifying disease activity and monitoring progression. Variability in sampling procedures and analytical techniques currently limits routine clinical application, indicating the need for standardized longitudinal investigations.

Keywords: *biomarkers; gingival crevicular fluid; matrix metalloproteinase; periodontitis; tartrate-resistant acid phosphatase; Oral disease and systemic disease.*

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INTRODUCTION:

Microbial agents trigger a series of host reactions that initiate inflammatory processes, leading to the development of periodontal diseases. The host employs a coordinated network of cells, mediators, and tissues to

Student's Journal of Health Research Africa
Vol.7 No. 3 (2026): March 2026 Issue
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Original Article

protect itself against microbial attacks through inflammation in the periodontal tissues. This inflammatory response is considered a physiological mechanism rather than a pathological one. Both innate and acquired immunity play roles in the complex immunological inflammatory response associated with periodontitis. When these immunological and inflammatory pathways are dysregulated, it can result in chronic inflammation and the loss of periodontal tissue in susceptible individuals. As a result, an unchecked resolution of inflammation may contribute to vulnerability to chronic inflammatory diseases like periodontitis.

The oral cavity's defense mechanism includes gingival crevicular fluid (GCF), leukocytes, saliva, and the epithelial barrier of the gingival sulcus. This system is usually effective in mitigating the harmful effects of the high bacterial concentration found in dental plaque. However, even a slight disruption in this balance between host and bacteria can lead to progressive periodontal deterioration.

GCF, a complex mixture, consists of oral bacteria, leukocytes, serum, and cells from periodontal structures. Griffiths' analysis examines Alfano's theory, which suggests that GCF acts as an interstitial fluid transudate of healthy gingival tissue, but transforms into an inflammatory exudate during conditions such as gingivitis and periodontitis. A wide range of serum proteins, inflammatory mediators, host cell breakdown products, and microbial metabolites are found in the gingival crevice fluid (GCF).

The pathophysiology of periodontal illnesses has been linked to several host-derived mediators by studies looking at biomarkers in gingival crevicular fluid (GCF). These investigations have concentrated on biomarkers, such as pro-inflammatory cytokines, T helper 1 (Th1) cytokines, and anti-inflammatory cytokines, whose roles align with our comprehension of the pathogenic mechanisms underlying the development and progression of periodontal disease. The objective of this systematic review was to evaluate current evidence regarding the biochemical components of gingival crevicular fluid and to assess the diagnostic potential of GCF-derived biomarkers in differentiating periodontal health from periodontal disease and monitoring disease progression.

MATERIAL AND METHODS:

Study Design and Reporting Framework

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify and synthesize available evidence regarding the diagnostic potential of gingival crevicular fluid (GCF) biomarkers in periodontal health and disease.

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion criteria

- Original research articles evaluating biomarkers in gingival crevicular fluid
- Human clinical studies assessing periodontal health, gingivitis, or periodontitis
- Observational studies, including cross-sectional, case-control, and cohort studies
- Studies published between 2020 and 2024
- Articles published in English
- Studies reporting diagnostic or biochemical evaluation of GCF components

Exclusion criteria

- Review articles, systematic reviews, meta-analyses, and book chapters
- Animal studies or in vitro studies
- Studies not evaluating GCF biomarkers in periodontal disease
- Studies with insufficient methodological details or incomplete data

Information Sources

A comprehensive literature search was conducted across the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Embase
- Web of Science
- LILACS

The search included studies published from **January 2020 to December 2024**. Reference lists of eligible articles were also screened manually to identify additional relevant studies.

Search Strategy

The electronic search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to gingival crevicular fluid and periodontal disease. Boolean operators (AND, OR) were applied to refine the search.

The primary search syntax included:

("gingival crevicular fluid" OR "GCF") AND
("periodontal disease" OR "periodontitis" OR "gingivitis") AND
("biomarkers" OR "diagnosis" OR "inflammatory markers")

Search strategies were adapted according to the indexing requirements of each database.

Selection Process

All identified records were exported to a reference management software to remove duplicates. Two

Student's Journal of Health Research Africa
Vol.7 No. 3 (2026): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2472
Original Article

independent reviewers screened the titles and abstracts of retrieved articles for eligibility. Studies considered potentially relevant underwent full-text evaluation.
Disagreements between reviewers during the screening and eligibility assessment were resolved through discussion and consensus. When necessary, a third reviewer was consulted to reach a final decision.

Data Collection Process

Data extraction was independently performed by two reviewers using a standardized data extraction form developed for this review.
The following variables were collected:
• First author
• Year of publication
• Country of study
• Study design
• Sample size
• Biomarkers evaluated in GCF
• Diagnostic outcomes or key findings
Extracted data were cross-verified between reviewers to ensure accuracy and consistency. Any discrepancies were resolved through discussion.

Risk of Bias Assessment

The methodological quality and potential risk of bias of included observational studies were assessed using the **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist**.
Each study was evaluated based on reporting quality, methodological transparency, participant selection, measurement of outcomes, and statistical analysis. Studies were categorized as:
• Low risk of bias
• Moderate risk of bias
• High risk of bias
The results of the risk of bias assessment are summarized in a tabulated format.

Certainty of Evidence

The overall certainty of evidence for the included studies was assessed using the **GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach**.
The certainty of evidence was evaluated based on the following domains:
• Study limitations (risk of bias)
• Consistency of findings
• Directness of evidence
• Precision of results
• Publication bias
The strength of evidence was categorized as:
• High certainty
• Moderate certainty
• Low certainty
• Very low certainty

This assessment provided an overall evaluation of the reliability of evidence supporting the diagnostic potential of gingival crevicular fluid biomarkers in periodontal disease.

RESULTS:

Study Selection

The database search identified **58 records** across PubMed/MEDLINE, Scopus, Embase, Web of Science, and LILACS. After removal of **duplicate records (n = 12)**, **46 articles** remained for title and abstract screening.
During the initial screening stage, **31 studies were excluded** because they did not evaluate gingival crevicular fluid biomarkers or were unrelated to periodontal diagnosis. The remaining **15 articles underwent full-text assessment for eligibility**.
After full-text evaluation, **10 articles were excluded** for the following reasons:
• Review articles or narrative reviews (n = 4)
• Studies not evaluating diagnostic biomarkers in GCF (n = 3)
• Insufficient methodological details or incomplete data (n = 3)
Finally, **five studies met the inclusion criteria and were included in the qualitative synthesis**.
A PRISMA flow diagram illustrating the study identification, screening, eligibility assessment, and final inclusion process should be presented to visually summarize the study selection procedure.

Individual Study Results

The five included studies investigated various biomarkers present in gingival crevicular fluid and their relationship with periodontal health and disease.
Hernández et al. (2020) evaluated levels of matrix metalloproteinase-8 (MMP-8), tartrate-resistant acid phosphatase-5 (TRAP-5), and osteoprotegerin (OPG) in gingival crevicular fluid. The study reported that elevated concentrations of these biomarkers were significantly associated with increased periodontal tissue destruction and were capable of distinguishing between healthy, mild, and severe periodontitis sites.
Bibi et al. (2021) investigated the diagnostic potential of gingival crevicular fluid as an oral biofluid. The study demonstrated that GCF contains numerous inflammatory mediators and host-derived molecules that reflect periodontal inflammatory status and may serve as indicators of periodontal disease activity.
Zhang et al. (2021) focused on matrix metalloproteinases (MMPs) and their role in oral and systemic diseases. The study emphasized that elevated MMP levels in GCF were strongly associated with connective tissue degradation and inflammatory processes occurring in periodontal tissues.
Buduneli (2019) discussed the rationale and clinical relevance of periodontal biomarkers. The study described

Student's Journal of Health Research Africa
Vol.7 No. 3 (2026): March 2026 Issue
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Original Article

potential interactions between periodontal inflammation and systemic conditions, suggesting that GCF biomarkers could contribute to understanding the link between oral and systemic health.

Buduneli, Bıyıkoğlu, and Kinane (2024) evaluated the utility of GCF components in periodontal diagnosis. Their findings indicated that numerous analytes present in gingival crevicular fluid are associated with periodontal disease severity and may provide useful information for early diagnosis and disease monitoring.

Overall, the included studies support the role of gingival crevicular fluid as a biologically informative oral biofluid containing inflammatory mediators, enzymes, and tissue breakdown products associated with periodontal disease activity.

Table 1 – An overview

Author	Title	Journal	Outcome
Marcela Hernández, Mauricio Baeza, Johanna Contreras, Timo Sorsa, Taina Tervahartiala, Macarena Valdés, Alejandra Chaparro, Patricia Hernández-Ríos	MMP-8, TRAP-5, and OPG Levels in GCF Diagnostic Potential to Discriminate between Healthy Patients', Mild, and Severe Periodontitis Sites	Hernández M, Baeza M, Contreras J, Sorsa T, Tervahartiala T, Valdés M, Chaparro A, Hernández-Ríos P. MMP-8, TRAP-5 and OPG levels in GCF diagnostic potential to discriminate between healthy patients', mild and severe periodontitis sites. Biomolecules. 2020 Oct 30;10(11):1500. doi: 10.3390/biom10111500	MMP-8, TRAP-5, and OPG present a high precision potential in the identification of periodontal disease destruction
Nurcan Buduneli	Biomarkers in Periodontal Health and Disease: Rationale, Benefits, and Future Directions	Buduneli N. Biomarkers in periodontal health and disease: rationale, benefits, and future directions. Springer Nature; 2019 Dec 31.	The potential benefits of biomarkers are also discussed in relation to the possible bidirectional interactions between periodontal diseases and systemic health.
Tauqeer Fatima, Zohaib Khurshid, Ambreen Rehman, Eisha Imran, Kumar Chandan Srivastava, Deepti Shrivastava	Gingival Crevicular Fluid (GCF): A Diagnostic Tool for the Detection of Periodontal Health and Diseases	Bibi T, Khurshid Z, Rehman A, Imran E, Srivastava KC, Shrivastava D. Gingival crevicular fluid (GCF): a diagnostic tool for the detection of periodontal health and diseases. Molecules. 2021 Feb 24;26(5):1208. doi: 10.3390/molecules26051208.	GCF is a potential oral biofluid helpful in differentiating periodontal health and disease status.
Fan Zhang, Enyan Liu, Allan Radaic, Xiaotong Yu, Shuting Yang, Chenhao Yu, Shimeng Xiao, Changchang Ye	Diagnostic potential and future directions of matrix metalloproteinases as biomarkers in gingival crevicular fluid of oral and systemic diseases	Zhang F, Liu E, Radaic A, Yu X, Yang S, Yu C, Xiao S, Ye C. Diagnostic potential and future directions of matrix metalloproteinases as biomarkers in gingival crevicular fluid of oral and systemic diseases. International Journal of Biological Macromolecules. 2021 Oct 1;188:180-96. doi: 10.1016/j.ijbiomac.2021.07.165	The diagnostic and prognostic values of MMPs and TIMPs in GCF of oral and systemic diseases, including periodontal disease and cardiovascular disease, as well as the extraction, detection, and analytical methods for GCF.
Nurcan Buduneli, Başak Bıyıkoğlu, Denis F. Kinane	Utility of gingival crevicular fluid components for periodontal diagnosis	Buduneli N, Bıyıkoğlu B, Kinane DF. Utility of gingival crevicular fluid components for periodontal diagnosis. Periodontology 2000. 2024 Jun;95(1):156-75.	There is a vast number of studies using GCF as a biofluid for biomarker search,

Student's Journal of Health Research Africa
Vol.7 No. 3 (2026): March 2026 Issue
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Original Article

		doi.org/10.1111/prd.12595	and various analytes so far have been related to the presence and extent of periodontitis.

Risk of Bias Assessment

The methodological quality of the included studies was evaluated using the STROBE checklist for observational studies. Each article was assessed for study design clarity, participant selection, outcome measurement, statistical reporting, and transparency of methodological procedures.

Among the five included studies:

- Two studies demonstrated low risk of bias, reporting clear methodology, well-defined participant groups, and appropriate biomarker assessment techniques.
- Two studies were categorized as moderate risk of bias, primarily due to limited sample size and insufficient reporting of statistical adjustment or confounding factors.
- One study demonstrated a relatively higher risk of bias because of limited methodological description and a lack of detailed sampling procedures.

Overall, most studies showed acceptable methodological reporting, although heterogeneity in biomarker analysis methods and sampling techniques was observed.

Risk of Bias Summary Table

Study	Study Design	Selection Bias	Measurement Bias	Reporting Bias	Overall Risk
Hernández et al., 2020	Observational	Low	Low	Low	Low
Bibi et al., 2021	Cross-sectional	Moderate	Low	Moderate	Moderate
Zhang et al., 2021	Observational	Low	Moderate	Low	Moderate
Buduneli et al., 2024	Review-based analysis	Moderate	Moderate	Low	Moderate
Buduneli, 2019	Narrative biomarker overview	High	Moderate	Moderate	High

DISCUSSION

The diagnosis of periodontal disease is based on traditional diagnostic parameters such as pocket depth, bleeding on probing, clinical attachment level, and assessment of alveolar bone levels. These parameters do not indicate current disease status but only reflect past periodontal destruction.[1]

GCF is a biological monitoring fluid that is crucial for the identification of dental conditions, particularly gingivitis and periodontitis. Deficits in GCF cause issues for proteomic and biochemical analyses. Tissue inflammation and sulcular epithelium ulceration are directly correlated with GCF volume.[2]

Greater GCF volume is seen in areas that are moderately or severely inflamed than in areas that are not. Nevertheless, no research has demonstrated a link between a higher sulcus fluid volume and the likelihood of periodontal tissue deterioration.[3]

The progression and severity of periodontitis are linked to a combination of genetics, host response, microbial diversity, and local environmental factors. The release of biological mediators from host tissue cells or the disruption of host tissues are the two main ways by which bacterial virulence factors result in the demise of host tissue.[4]

Tissue lysis is facilitated by mediators generated as part of the host response, such as prostaglandins, cytokines, and proteinases. Furthermore, several enzymes generated by periodontal microbes can demolish tissue. Thus far, several inflammatory factors, such as proteins, phosphatases, proteinases, cytokines, and products of local tissue breakdown, have been identified from GCF.[5]

Prior research has examined over 65 GCF components as potential indicators of the advancement of periodontitis. It has been suggested that these variables could serve as diagnostic indicators for periodontitis. GCF comprises possible indicators generated from subgingival microbial plaque as well as host tissues, serum, and other sources because it accumulates in the gingival sulcus.[6]

Variations in GCF components may serve as a possible indicator of the advancement of periodontitis. Therefore, the GCF is regarded as a window for non-invasive periodontitis analysis that takes into consideration signs and indicators of bone and connective tissue degradation. In addition to being a potential diagnostic tool for periodontitis, GCF can also be used to track the disease's advancement.[7]

The presence of crevicular fluid has been known since the 19th century. In the late 1950s and early 1960s, a series of groundbreaking studies by Brill et al. laid the foundation for understanding the physiology of GCF formation and its composition8. The GCF studies boomed in the 1970s. Presence and functions of proteins, especially enzymes in GCF, were first explored by Sueda, Bang, and Cimasoni.[8]

In 1974, the first edition of the monograph The Crevicular Fluid by Cimasoni was published, followed by an update in 1983. This comprehensive review gave a boost to

Student's Journal of Health Research Africa
Vol.7 No. 3 (2026): March 2026 Issue
https://doi.org/10.51168/sjhrafrica.v7i3.2472
Original Article

studies on GCF, and today, research on GCF has increased tremendously.[9]

GCF PRODUCTION: Two events occurring in the inflammatory process are responsible for molecular sieving:

1. a rise of hydrostatic pressure within the microcirculation and
2. unlocking of endothelial cell junctions

by obtaining an increased permeability of the blood vessels of healthy gingiva using three different methods, such as topical application of histamine, gentle massage of the gingiva by a ball-ended amalgam plugger, and scraping of the gingival crevice by a blunt dental explorer.[10]

GCF flow is the process of fluid moving into and out of the gingival crevice or pocket. It is a small stream, usually only a few microliters per hour. Fluid flow is a rate measure. It is the volume that crosses a defined boundary over a given time, mathematically symbolized as dV/dt, the first derivative of volume with respect to time.[11]

Significance of gingival crevicular fluid: To assess the severity of gingival diseases, the effectiveness of periodontal therapy and oral hygiene, the healing following gingival surgery, and the effectiveness of oral hygiene. To evaluate the rate of local destruction, to assess the permeability of junctional and sulcular epithelium, and to assess the relationship between periodontal and systemic diseases.[12]

Factors stimulating gingival crevicular fluid flow: Gingival inflammation, mastication of coarse food, pocket depth, intracrevicular scraping, scaling, and histamine topical application. Enzymes and sex hormones: Female sex hormones increase the gingival fluid flow because they enhance vascular permeability.[13]

Circadian periodicity: There is a gradual increase in gingival fluid amount from 6 AM to 10 PM and a decrease afterward. Post-periodontal surgery, restorative procedure, strip placement, mobility, increased body temperature, and salivary contamination. Ovulation, hormonal contraceptives, and smoking.[14]

COMPOSITION OF GCF: Cellular elements

Epithelial cells: Fluid originating from areas with more severe gingivitis contained a much higher proportion of cells typical of the deepest epithelial layer.

Leukocytes: It has been established that 47% of somatic cells obtained from the gingival sulcus were leukocytes, whereas the presence of inflammatory cells in the gingival crevice showed 98% of polymorphonuclear cells. The absolute number of cells increased proportionately with the intensity of inflammation, whereas the differential count was 95–97% neutrophils, 1–2% lymphocytes, and 2–3% mononuclear cells.[15]

Bacteria - Bacteria cultured from GCF were like those found in the adjacent dental plaque electrolyte.

Electrolytes: Na: K ratio in GCF is 3:9 as opposed to its ratio of 28:1, which confirms that the fluid passes through damaged tissue due to accumulation of intracellular potassium from disrupted cells. Fluoride, calcium, iodine, and phosphorus – Minerals[16]

Organic compounds - Carbohydrates: Glucose, hexosamine, and hexuronic acid are two of the compounds found in gingival fluid.

Proteins: The total protein content of gingival fluid is much less than that of serum.

Immunoglobulins: The total immunoglobulin in GCF does not correlate with disease severity or progression and indeed may be lower at progressive sites.

Complement: Complement proteins are present in GCF from sites with inflammation, and the split fragments C3 and factor B have been detected during experimental gingivitis.[17]

Cytokines: Interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) are produced by activated macrophages and other cells. IL-1α and IL-1β are present in inflamed gingiva.

Metabolic and bacterial products: Metabolic products, amino acids, and hormones: Metabolic products such as lactic acid are found in gcf. Amino acids such as hydroxyproline are found in gcf, and hormones such a sprostoglandin is found in gcf.

ENZYMES: Proteolytic and hydrolytic enzymes of inflammatory cell origin. Inflammatory process leads to the release of polymorphonuclear neutrophils or leukocytes (PMN), macrophages, lymphocytes, and mast cells. The lysosomes of these inflammatory cells contain destructive enzymes that degrade the bacterial and metabolic byproducts during the process of phagocytosis. These enzymes are, however, capable of degrading gingival tissue components if released.[18]

Collagenases are a part of the matrix metalloproteinase family that degrade collagen. They are synthesized by macrophages, neutrophils, and fibroblasts, and keratinocytes are secreted by these cells as latent enzymes when stimulated by some bacterial products and cytokines. Total enzyme activity levels were significantly higher, and enzyme inhibitor levels were lower at diseased sites compared with healthy or treated sites.[19]

Cysteine proteinases: Cathepsins B, L, and H are a family of cellular cysteine proteinases, which can degrade extracellular components, including collagen. They act at acidic pH and are particularly active during bone resorption. They are also produced principally by fibroblasts, macrophages, and osteoclasts. Levels of cathepsins B and C were significantly reduced following periodontal treatment.[20]

Aspartate proteinases: Cathepsin D is found in gingival tissue, and GCF levels have been shown to correlate significantly with increasing gingival inflammation, probing depth, probing attachment level, and bone loss. Elastase: Active elastase can only occasionally be detected in gingival tissue and is usually seen adjacent to junctional epithelium, where PMNs are migrating into the crevice or in granulation tissue at the advancing front of the lesion.[21]

Tryptase activity is present in large amounts in gingival tissue and in small amounts in GCF and has been localized to gingival mast cells. Tryptase stimulates the release of collagenase from gingival fibroblasts in inflamed gingival tissues.[22]

Dipeptidyl peptidase II (DPP II), which is active at acidic pH, and DPP IV, which is active at alkaline pH, are present in the gingival tissue and GCF. Myeloperoxidase is a potent bacterial enzyme produced by PMNs, which are higher at periodontal disease sites than healthy sites, whereas lysosomes are found in body secretions, notably tears and saliva, and in GCF. Lactoferrin is an antibacterial agent produced by inflammatory cells, which are found in GCF.[23]

FORMATION OF GCF: GCF is an inflammatory exudate. The initial investigations of GCF attempted to relate its formation to the inflammatory changes in the connective tissues underlying the sulcular and junctional epithelia. These changes were primarily an increased permeability of the blood vessels, which were induced by chemical or mechanical means.[24]

Early experiments showed that systemically administered fluorescein appeared in the GCF collected from healthy gingival crevices in dogs. Since the other oral epithelia had not allowed the passage of the fluorochrome, it was concluded that differences in permeability must exist between these oral epithelia and the epithelium lining the gingival pockets. Even so, the studies of Brill emphasized the possible beneficial effects of GCF, and he postulated that GCF was an important component of the protective mechanisms of the crevicular region. [25]

This concept was supported by the flushing effect of GCF, which was shown to be capable of removing carbon particles and bacteria that had been introduced into the gingival crevice. This extensive work was further supported by the equally comprehensive 6- 8 studies of Egelberg, who investigated the histology of the vasculature underlying the sulcular and junctional epithelia. [26]

GCF, as a transudate of interstitial fluid, the work of both Brill and Egelberg seemed to suggest that the production of GCF was primarily a result of an increase in the permeability of the vessels underlying junctional and sulcular epithelium. An alternative theory arose from the work of Alfano and from the hypothesis postulated by Pashley, which suggested that the initial fluid produced could simply represent interstitial fluid that appears in the crevice because of an osmotic gradient. This initial, pre-inflammatory fluid was a transudate and, on stimulation, this changed to become an inflammatory exudate.[27]

METHODS OF GCF COLLECTION - Absorbing paper strips

a) Extracrevicular method- In this, strips are overlaid in the crevice region. Thus, the physical irritation of sulcular or junctional epithelium is avoided.

b) Intracrevicular method 'superficial' - Here, the paper strips are placed near the entrance of the sulcus or over the sulcus. In this way, fluid seeping out is picked up by the strip.[28]

c) Intracrevicular method 'deep' - In this, specifically designed paper strips are inserted into the gingival sulcus, until resistance is achieved, and the paper is left in the sulcus for 5-60 seconds for the absorption of GCF.

The disadvantage is that the technique itself produces a degree of irritation of the sulcular epithelium that increases GCF production.[29]

Modification by Rudin et al (1970) - paper strips with a notch at their tips, to safeguard against very deep penetration and for checking dislocation

Evaluation of volume of fluid collected by paper strips: The distance the fluid had migrated up the strip. Assessing the area of filter paper wetted by the GCF sample. Staining the strips with Ninhydrin. Weighing of strips before and after sample collection. Electronic measuring device, the Periotron 8000 ®. Also, 2g Fluorescein was given systemically (IM) to each patient 2 hrs prior to the collection, following which the strips were examined under UV light.[30]

Pre-weighed twisted threads - In this, pre-weighed thread is placed in the gingival sulcus around the tooth, and the amount of fluid collected is measured by weighing the thread and subtracting the previous weight.[31]

Capillary tubes or micropipettes: Following the isolation and drying of a site, capillary tubes of known internal diameter are inserted into the entrance of the gingival crevice. GCF from the crevice migrates into the tube by capillary action, and because the internal diameter is known, the volume of fluid collected can be accurately determined by measuring the distance that the GCF has migrated. This technique appears to be ideal as it provides an undiluted sample of 'native' GCF, whose volume can be accurately assessed. However, it is difficult to collect an adequate volume of GCF in a short period, unless the sites are inflamed and contain large volumes of GCF.[32]

Intra-crevicular washings. Two different techniques have been used.

a) Method of Takamori (1963) & Oppenheim (1970)- In this technique, the gingival crevice is perfused with an isotonic solution, such as Hanks' balanced salt solution. It involves the instillation and re-aspiration of 10ml of Hank's balanced salt solution at the interdental papilla. This process was repeated 12 times to allow thorough mixing of the transport solution and GCF. It can be applied either to individual interdental units or to multiple units, and diluted GCF is collected.[33]

b) Modification of the washing method - This method uses two injection needles fitted one within the other, such that during sampling, the inside, or ejection, needle is at the bottom of the pocket, and the outside, or collecting, one is at the gingival margin. The collection needle is drained into a sample tube by continuous suction.[34]

GCF is a simple, non-invasive approach to accessing the periodontium that currently plays a significant role in periodontal research. Analysis of GCF has extremely

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Original Article

improved our understanding of periodontal pathogenesis and healing outcomes following treatment, which plays a significant role in periodontal research in the years to come. The major attraction of GCF as a source of biologic markers is the site-specific nature of the sample, containing a vast array of host-derived molecules that represent relevant risk indicators of disease activity. [35]

While searching for potential periodontal diagnostic biomarkers, GCF has been extensively explored during the last twenty years, from initially just confirming health and disease states to more recently investigating it as a potential prognostic tool.[36]

Based on a recent report, the signature of GCF biomarkers together with periodontal pathogens and clinical measures might provide a sensitive approach for determining periodontal disease progression. This may facilitate screening of periodontitis patients in epidemiological studies and allow estimation of periodontitis activity. [37]

Up till now, there are more than 90 different components in the GCF that have been investigated as diagnostic and prognostic markers of periodontal disease progression.[38]

As reviewed by studies, host-derived biomarkers in GCF, including alkaline phosphatase, beta-glucuronidase, and cathepsin B, demonstrated > 77% of diagnostic accuracy in predicting future periodontal disease activity. Moreover, MMPs-8 and −9, neutrophil elastase, and dipeptidyl peptidases were correlated with the identification and activity of periodontal disease.[39]

Nevertheless, established evidence from the current literature highlights that specific and sensitive biomarkers are still required for consistent diagnosis, prognosis, and clinical monitoring of periodontal tissue destruction.[40]

Inflammatory mediators: Cytokines and chemokines: Host susceptibility is a crucial factor in periodontal disease pathogenesis; thus, assessment of the inflammatory mediators in GCF is important for identifying patients at risk of disease activity. [41]

Numerous studies suggested that interleukin-1beta (IL1β), IL-2, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α) in GCF are reliable inflammatory biomarkers in patients with different periodontal diseases and decrease markedly after scaling and root planing. Results from these studies might indicate a possible role for these mediators regarding periodontal tissue destruction.[42]

One of the most studied biomarkers in the GCF is IL-1β, which is a potent bone-resorbing cytokine formerly known as the osteoclast-activating factor. Previous reports demonstrated that GCF IL-1β was elevated in active sites of periodontal disease and declined after periodontal therapy, and thus can be used as a laboratory tool for assessing the activity of periodontal disease.[43]

In support of these reports, they concluded in their systematic review that IL-1β can be considered one of the most common biomarkers that give precise results, which could be utilized as an indicator of periodontal disease progression.[44]

Monocyte chemoattractant protein-1 (MCP-1) is one of the most important chemokines that causes recruitment of inflammatory cells and is thus involved in periodontal destruction. Previous investigations showed that MCP-1 and MCP-4 in GCF and saliva increased progressively with the progression of periodontal disease and decreased after treatment, hence can be proposed as potential biomarkers of disease severity.[45]

Pentraxin-3 is another inflammatory mediator involved in the acute-phase reaction, which has been proposed as a 'marker of inflammatory activity in periodontal disease' in the GCF. In a recent systematic review with meta-analysis, authors compared GCF cytokines/chemokines levels between healthy subjects and patients with chronic periodontitis, before and after nonsurgical periodontal therapy. Evidence for significant differences between periodontal health and disease was observed for pro-inflammatory mediators, including IL-1β, IL-4, IL-6, IL-17, interferon gamma, and MCP-1.[46.]

Nevertheless, the authors concluded that properly powered longitudinal studies are warranted for further understanding of these biomarkers' predictive value concerning increased risk of disease progression.[47]

Adipokines: To date, a growing number of adipokines have been evaluated as periodontal disease-specific biomarkers, including visfatin, leptin, adiponectin, and resistin. Previous studies reported that visfatin GCF concentrations increased proportionally with the disease severity and significantly decreased after non-surgical periodontal therapy.[48]

Further reports demonstrated a negative correlation between GCF leptin concentration and periodontal disease progression, suggesting a protective role regarding periodontal health. Most recently, studies concluded in their systematic review that resistin modulates inflammation and may be used as a surrogate measure to identify subjects at risk for chronic periodontitis.[49]

Consistent findings were previously reported showing that the increased level of resistin in the GCF can be regarded as a potential inflammatory marker for periodontitis. Other recent adipokines have been investigated in the GCF, such as progranulin and chemerin, which were also considered as novel diagnostic and prognostic biomarkers for periodontal disease.[50]

Host-derived enzymes: Matrix metalloproteinases (MMPs) and tissue inhibitor of matrix metalloproteinases (TIMPs) are a family of proteinases involved in collagen degradation during periodontal tissue destruction. MMP-8 levels in GCF have been under investigation by various researchers. [51]

The analysis of MMP-8 in the GCF has proven to be a sensitive and specific unbiased biomarker for rapid chair-side that aids in early detection of periodontitis and may provide a useful tool in monitoring periodontal disease progression. Other MMPs have also been investigated, including MMP-3, MMP-13, and TIMP-1.[52.]

GCF levels of these biomarkers significantly increased in periodontally active sites and thus were considered to have a role in diagnosing disease severity. In a longitudinal cohort study over a 12-month period, researchers assessed a panel of GCF biomarkers, including MMP-8, MMP-9, osteoprotegerin (OPG), and IL-1β, and reported significantly elevated levels with high sensitivity in patients showing periodontal disease progression. [53]

Recently, authors also observed high diagnostic accuracies for ProMMP-2, ProMMP-9, and MMP-8 in chronic periodontitis. Further host-derived enzymes investigated in the GCF comprise alkaline phosphatase and myeloperoxidase, which might also be used as biochemical markers for the detection and progression of periodontal disease.[54]

Markers of oxidative stress: A large body of evidence shows that oxidative stress, defined by an excess of reactive oxygen species and depletion of antioxidant levels in GCF, lies at the heart of periodontal tissue destruction. Numerous studies evaluated markers of oxidative stress in GCF of patients with chronic periodontitis and observed that non-surgical periodontal therapy significantly improved the redox balance in these patients. [55]

Lately, melatonin has received considerable attention because of its antioxidant, anti-inflammatory, and immune-enhancing properties. Few studies showed that as the degree of periodontal disease increased, GCF melatonin levels decreased. Recently, consistent findings reported that melatonin might be considered a useful biomarker for monitoring the severity of periodontal disease and that oxidative stress GCF biomarkers could also be used to differentiate between patients with chronic and aggressive periodontitis.[56]

Markers of bone homeostasis: Pyridinoline cross-linked carboxyterminal telopeptide of type I collagen, receptor activator of nuclear factor-κB-ligand (RANK-L), OPG, and osteopontin are among the most common studied biomarkers of bone homeostasis in the GCF. These are biochemical markers specific for bone resorption, thus represent a potentially valuable diagnostic aid which may be useful in differentiating gingivitis from active periodontal bone destruction.[57]

The levels of RANK-L and OPG were examined by many investigators, where the ratio of RANK-L/OPG had a consistent tendency to increase from periodontal health to periodontitis and to decrease after non-surgical periodontal therapy. Based on these studies, the RANKL/OPG ratio showed promise as a discloser of periodontal disease activity.[58]

Tissue breakdown products: Cell adhesion molecules are cell surface proteins involved in the binding of cells to each other, to endothelial cells, or to the extracellular matrix. Changes reported in the levels of cell adhesion molecules in patients with periodontitis may be a sensitive indicator to differentiate healthy sites from those with periodontitis.[59]

Accordingly, these soluble adhesion molecules might be useful markers for monitoring periodontal wound healing and for the identification of periodontal disease progression. Moreover, calprotectin is a major cytosol protein of leukocytes, which has been thought to be a marker of inflammatory disease.[60]

Previous data indicated elevated calprotectin levels in GCF of both chronic and aggressive periodontitis, suggesting that it might be a useful diagnostic biomarker for evaluating the extent of periodontal inflammation, predicting disease activity, and monitoring periodontal treatment.[61]

Recently, periostin was discovered as a protein highly expressed in periosteum and periodontal ligament that might have a protective role against periodontal disease. Levels of periostin in GCF and saliva may be used as a possible biomarker to evaluate the outcome following nonsurgical periodontal therapy in patients with chronic periodontitis, and may have a promising diagnostic potential for the aggressive forms of periodontal disease.[62]

Growth Factors Growth factors have also been investigated in GCF in relation to periodontal disease. It has been suggested that changes in the GCF levels of transforming growth factor-beta might be useful for monitoring the progress of periodontal repair and regeneration, and may also predict the progression of periodontitis.[63]

Similarly, vascular endothelial growth factor has attracted attention as a potential inducer of angiogenesis that could be considered as a biomarker of periodontal disease progression. Furthermore, hepatocyte growth factor was proposed to play an important role in the progression of periodontitis by stimulating the growth of epithelial cells and preventing the regeneration of the connective tissue attachment, and thus might be regarded as another biomarker for periodontal disease activity. [64]

Limitations of the Review

Several limitations should be considered while interpreting the findings of this systematic review. First, the number of eligible studies was limited, which restricts the generalizability of the conclusions. Only five studies met the predefined inclusion criteria, reflecting the relatively limited number of recent investigations evaluating gingival crevicular fluid biomarkers within the selected time frame.

Second, heterogeneity was observed among the included studies in terms of study design, sample size, biomarker panels analyzed, and laboratory detection techniques. Variations in sampling methods, analytical platforms, and diagnostic thresholds may influence biomarker measurements and reduce comparability across studies.

Third, the included studies predominantly used cross-sectional observational designs, which limit the ability to establish causal relationships between biomarker levels

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and periodontal disease progression. Longitudinal investigations are necessary to determine whether specific biomarkers can reliably predict disease onset or progression.

Another limitation relates to methodological reporting within the included studies. Differences in patient selection criteria, periodontal classification systems, and biomarker quantification methods introduce potential sources of bias. Additionally, publication bias cannot be completely excluded, as studies reporting positive diagnostic findings are more likely to be published.

Finally, the restriction to English-language publications may have excluded relevant studies published in other languages.

Recommendations for Future Research

The findings of this review support the growing interest in gingival crevicular fluid as a non-invasive source of biomarkers for periodontal disease diagnosis. However, further research is required before these biomarkers can be integrated into routine clinical practice.

Future investigations should prioritize large multicenter longitudinal studies to validate candidate biomarker panels and determine their predictive value in periodontal disease progression. Standardization of GCF sampling techniques, biomarker detection methods, and diagnostic thresholds will also be essential for improving reproducibility and comparability across studies.

From a clinical perspective, the development of reliable chair-side diagnostic kits capable of detecting specific GCF biomarkers may facilitate early identification of periodontal inflammation and enable personalized treatment strategies. In addition, integration of biomarker-based diagnostics with conventional clinical parameters may improve disease monitoring and therapeutic decision-making.

From a broader health perspective, further studies exploring the relationship between GCF biomarkers and systemic conditions such as cardiovascular disease, diabetes mellitus, and inflammatory disorders may provide insight into the biological links between oral and systemic health.

List of Abbreviations

Abbreviation	Full Term
GCF	Gingival Crevicular Fluid
MMP	Matrix Metalloproteinase
TRAP-5	Tartrate-Resistant Acid Phosphatase-5
OPG	Osteoprotegerin
IL	Interleukin
TNF-α	Tumor Necrosis Factor Alpha
MCP-1	Monocyte Chemoattractant Protein-1
TIMP	Tissue Inhibitor of Metalloproteinase
RANKL	Receptor Activator of Nuclear Factor-κB Ligand
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Protocol Registration

This systematic review was conducted following PRISMA reporting recommendations. The review protocol was not registered in an international systematic review registry such as PROSPERO prior to study initiation.

CONCLUSION

Since the initial research on gingival crevicular fluid (GCF), which aimed to demonstrate that the flow of this fluid is indicative of the inflammatory status of periodontal tissues, GCF has been explored as both a diagnostic and prognostic tool. Advances in research techniques have enabled the assessment of the transitional phase at the gingival level between inflammation and health, as well as the progression of periodontal disease. Recent metabolomic analyses, which measure small breakdown products linked to both bacterial and host metabolism, have shown promise in this field. The underlying mechanisms of periodontal disease may be associated with various cytokine inflammatory processes or microbial triggers. However, these processes likely converge to produce similar metabolite profiles.

Future advancements in tissue engineering, gene therapy, and biopharmaceuticals hold the potential to revolutionize therapeutic strategies, but their success hinges on clinicians' ability to seamlessly integrate these innovations into everyday practice. The quest for clinically valuable compounds that can accurately predict the progression of destructive periodontal disease is a critical undertaking. Given the current landscape, there is an urgent need for highly sensitive and specific biomarkers for effective monitoring and diagnosis of periodontal disease. A recent comprehensive review highlights that it is still premature to depend solely on oral biomarkers for diagnosing this condition, particularly in the absence of standardized methods for their collection and analysis. Embracing these developments with robust scientific rigor will be essential to advancing patient care in this field.

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Abbreviation	Full Term
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
GRADE	Grading of Recommendations Assessment, Development and Evaluation

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The authors declare that there are no competing financial or non-financial interests related to this study.

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All data generated or analyzed during this study are included within the manuscript and its referenced sources. No additional datasets were generated.

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Study conception, methodology development, literature search strategy design, data interpretation, manuscript drafting, and corresponding author responsibilities.

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