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Inflammatory Cytokines in Saliva as Biomarkers of Periodontal Disease

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ABSTRACT

Periodontal disease is just prevalent chronic inflammatory condition of the supporting tissues of the teeth, with well-established associations with systemic health outcomes. The shortcomings of conventional clinical diagnostic methods have driven research into non-invasive salivary biomarkers, particularly inflammatory cytokines. This current review synthesises current evidence regarding the diagnostic utility of salivary cytokines in periodontal disease. A review of 18 studies found that a multi-cytokine panel is better than single-marker approaches, showing that the disease is caused by more than one thing. A 2026 study looking at samples from different parts of the body showed much higher levels of certain chemicals (IL-8 and IL-17A) in people who had gum disease. IL-6 and IL-1β also increased. Researchers also found a link between Megasphaera and salivary IL-8 in gingivitis. The available evidence suggests that measuring the levels of certain proteins in the saliva (called cytokines) could be useful in precision dentistry. However, this would only be possible if the collection and analysis of the samples were done in the same way every time.

Keywords: Periodontal disease; saliva; cytokines; biomarkers; IL-1β; IL-8; IL-17A; gingivitis; inflammation.

1. INTRODUCTION

Periodontitis is a common long-lasting disease that causes the tissues that support your teeth to be destroyed, bit by bit. It is thought to affect around 10% of people around the world, which makes it one of the most common mouth diseases. In Germany, we know that one in five people aged 35–44 and one in two people over 65 have moderate gum disease. Getting older is a well-known risk factor for disease getting worse (Gottschalk et al., 2026; Sanz et al., 2020). Periodontitis is now seen as a disease that can have consequences for other parts of the body. It has been linked to heart disease, metabolic issues, rheumatoid arthritis, autoimmune conditions, cancer, and problems during pregnancy (Konig et al., 2016).

Currently, we diagnose gum disease by looking at things like how deep the gums are (PD), the gums' attachment to the bone (CAL), whether there is bleeding when we check, and X-rays to assess bone loss (Bertolini et al., 1986). These steps are well-known, but the person doing the test (the examiner) has a big impact on the results. The test also needs professional equipment, and mostly shows past

damage, not current disease activity. Importantly, they cannot spot the disease before it causes permanent damage to the tissue (Yaghmoor, 2025; Gottschalk et al., 2026). So there is a strong need for tests that can do this in a way that is easy to understand and that do not require any kind of surgery.

Saliva shows potential as a way to diagnose gum disease. It contains gingival crevicular fluid (GCF), which is a liquid produced at the gum line that shows if the gums are inflamed (Chapple et al., 2018). Saliva collection is simple, non-invasive and suitable for large-scale screening, unlike venepuncture or biopsy. Saliva contains a range of measurable inflammatory proteins, including cytokines that are linked to how bad the disease is. A review of the research by Yaghmoor (2025) confirmed that biomarkers in saliva can provide valuable information for diagnosing gum disease. Combining different panels of biomarkers often works better than using a single marker on its own.

This review provides a thorough, evidence-based analysis of inflammatory proteins in saliva as diagnostic markers of gum disease. After reviewing the research done by Yaghmoor (2025) and the study by Gottschalk et al., (2026), we have looked at the roles of key cytokines, how well they can be used to make diagnoses, the problems with the methods used, and what they could mean for patients.

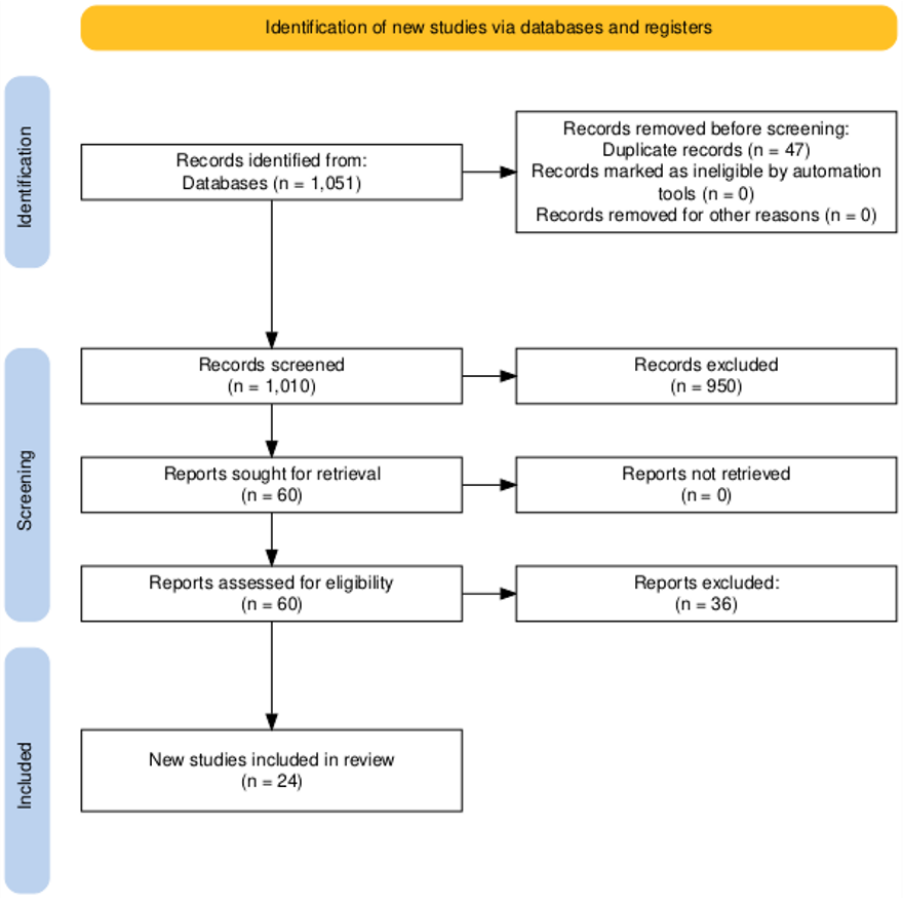

Figure 1. Search and selection process to identify relevant studies.

2. REVIEW METHODS

This review summarizes the evidence regarding the use of salivary inflammatory cytokines as a diagnostic tool for periodontal disease. A search and selection process was used to identify relevant studies.

Search Strategy and Databases: A broad search of publications from January 1997 to February 2026 was conducted across several databases. The search terms included a combination of controlled vocabulary and free-text keywords, such as "periodontal disease," "salivary biomarkers," "cytokines," "IL-1β," "IL-6," "IL-8," "IL-17A," and "TNF-α." These terms were connected using Boolean operators (AND/OR). The reference indexes of the retrieved reports were manually screened to identify additional eligible studies. Study

Duration and Inclusion Period: To capture the latest clinical evidence, we restricted the search to studies published between January 2000 and February 2026.

Inclusion and exclusion criteria: Studies were retained if they reported the measurement of at least one inflammatory cytokine in saliva or gingival crevicular fluid (GCF) (IL-1β, IL-6, IL-8, IL-17A or TNF-α) in relation to a clinically defined periodontal diagnosis (health, gingivitis or periodontitis). Both cross-sectional and longitudinal human studies were eligible. Studies were excluded if they lacked a clinical periodontal outcome, did not report cytokine concentrations, were animal or in vitro studies lacking translational relevance, or were case reports, commentaries, or conference abstracts lacking original data.

Study Selection Process: Records identified through the database search were preferably screened by title and abstract to remove duplicates and clearly irrelevant studies. The remaining documents were assessed against the inclusion and exclusion criteria described above. This process is outlined in the PRISMA flow diagram (Figure 1), which describes the number of analyses identified, screened, excluded (with reasons), and included in the final synthesis.

Data Extraction and Synthesis: Data from each included study were extracted and organized into the following categories: analysis design, sample size, participant diagnostic groups, saliva versus GCF sampling method, cytokines measured, analytical method (e.g., ELISA), and key statistical results. Due to the heterogeneity of the study designs, cytokine panels, and outcome measurements, a narrative synthesis approach was taken instead of a meta-analysis.

3. RESULTS AND DISCUSSION

The change from healthy gums to gum disease is caused by a big change in the bacteria under the gum tissue. These bacteria go from gram-positive aerobic bacteria to gram-negative anaerobic bacteria. In a group of 60 people, Gottschalk et al., (2026) showed that people with periodontitis had 50% fewer Actinobacteriota and Proteobacteria than healthy people. However, there were significantly more Bacteroidota, Fusobacteriota, and Spirochaetota bacteria in periodontitis. In healthy samples, Rothia and Streptococcus were the most common types of bacteria, but their numbers went down as the disease got worse. A classification model identified Tannerella forsythia, Fretibacterium species, and Rothia as the strongest predictors of clinical attachment loss — a pattern consistent with the "red complex" model of periodontal pathogenesis (Gottschalk et al., 2026).

Metagenomic analyses also showed higher levels of bacterial genes, lipids and amino acids in people with the disease. These were linked to the genera Porphyromonas, Tannerella, Fusobacterium and Prevotella (Gottschalk et al., 2026). These organisms produce substances that activate the immune system, mainly lipopolysaccharide (LPS) and peptidoglycan fragments. These substances trigger a immune and cell response in the mouth, which eventually causes irreversible alveolar bone loss. This is a defining feature of advanced periodontitis.

The body's natural defences recognise microbial components and start a process that leads to the destruction of tissue. This is what causes periodontitis. The bacterial lipopolysaccharide (LPS) is a structural component of the outer membrane of gram-negative periodontal pathogens, and peptidoglycan fragments derived from gram-positive species engage pattern recognition receptors — principally Toll-like receptors (TLRs) — on macrophages, dendritic cells, and gingival fibroblasts. This interaction triggers the transcription of pro-inflammatory genes and the release of a broad array of cytokines and chemokines into the periodontal microenvironment (Gottschalk et al., 2026).

The first mediators released are IL-1β and TGF-β1. IL-1β is a strong cytokine that's produced by activated macrophages and monocytes. It controls the body's inflammatory response. TGF-β1 is linked to tissue repair and immune control, otherwise it can cause inflammation. It causes bone loss in the jaw by promoting the growth of bone-breaking cells and stunting the growth of bone-building cells (Gottschalk et al., 2026). These cytokines create an inflammation that supports the immune system.

IL-8 (CXCL8) is the main substance that attracts neutrophils in the gums. Released in high concentrations by gum cells and tissue cells in response to IL-1β signals and direct bacterial stimulation, IL-8 creates a chemical gradient that attracts circulating neutrophils into the gum and tissue. IL-8 is special because it is very stable in inflamed gum tissue (periodontal tissues) where there is no ongoing bacterial stimulation. It can be found there for several weeks (Papapanou et al., 2018). Once they have been recruited, neutrophils release molecules that break down tissue, including matrix metalloproteinases (MMPs) — particularly MMP-8 (collagenase-2) and MMP-9 (gelatinase B) — as well as reactive oxygen species (ROS) and neutrophil extracellular traps (NETs). The body's initial reaction to bacteria is to release certain cells called 'neutrophils'. These help to fight off infection. However, if the bacteria that cause gum inflammation (called 'dysbiotic biofilm') are not dealt with, the body's own cells can be damaged as well (Gottschalk et al., 2026).

The actions of IL-1β, IL-6 and TGF-β1 work together to create a environment where new CD4+ T cells can become Th17 helper cells. When everything is normal, Th17 cells protect mucosal surfaces, like the mouth, by making antimicrobial peptides and helping to coordinate a response by neutrophils to pathogens outside the body. However, when they are constantly activated — as they are in severe gum disease — Th17 cells can cause a lot of tissue damage. Large amounts of IL-17A are produced, which causes special cells in the mouth (gingival fibroblasts and osteoblasts) to produce more pro-inflammatory chemicals and enzymes. IL-17A also directly causes the formation of new bone cells (osteoclasts) by increasing the expression of a protein called RANKL on certain immune cells and bone cells. Increased activity of the osteoclasts leads to the gradual and mostly irreversible destruction of the alveolar bone, which is the defining pathological endpoint of advanced periodontitis (Gottschalk et al., 2026). The Th17-mediated amplification loop is therefore a vital and self-sustaining process that leads from the initial innate immune response to the chronic adaptive immune destruction seen in severe periodontal disease (Engebretson and Kocher, 2013).

A substance called interleukin-1β is one of the most thoroughly studied substances that cause inflammation in gums. It is produced by cells called macrophages and monocytes when they are faced with a microbial challenge. It is one of the first steps in the process that leads to gum disease. Basically, IL-1β gets epithelial cells to produce IL-6 and IL-8, activates certain proteins, starts to break down connective tissue, increases a substance that causes inflammation (Hajishengallis, 2015; Hajishengallis and Lamont, 2012). All of these things are directly linked to the destruction of gums and bone loss.

A review of 18 studies by Yaghmoor (2025) found that IL-1β levels are consistently higher in patients with periodontal disease. This establishes IL-1β as one of the most useful individual biomarkers for diagnosing periodontal disease. IL-1β is a useful diagnostic tool on its own, but it works even better when used with other tests. Gottschalk et al., (2026) confirmed this in a group of 60 people divided into three groups: those with healthy gums, those with gingivitis, and those with moderate chronic periodontitis. IL-1β levels were 5.1 times higher in people with periodontitis than in those with healthy gums, and 3.7 times higher than in people with gingivitis. These differences weren't statistically significant ($p = 0.052$; age-adjusted $p = 0.051$), probably because of our small sample size ($n = 20$). IL-1β is the main inflammatory agent, and the levels of these chemicals in the saliva show what the disease is like and how bad it is. IL-1β is the main inflammatory agent. Saliva levels of these chemicals show what the disease is like at the time of testing. These levels vary from person to person and can be affected by other illnesses.

Interleukin-6 is a cytokine produced by macrophages, fibroblasts, and endothelial cells in reaction to upstream IL-1β signaling. This makes it a secondary amplifier of the inflammatory response in the gums. The periodontium is a part of the body that helps support teeth. IL-6 is a key player in the process that leads to the formation of bone cells that break down teeth, as well as the maturation of B-cells (a type of immune cell) and the body's response to inflammation.

A pattern in the results was seen in the three groups of patients. This pattern was confirmed using a statistical test ($p = 0.036$). People with gum disease were more than six times more likely to have a detectable IL-6 signal than people with healthy gums. This was after adjusting for age (OR = 6.57) (Gottschalk et al., 2026). The test can still provide a useful result even when the levels of certain molecules (cytokines) in the saliva are low. This is often the case with IL-6, where the levels are usually very low or very high.

Interleukin-8 (also called CXCL8) is created by certain cells in the mouth, like gingival epithelial cells, fibroblasts, and macrophages. These cells make the interleukin-8 in response to bacterial LPS and other signals of pathogens. This substance is the main thing that attracts neutrophils in the gums, which connects the bacteria under the gum tissue to the body's natural defenses. Gottschalk et al., (2026) found that IL-8 was the cytokine that increased the most in saliva in their study. People with periodontitis had about twice as much IL-8 in their saliva as people without periodontitis ($p = 0.021$).A "cytokine" is a protein that helps control inflammation in the body. Tumor necrosis factor-alpha (TNF-α) is one of these proteins. It is produced by cells called macrophages and monocytes. TNF-α activates the vascular endothelium, makes neutrophils work better, increases IL-1β and IL-6 production, and directly causes bone loss via RANK/RANKL signaling.

Interleukin-17A is made mostly by Th17 lymphocytes, innate lymphoid cells, and neutrophils. It has two roles in causing periodontal disease. It protects by creating antimicrobial peptides and bringing in neutrophils. It also causes tissue to break down and makes more osteoclasts.

Since IL-17A was found in less than 60% of the samples, Gottschalk et al., (2026) studied it as a binary outcome. There were big differences in how well they could be detected across all diagnostic groups in both the global chi-square test ($p = 0.018$) and the chi-square trend test ($p = 0.005$) (Tonetti et al., 2017). One difference had one of the largest effect sizes (Cramer's V) among all the immunological parameters they looked at. The chances of finding IL-17A in periodontitis patients compared to healthy people was 13.93 times higher (95% CI: 1.01–192.12) (Kassebaum et al., 2014). After reviewing the results, researchers found that the study had

78.5% power for IL-17A. This supports the validity of the findings (Gottschalk et al., 2026). Saliva can contain a protein called IL-17A, which can indicate that a person has gum disease or Th17 immunity.

Tumor necrosis factor-alpha (TNF-α) is an inflammatory cytokine produced by cells like macrophages and monocytes. It is also produced by certain cells in inflamed periodontal tissues (Graves, 2008; Graves & Cochran, 2003). At the cellular level, TNF-α activates a pathway called nuclear factor kappa B (NF-κB) signaling. This is a central place where genes are controlled, and it controls the expression of numerous inflammatory mediators. TNF-α and IL-1β work together to sustain and amplify the periodontal inflammatory response (Dinarello, 2009). It causes blood vessels to widen, allowing white blood cells to leak into the gum tissue. It also increases the activity of a type of white blood cell called a neutrophil, which helps fight infection but can also damage nearby tissue. TNF-α has a direct effect on the alveolar bone through the RANK/RANKL/OPG axis. It increases the expression of a protein called RANKL on cells that form bone, while decreasing another protein called osteoprotegerin (OPG). Osteoprotegerin is the decoy receptor that normally counterbalances RANKL. TNF-α shifts the bone remodeling equilibrium toward resorption. TNF-α also causes the body to produce more MMPs, which speeds up the breakdown of collagen fibers in the periodontal ligament (Graves, 2008).

Gottschalk et al., (2026) found no significant differences in TNF-α levels in the saliva of healthy individuals, those with gingivitis, and those with periodontitis. This apparent difference between the biological importance of TNF-α and its limited use in diagnosing conditions using saliva is probably due to several factors. TNF-α is quickly broken down from cell tops by a protein called ADAM17. This process creates a water-soluble form of TNF-α that TNF receptors in the blood quickly inactivate. Because of this, the amount of TNF-α in a person's body can change a lot and is short-lived (Giannobile et al., 2000). A 2025 review by Yaghmoor confirmed that patients with periodontal disease have higher levels of TNF-α in their saliva. However, the other health problems, such as smoking regular cigarettes, having type 2 diabetes, and having other health conditions at the same time, can affect the levels of TNF-α in saliva (Yaghmoor, 2025). These confounders make it hard to use TNF-α as a single salivary marker for periodontal disease.

Yaghmoor's 2025 review looked at data from 18 studies (out of a total of 1,051) and showed that multi-cytokine panels are better than single-marker assays for diagnosing periodontal disease. Periodontal disease is a condition where different factors work together to cause it. It is also a complex condition where different parts of the body's immune system are involved. The disease has different stages, and each stage is caused by different things. IL-8 and IL-1β are mainly active during the early phase of the immune system's response to a foreign substance or infection; IL-6 increases and maintains inflammation through a process called the acute phase response; IL-17A marks the involvement of a type of immune cell called Th17 cells, which is associated with the formation of bone-eating cells called osteoclasts; and TNF-α serves as a amplifier of local inflammatory signals throughout the body (Kolls and Linden, 2004).

Gottschalk et al., (2026) talk about this biological complementarity explicitly, noting that given the many factors involved in periodontal inflammation and the fact that people vary a lot in their salivary cytokine levels, a single biomarker is unlikely to be effective enough for diagnosis. A group of different immune system chemicals (IL-1β, IL-6, IL-17A, and IL-8) is suggested as a better way to see how the body's immune system is responding to a disease. This can help find the disease earlier. Table 1 shows the main evidence that was used to identify the major salivary cytokine biomarkers.

Table 1. Salivary biomarkers in periodontal disease: integrated evidence from primary and corroborating studies.

Cytokine	Yaghmoor 2025	Gottschalk 2026	Corroborating evidence	Primary pathological role
IL-1β	Consistently elevated in 18 studies; high individual diagnostic value	5.1-fold increase in periodontitis vs. healthy; borderline p = 0.052	Ebersole 2013: healthy baseline ~7.24±7.69 pg/mL; Miller 2006: 11.3–15.4-fold increased odds, 45-fold with MMP-8; Arias-Bujanda 2019: sensitivity 78.7%, highest of all single markers	Initiates cytokine cascade; RANKL/bone resorption
IL-6	Elevated in chronic and aggressive periodontitis	Significant trend in detectability (p = 0.036); OR 6.57 periodontitis vs. healthy	Arias-Bujanda 2019: sensitivity 72.0%; Ramseier 2009: correlated with pathogen load in longitudinal cohort	Osteoclastogenesis; acute phase response

IL-8 (CXCL8)	Elevated; inconsistent specificity in some reviews	Significant twofold elevation (p = 0.021); correlation with Megasphaera in gingivitis	Kinney 2011: component of biomarker/pathogen signature predicting disease progression (71% active vs. 76% stable, p<0.0007)	Neutrophil recruitment; early innate response
IL-17A	Elevated in aggressive/destructive forms	Significant trend (p = 0.005); OR 13.93 periodontitis vs. healthy	No independent corroborating data identified among added sources	Th17 activation; osteoclastogenesis
TNF-α	Elevated across studies; more variable	No significant difference across groups	Confounded by smoking, diabetes per Yaghmoor 2025; not among top-5 biomarkers in Arias-Bujanda 2019 panel	Systemic amplification; RANKL induction
MMP-8 (added marker)	Not primary focus	Not measured	Arias-Bujanda 2019: sensitivity 72.5%, specificity 70.5%; Miller 2006: 45-fold risk increase combined with IL-1β	Collagenase-2; connective tissue degradation

Salivary biomarker research has employed two principal sample types: GCF and whole saliva. GCF is produced locally at the site of inflammation and directly reflects the extent of periodontal tissue involvement; cytokine concentrations in GCF are substantially higher than in whole saliva. For site-specific diagnosis, GCF sampling using calibrated filter paper strips (Periopaper) provides the most accurate and localised cytokine profile.

Earlier studies by Yaghmoor (2025) and Gottschalk et al., (2026) support these findings. These studies substantially strengthen the evidentiary basis of this review beyond its two primary sources.

Ebersole et al., (2013) established a specific reference range for IL-1β concentrations in the saliva of periodontally healthy individuals, reporting values of approximately 7.24 ± 7.69 pg/mL. The baseline offers a useful benchmark for interpreting the increase in periodontitis patients, though it did not reach statistical significance. Miller et al., (2006) found that higher salivary IL-1β levels increased the odds of periodontal disease. Elevated IL-1β and MMP-8 levels increased the risk of periodontal disease 45-fold. The greater impact size shows that the marginal non-significant IL-1β finding of Gottschalk et al., (2026) is probably due to the small sample size. This finding supports a larger IL-1β signal that Yaghmoor (2025) found through a review of 18 studies.

A more recent meta-analysis (Arias-Bujanda et al., 2019) via a systematic protein-biomarker synthesis) corroborates this pattern, identifying IL-1β as the salivary marker with the highest applicability for differentiating periodontitis from gingivitis, with an observed effect size of 73.5 pg/mL between groups. Taken together, three independent quantitative sources—Ebersole et al., (2013), Miller et al., (2006), and subsequent meta-analytic work—confirm this finding.

Yaghmoor (2025) and Gottschalk et al., (2026) both used a single-time-point selection method. They captured how the disease looked at a specific moment, but not how it changed over time. Kinney and their team spent 12 months studying 100 people to solve a problem. The researchers used protein arrays for 14 pro-inflammatory and bone-turnover markers, as well as qPCR-based pathogen detection. Their method of organizing the samples into groups based on how similar they were identified three different profiles of biomarkers and pathogens. Participants with high salivary biomarker levels and a high biofilm load showed active periodontal disease progression in 71% of cases. In contrast, those with low biomarker and biofilm levels remained stable in 76% of cases. This association with disease severity was highly significant (p < 0.0007). This additional proof adds a part of the study that looked at what might happen in the future. This part was not included in the design of Gottschalk et al., (2026). While Gottschalk et al., (2026) demonstrated that IL-8 and IL-17A can differentiate between periodontitis and health at a single point in time, the data of Kinney et al., (2011) show that a similar biomarker/pathogen signature can predict future disease activity before clinical progression becomes evident. This suggests the real potential of salivary cytokine panels in predictive, as well as diagnostic, dentistry (Yoshizawa et al., 2013).

Ramseier et al., (2009) reinforce the multi-marker rationale advocated by both anchor studies by identifying direct correlations between subgingival pathogen load and host-response biomarkers (Socransky et al., 1998). They used data drawn from the cohort that Kinney et al., (2011) later analyzed. These findings provided early mechanistic support for the combined pathogen–cytokine profiling strategy that Gottschalk et al., (2026) later operationalized through their dual-matrix design, which links salivary IL-8 to Megasphaera

abundance in gingivitis. The convergence of these studies, despite a 17-year gap, the use of different cohorts, analytical platforms, and statistical approaches.

The most significant challenge to the analytic approach of using a single marker comes from the work of Arias-Bujanda et al., (2019), Yaghmoor (2025), and Gottschalk et al., (2026) - they used data from five biomarkers (IL-1β, IL-6, MMP-8, MMP-9, and hemoglobin) to make a summary of how well different tests can identify periodontitis. They found that IL-1β was the best at identifying periodontitis, with a sensitivity of 78.7%. MMP-8 was 72.5% sensitive, and IL-6 was 72.0% sensitive. The specificity ranged from 70.5% (MMP-8) to 81.5% (MMP-9). It's important to note that there isn't one specific high-quality biomarker that can be used on its own for medical purposes. This finding supports Yaghmoor's (2025) claim that testing multiple cytokines is better than testing just one. The ceiling on single-marker performance explains why Gottschalk et al., (2026) found TNF-α alone to be uninformative. However, no differences were observed despite TNF-α's role in RANKL-mediated bone resorption. No single inflammatory mediator, no matter how important it is biologically, can explain the full range of immune responses in periodontal disease.

Future Perspectives

Salivary biomarkers have a lot of potential to become a key part of next-gen precision dentistry, even with the methodological challenges that still need to be sorted out. Instead of relying on cytokines alone, a broad-spectrum multi-analyte strategy incorporating MMPs, oxidative stress markers, and nucleic acid-derived targets is recommended because it's better suited to the heterogeneous, multi-factorial nature of periodontal pathology. We've already passed the proof-of-concept testing on miniaturized point-of-care platforms that can measure IL-1β and IL-8 in tiny amounts of saliva. This means we're close to being able to use them in the clinic.

4. CONCLUSION

The evidence we reviewed shows that certain proteins in your saliva, like IL-8 and IL-17A, can effectively diagnose and measure the severity of periodontal disease. An integrated multi-cytokine panel approach tends to show better diagnostic performance compared to any single marker. There's a new connection between certain proteins in your saliva and the microbes in your mouth. This could be a way to spot disease early on, but we need to confirm it. To get this done, we'll need to standardize how we collect and analyze saliva. We'll also need to do some rigorous studies over time to make sure everything's working right. And we'll have to develop some validated algorithms that can be used at the point of care.

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Informed consent

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Ethical approval

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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