Salivary Galectin-9 Elevated in Primary Sjögren's, Lacks Disease Activity Correlation

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The identification of objective, non-invasive biomarkers for primary Sjögren's disease (pSS) remains a clinical challenge, particularly for assessing local glandular involvement and immune activity. A recent observational cross-sectional study found elevated salivary galectin-9 levels in pSS patients compared to healthy controls, yet these levels did not correlate with established disease activity scores or patient-reported symptoms.1

KEY TAKEAWAYS

- The Pivot: Salivary galectin-9 is elevated in pSS, suggesting a role in local glandular immune processes.
- The Data: Salivary galectin-9 levels were significantly higher in pSS patients (N=34) compared to healthy controls (N=34), but showed no significant associations with disease activity scores after correction for multiple comparisons.1
- The Action: Salectin-9 is not currently a useful biomarker for assessing pSS disease activity or symptom burden in clinical practice.

Primary Sjögren's disease is a systemic autoimmune condition characterized by chronic inflammation of exocrine glands and diverse clinical manifestations.1 The need for objective, non-invasive biomarkers that reflect local glandular involvement and disease-related immune activity persists.1

Sjögren's disease primarily affects women, with a female-to-male ratio as high as 9:1, and typically manifests in middle age. Its prevalence is estimated to be between 0.1% and 0.5% of the adult population. The disease is characterized by lymphocytic infiltration of the lacrimal and salivary glands, leading to sicca symptoms such as dry eyes (xerophthalmia) and dry mouth (xerostomia). Beyond glandular involvement, patients can experience extraglandular manifestations affecting various organ systems, including the joints, skin, lungs, kidneys, and nervous system. The heterogeneous nature of primary Sjögren's disease, coupled with the variability in disease progression and response to therapy, underscores the challenge in its management and the critical need for reliable biomarkers.

Study Design and Findings

An observational cross-sectional case-control study included 34 patients fulfilling the 2016 ACR/EULAR classification criteria for primary Sjögren's disease and 34 healthy controls.1 The study was conducted between December 2024 and February 2025.1 Unstimulated whole-saliva samples were collected in the morning using the passive drool method.1 Salivary galectin-9 concentrations were measured via enzyme-linked immunosorbent assay.1 Disease activity and symptom burden were assessed using validated indices.1 Receiver operating characteristic analysis was performed to evaluate discriminatory performance.1

The patient cohort was carefully selected to ensure homogeneity based on the established ACR/EULAR criteria, which include objective measures of ocular and oral dryness, presence of autoantibodies (anti-Ro/SSA and anti-La/SSB), and histopathological evidence of focal lymphocytic sialadenitis in minor salivary gland biopsies. Healthy controls were age- and sex-matched to minimize confounding factors. Saliva collection followed standardized protocols to ensure sample integrity and minimize diurnal variations. The enzyme-linked immunosorbent assay (ELISA) technique employed is a widely accepted method for quantifying protein concentrations in biological fluids, providing a robust measure of galectin-9 levels. Disease activity was assessed using tools such as the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), which capture both objective clinical manifestations and patient-reported symptoms, respectively. These indices are crucial for a comprehensive evaluation of disease impact.

Salivary galectin-9 levels were significantly higher in patients with primary Sjögren's disease compared with healthy controls.1 However, the study observed no significant associations between salivary galectin-9 levels and disease activity scores after correction for multiple comparisons.1 Furthermore, no significant associations were found with patient-reported symptoms, autoantibody profiles, Schirmer test results, or minor salivary gland biopsy findings.1 Salivary galectin-9 demonstrated limited discriminative ability between patients and controls.1

Galectin-9 is a tandem-repeat type galectin known to play a role in immune regulation, including T-cell apoptosis and modulation of inflammatory responses. Its elevation in primary Sjögren's disease suggests its involvement in the local immune dysregulation characteristic of the condition, potentially reflecting the ongoing inflammatory processes within the salivary glands. However, the lack of correlation with established disease activity markers, such as ESSDAI or ESSPRI, indicates that while galectin-9 may be a marker of immune activation, it does not appear to track the overall systemic disease burden or the severity of patient-reported symptoms. Similarly, its independence from autoantibody profiles (e.g., anti-Ro/SSA, anti-La/SSB), which are key diagnostic and prognostic markers, further limits its utility as a comprehensive biomarker. The Schirmer test, which measures tear production, and minor salivary gland biopsies, which provide histological evidence of inflammation, are direct indicators of glandular function and pathology. The absence of correlation with these measures suggests that salivary galectin-9 may not directly reflect the extent of glandular damage or dysfunction.

Limitations and Next Steps

The study's cross-sectional design limits the ability to infer causality or track changes over time. The sample size of 34 patients and 34 controls is relatively small. While salivary galectin-9 levels were elevated, their lack of correlation with established disease activity markers and patient-reported outcomes suggests limited utility as a standalone biomarker for monitoring disease progression or treatment response. The authors concluded that salivary galectin-9 levels were elevated in primary Sjögren's disease and may be associated with local glandular immune processes.1 They recommend further prospective studies to determine the clinical relevance of these findings.1

The relatively small sample size may have limited the statistical power to detect subtle associations, particularly after correction for multiple comparisons. A larger cohort would provide more robust statistical insights and potentially reveal correlations that were not evident in this study. The cross-sectional nature also precludes an understanding of how galectin-9 levels fluctuate with disease flares, remission, or in response to therapeutic interventions. Longitudinal studies are essential to determine if galectin-9 could serve as a prognostic marker or a marker of treatment efficacy. Furthermore,

the study focused solely on unstimulated whole saliva. Future research could explore galectin-9 levels in stimulated saliva or other biological fluids, such as tears or serum, to provide a broader perspective on its systemic and local involvement. Investigating the specific cellular sources of galectin-9 within the salivary glands and its precise immunomodulatory functions in the context of Sjögren's pathogenesis could also shed light on its clinical significance. Combining galectin-9 measurements with other emerging biomarkers or panels of biomarkers might enhance its diagnostic or prognostic value, addressing the complex and heterogeneous nature of primary Sjögren's disease.

CLINICAL IMPLICATIONS

The persistent search for reliable, non-invasive biomarkers in primary Sjögren's disease highlights a critical gap in current diagnostic and monitoring strategies. While the elevation of salivary galectin-9 in pSS patients is an interesting biological observation, its failure to correlate with established disease activity scores or patient-reported symptoms means it offers no immediate practical benefit for clinicians. This study reinforces that a biomarker's presence does not automatically equate to clinical utility; correlation with disease progression or treatment response is paramount for adoption into practice.

For patients, the promise of a simple saliva test to monitor their condition remains elusive. The current reliance on subjective symptom assessment, autoantibody profiles, and invasive biopsies underscores the need for more objective measures. Pharmaceutical companies developing treatments for pSS should note that novel biomarkers must demonstrate clear associations with clinically meaningful endpoints to gain traction, both for trial stratification and post-market monitoring. Without such correlations, even statistically significant differences in biomarker levels are unlikely to influence prescribing patterns or guideline recommendations.

This research, while methodologically sound within its scope, serves as a reminder that the path from biological discovery to clinical application is often long and fraught with null results. Future research should focus on longitudinal studies with larger cohorts, exploring galectin-9's role in specific disease subsets or its potential as part of a multi-biomarker panel, rather than as a solitary indicator.

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