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Saliva: An Emerging Adjunct Biomarker for Psoriasis –Trends, Scope and Relevance

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ABSTRACT:
Psoriasis is a widely prevalent chronic immuno-inflammatory dermatological disease resulting from a complex and dynamic interplay of genetic, environmental, and immunological aetiologies. It manifests as characteristic erythematous psoriatic plaques visible to the naked eye, but prognostic biomarkers for disease monitoring and therapeutic effectiveness are still absent. Saliva is a biological fluid that, besides being critical to maintaining oral homeostasis, harbors various salivary microbiota and inflammatory markers. It can be easily collected, stored, and analyzed. Oral fluids offer an excellent advantage for biomarker study as they are non-invasive and fast techniques. Studies showed that the saliva of healthy individuals and those with psoriasis had differences in the levels of inflammatory cytokines, immunoglobulin A, and anti-oxidant biomarkers. In GCF, individuals with psoriasis showed higher levels of S100A8, IL-18, and sE-selectin than healthy individuals, independent of periodontal status. Oxidative stress(OS) is one of the pathogenetic factors of psoriasis. Thus levels of ROS and anti-oxidants can also become important factors in diagnosis.

Keywords: Psoriasis, Saliva, Biomarker

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INTRODUCTION

Psoriasis, a prevalent and persistent skin condition affecting approximately 125 million people worldwide, is characterized as an immune-mediated inflammatory disorder. This complex disease entity results from interactions between genetics, the immune system, and environmental factors. The core pathological feature in psoriasis is the excessive proliferation of keratinocytes, leading to the formation of distinct, well-defined, scaling, and erythematous skin patches[1]. These patches emerge as a result of disrupted keratinocyte differentiationand excessive proliferation of keratinocytes, in conjunction with the presence of diverse inflammatory cellsand the development of new blood vessels. Patients often experience recurring episodes throughout their lives, and treatment can frequently lead to improvement, albeit with few instances of spontaneous remission. Furthermore, an expanding body of research has established associations between psoriasis and various comorbidities, including cardiovascular and periodontal conditions (Yamanaka et al., 2021; Boehncke et al., 2022).

Gathering clinical and experimental data from literature, strongly suggests that the immune system occupies a pivotal and vital position in the development of the disease. Psoriasis was long regarded as a condition driven by T helper type 1 (Th1) immune responses, but researches has revealed that the interleukin (IL)-23/Th17 cell axis is of utmost importance in the pathogenesis of psoriasis (Grozdev et al., 2014; Gaffen et al., 2014).

The primary approach to diagnosing psoriasis primarily centers on the clinical evaluation of skin lesions, given the absence of clearly established diagnostic criteria. At present, the most widespread and effective clinical means for identifying psoriasis is the histopathological examination of a skin biopsy specimen. Nevertheless, this procedure is invasive and may not clearly reveal pathological changes during the initial stages of psoriasis. Consequently, in the path for diagnosis of psoriasis, there appears a pressing demand for development of some diagnostic techniques or identification of some biomarkers that are not only easy to perform but are reliable with high sensitivity and specificity.

Of the various bodily fluids suitable for identifying psoriasis biomarkers, the utilization of saliva is particularly notable due to its non-invasive and rapidly available nature (Villanova et al., 2021; Valenzuela et al., 2013; Ganzetti et al., 2016). Therefore, in this present review, we aim to consolidate an in-depth exploration of current research focused on using saliva as a tool for the study of psoriasis

SIGNIFICANCE OF SALIVARY BIOMARKERS IN PSORIASIS

Saliva, produced by the salivary glands, serves as more than just a vital component in maintaining oral equilibrium. It houses an array of biological substances, including the salivary microbiota and inflammatory markers, and participates in immune responses. What makes saliva particularly advantageous as a diagnostic tool is its non-invasiveness and the lesser need for highly specialized equipments to collect it in comparison to blood. As a result, scientific endeavors have shifted their focus towards harnessing the potential of this easily manageable biological fluid—saliva (Jiménez et al., 2022; Zalewska et al., 2013)

The recognition of specific biomarkers in saliva and their eventual incorporation into clinical settings represents a highly ambitious goal among contemporary researchers. In recent years, numerous studies have been conducted to identify salivary biomarkers for both oral and systemic diseases, including psoriasis, employing diverse protocols and cutting-edge technologies. Individuals with psoriasis have unveiled notable disparities in their molecular, immunological, and microbial composition of

saliva, as well as variations in saliva secretion, when compared to healthy controls. Additionally, various salivary inflammatory markers such as TNF, IL and CRPs, salivary immunoglobulins such as IgA and IgG have been studied by various authors in psoriatic patients. Nevertheless, despite these efforts, an autonomous prognostic marker for psoriasis remains elusive (Jiménez et al., 2022; Zalewska et al., 2013).

The role of salivary biomarkers in psoriasis is of increasing interest in research and clinical practice. Salivary biomarkers, which are measurable substances or indicators in saliva, serve several significant functions like diagnosis, for disease monitoring, evaluating the treatment effectiveness and also in early detection of comorbidities. In this present review, we aim to consolidate an in-depth exploration of current research focused on using saliva as a tool for the study of psoriasis.

Table 1: List of Salivary Biomarkers and Psoriasis from Available Literature

Inflammatory markers	**Oxidative stress markers**	**Salivary Immunoglobulins:**	**Salivary c omponents**
TNF- β, IFN-α, IL IL-1β MCP-1 CRP Haptoglobin Neutrophil gelatinase-associated lipocalin (NGAL)	NO Nitrotyrosine Peroxynitrite	IgA Beta 2-microglobulin Lysosyzme	Sodium ions Potassium ions Chloride ions Alpha amylase (sAA) levels

INFLAMMATORY MARKERS

In alignment with the inflammatory nature of psoriasis, numerous studies have shed light on an imbalanced cytokine profile associated with this condition. Researchers have reported decreased levels of cytokines like IL-1,4,5 &10, alongside elevated levels of various cytokines like TNF-α , IL-2,6,8,12,23,23R, and LIF-1 (Villanova et al., 2013; Liu et al., 2013). These findings have led to the hypothesis that psoriasis primarily results from an atypical immune response. Further, specific studies focused on saliva have revealed that patients with psoriasis exhibit abnormal elevation of TNF-α, IL-2, and interferon-gamma in both unstimulated and stimulated saliva, while interleukin-10 (IL-10) content is notably lower (Skutnik-Radziszewska et al., 2020) This cytokine profile mirrors the imbalances seen in psoriatic skin lesions, supporting the theory of a Th1/Th2 cell imbalance. Moreover, elevated salivary IL-1β levels in patients with psoriasis activity (Skutnik-Radziszewska et al., 2020), suggest that measuring the salivary IL-1β levels, could potentially offer a non-invasive approach to monitor disease progression in psoriatic individuals.

Furthermore, increased TGF-β1 and MCP-1 in both saliva and serum among psoriasis patients suggest an association between psoriasis and the oral mucosa (Ganzetti et al., 2016; Mastrolonardo et al., 2007). The salivary levels of C-reactive protein (CRP) were significantly increased in psoriasis patients, reflecting the condition's inflammatory nature and CRP's prognostic value for psoriasis worsening (Zaher et al., 2009). Similarly, higher salivary Haptoglobin levels in saliva(an acute-phase reactant,) indicates a local defense mechanism against psoriasis (Rocha Pereira et al., 2004) These findings collectively underscore the intricate relationships between psoriasis, immune imbalances, and salivary biomarkers,

offering a multifaceted view of this complex dermatological condition.

OXIDATIVE STRESS MARKERS

Oxidative stress denotes an imbalance in redox status that results in oxidative harm to cellular constituents, including proteins, lipids, and nucleic acids. This imbalance can disrupt cellular metabolism and trigger cell death through apoptosis. Consequently, the levels of reactive oxygen species (ROS) and antioxidants may play a crucial role in the diagnostic process (Krasteva et al., 2009; Asa'ad et al., 2018; Kadam et al., 2008; Wagener et al., 2018). In recent times, psoriasis has come to be recognized as a systemic condition linked with various metabolic syndromes like insulin resistance, obesity and dyslipidemia. Psoriasis patients have shown to exhibit irregularities in lipid metabolism and heightened oxidative stress (OS). These findings suggest that an imbalance in oxidative status significantly impacts cell proliferation, differentiation, and apoptosis in psoriasis (Villanova et al., 2013)

Studies have demonstrated that NO and other reactive nitrogen compounds impact various physiological processes within salivary glands (Stichtenoth et al., 1998; Brüne et al., 1889; Modin et al.,1994). A study showed elevated levels of Nitric oxide (NO), particularly nitrotyrosine, in the plasma of psoriatic patients, and this correlated positively with the duration of the disease, confirming the involvement of nitrosative stress in the condition (Dilek et al., 2016). In reference to a study utilizing saliva of psoriatic patients, individuals with reduced saliva production, demonstrated excessive Nitric oxide and peroxynitrite levels. Furthermore, it was observed that there was a direct association between TNF-α and Nitric oxide levels in individuals with reduced salivation in those with normal salivation (De La Cal et al., 2006). These findings were in accordance with the previous findings that proinflammatory cytokines stimulate inducible NO synthase (iNOS) expression in salivary gland cells, leading to increased NO and its derivatives production. The results suggest that impaired function of salivary glands in individuals with psoriasis results from both inflammation and nitrosative stress. However, the role of nitrosative stress in the pathophysiology of salivary glands during psoriasis still remains unclear.

SALIVARY IMMUNOGLOBULINS

Research on the immunological aspects of saliva in individuals with psoriasis has yielded conflicting results. Some studies have indicated higher levels of IgA in the saliva of psoriatic subjects compared to controls (del Castillo Carrillo et al., 1982), while others have suggested lower IgA levels (Koh et al., 2004). In both groups, the levels of IgM and IgE appear to be similar. Furthermore, a study detected elevated levels of salivary IgA, alpha-amylase, and sodium (Na+) in psoriatic individuals compared to controls, along with significantly reduced levels of lysozyme. The interrelationship between salivary IgA, beta 2-microglobulin, and lysozyme was noticeable (Koh et al., 2004).

The theory that lysozyme and IgA may play a role in the pathophysiology of psoriasis was also supported by Gasior-Chrzan and his colleagues who also showed significantly lower lysozyme concentrations in the saliva of psoriatic patients compared to controls, with serum lysozyme activity higher in patients than in controls. In contrast, IgA concentrations in the serum of psoriatic patients were significantly higher than in controls, while in saliva, IgA concentrations did not differ significantly (Gasior-Chrzan et al., 1992).

In yet another study, although there was no statistically significant difference in salivary IgA levels between psoriasis patients and healthy controls, those with a higher Psoriasis Area and Severity Index (PASI) score i.e PASI> 10, tended to exhibit lower IgA levels (Krasteva et al., 2009). These findings imply a potential influence on the composition of oral microbial communities and a higher risk of microbial infections triggering psoriasis.

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN & TRANSFERRIN

Transferrin is considered an inflammation-related protein, and inflammation has been linked to a reduction in circulating transferrin levels. Neutrophil gelatinase-associated lipocalin (NGAL) is another known protein associated with inflammation and its elevated blood and urine titers have been extensively studied as a potential marker (Belstrøm et al., 2020) Nevertheless, individuals with psoriasis exhibited decreased salivary levels of both NGAL and transferrin when compared to individuals with good oral health and patients with periodontitis (Belstrøm et al., 2020).

SALIVARY COMPONENTS

Studies investigating variations in saliva and its contents, along with their potential relation to the severity of psoriasis have been carried out in the past. In one such study higher salivary potassium ion and salivary alpha-amylase (sAA) concentrations were observed in psoriasis patients when compared to the controls (Syrjänen, et al., 1983; Soudan et al., 2011). However, it seemed that these alterations in saliva are not evidently connected to the seriousness or duration of the skin condition, highlighting the need for additional research to confirm these findings (Soudan et al., 2011).

The Future of Salivary Biomarker Research in Psoriasis with Advancing Technologies

In the ongoing quest for biomarkers, emerging technologies have the potential to streamline the identification of highly effective biomarkers in a comprehensive and impartial fashion. In a recent study led by Da Silva JB and colleagues explored the connection between salivary Fourier transform Infrared Spectroscopy (FTIR) metabolic patterns and extent of severity psoriasis, utilizing chemometric approaches, and relied on the Dermatology Life Quality Index (DLQI) as a measurement. Their findings revealed that FTIR analysis of saliva, coupled with OPLS-DA or OPLS, effectively distinguishes between psoriasis patients with DLQI scores of ≤ 10 and those with DLQI scores of > 10, while also quantifying the DLQI score. The combination of salivary FTIR with chemometric algorithms like OPLS-DA and OPLS offers the potential to serve as a clinical tool for categorizing or forecasting the extent of psoriasis based on DLQI in individuals diagnosed with psoriasis (da Silva et al., 2022) Such researches suggest that in the future, saliva could provide a means to combine clinical and laboratory data with existing resources for the improved care of individuals with psoriasis.

CONCLUSION

This review provides a comprehensive overview of current research on the application of saliva in studying psoriasis. In the context of precision medicine, the field of salivaomics holds great promise. The analysis of biomarkers in oral fluids presents practical advantages in terms of collection, storage, and analysis. However, it is worth noting that, despite the promising findings presented in this review, a noteworthy limitation is that none of the examined salivary biomarkers can be considered a standalone diagnostic tool, as they are associated with various diseases. A dedicated prognostic marker for psoriasis has yet to be identified. Furthermore, the wide range of methods for collecting, processing, and quantifying salivary components still hinders its practical application in clinical settings. It is evident that further extensive investigations are necessary to establish a reliable and accurate panel of biomarkers suitable for practical clinical use. Additional research and validation of these biomarkers are essential to fully unlock the potential of saliva-based diagnostics in psoriasis management. Developing a well-defined panel of biomarkers from saliva has the potential to enhance prognostic predictions, potentially leading to improved early diagnosis, monitoring of disease progression, and assessing treatment effectiveness in psoriasis patients.

Declaration Statements

Compliance with Ethical Standards: Authors declare that all ethical guidelines have been strictly followed and complied to while writing this manuscript. This is to declare that all the data has been shared in the manuscript and there is no associated data.

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