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Perspective

# Perspectives on salivary cytokines as noninvasive biomarkers for monitoring disease activity and therapeutic response of oral lichen planus

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Oral lichen planus (OLP) is a chronic inflammatory disease characterized by T cell-mediated vacuolar degeneration of basal keratinocytes secreting a mass of cytokines.[1–3] Inflammation-related cytokines are the crucial immune molecules of communication, which are able to modulate the inflammatory microenvironment. The abnormal expression of over a dozen cytokines in saliva and sera samples from OLP patients are described to be involved in the immunopathogenesis of this disease.[3–5] Hence, it is reasonable for clinicians to utilize serum and salivary

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**Table 1** Characteristics of included studies on serum and salivary cytokines in the treatment of patients with oral lichen planus.

| Author, year | Country/Region | Study design | Case (n) | Treatment | Sample | Detection method | Cytokine detected | Cytokines with significant difference after treatment |
|---|---|---|---|---|---|---|---|---|
| Tarasenko et al., 2021[6] | Germany | Randomized controlled | 93 | High-level laser therapy vs. scalpel surgery | Saliva | ELISA | IL-1β, IL-6, IFN-γ | IL-1β, IL-6, IFN-γ |
| Abboud et al., 2021[7] | Brazil | Randomized controlled | 34 | Photobiomodulation vs. topical corticosteroid | Serum, saliva | ELISA | IL-1β, TNF-α, IL-4, IL-6, IL-10, IL-17A | Only salivary IL-1β |
| Vohra et al., 2016[8] | India | Randomized controlled | 40 | Topical calcineurin inhibitors | Serum | ELISA | IL-6, IL-8 | IL-6, IL-8 |
| Goel et al., 2015[9] | India | Comparative study | 42 | Topical Methotrexate | Serum | ELISA | IL-6 | IL-6 |
| Zhu et al., 2014[10] | China | Randomized controlled | 150 | Systemic prednisone vs. hydroxychloroquine | Serum | Flow cytometry | IL2, IL8, IL10, TGFβ1 | Not available |
| Ghallab et al., 2010[11] | Egypt | Comparative study | 20 | Systemic prednisone | Saliva | ELISA | IFN-γ, TNF-α, TNFR-2 | IFN-γ, TNF-α, TNFR-2 |
| Youngnak et al., 2009[12] | Thailand | Comparative study | 20 | Topical fluocinolone acetonide in orabase | Serum | ELISA | IFN-γ | Not available |
| Rhodus et al., 2006[13] | USA | Comparative study | 13 | Topical dexamethasone mouthwash | Saliva | ELISA | IL-1α, IL-6, IL-8, TNFα | IL-1α, IL-6, IL-8, TNF-α |
| Sun et al., 2005[14] | China, Taiwan | Comparative study | 158 | Systemic levamisole | Serum | Immulite assay | IL-6, IL-8 | IL-6, IL-8 |
| Sun et al., 2002[15] | China, Taiwan | Comparative study | 149 | Systemic levamisole and Chinese medicinal herbs | Serum | Immulite assay | IL-6 | IL-6 |

ELISA, enzyme-linked immunosorbent assay; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; TGF, transforming growth factor.

cytokines in the clinical management of OLP due to minimally invasive collection of the samples. Compared to sera sample, saliva from OLP patient provides a preferability for samples to be obtained noninvasively, easily, and repeatedly.

A majority of Th1/2 associated cytokines were abnormally expressed in saliva of OLP compared to normal control, while a minority of cytokines with controversial findings were also reported by the previous studies.[4,5] For instance, Zhu et al.[4] newly reported salivary cytokine profile of OLP in *Journal of Dental Sciences*. The difference in salivary IL-6 and IL-10, as the common Th2 cytokines, were not found between OLP and normal control in this study,[4] which is inconsistent with the study by Wei et al.[5] The association of salivary IL-10 with the disease severity of OLP was also inconsistent in the 2 studies.[4,5] These inconsistencies were not mentioned in the paper,[4] and could be explained by different test methods and sampling bias. On the whole, aberrant expression of salivary cytokines have been largely recognized to contribute to the pathogenesis of OLP.

Compared with the diagnostic utility, we are further attracted to the issue of cytokines in sera and saliva can be used as biomarkers to reveal therapeutic utility in the clinical management of OLP. However, there is a lack of certain review and discussion focusing on the issue. Therefore, we provide a short review of the current state of research, and highlight the viewpoint on therapeutic implications of salivary cytokines. According to the search strategy described in Supplementary Table S1, literature search in Scopus, Web of Science, and PubMed databases was performed in order to retrieve the relevant papers.[6—15] Sun et al.[15] could for the first time report serum IL-6 level is a useful marker in evaluating therapeutic response of OLP.

As presented in Table 1, a total of 10 eligible studies on changes of serum and salivary cytokines in treatment of 754 cases of OLP were identified for detailed evaluation from literature databases. There were 4 randomized controlled trials and 6 comparative studies. There were 6 studies on serum cytokines, 3 studies on salivary cytokines, and 1 study on both salivary and serum cytokines. Among over ten kinds of cytokines in sera and saliva, some investigators selected only one cytokine and some selected several cytokines in their study. Of these, IL-6 as most common cytokine for the assessment indicator of various therapies was significantly confirmed by 6 studies containing 530 cases of OLP, followed by IL-8 (3 studies containing 211 cases), IL-1$\beta$, TNF-$\alpha$, and IFN-$\gamma$ (by 2 studies).

Currently, the evaluation of OLP disease severity and therapeutic response mainly rely on the subjective indicators, such as clinical presentation, score of disease activity, and visual analog scale for symptoms.[6,7] As proposed by the studies,[6,7] the objective laboratory indicators like cytokines are required to be researched and established in clinical practice. Interestingly, detection of serum and salivary cytokines has the potential in monitoring disease activity status and therapeutic response of OLP. Intriguingly, Abboud et al.[7] investigated the changes of 6 cytokines in sera and saliva in OLP patients treated with photobiomodulation; only salivary IL-1$\beta$ was a significant marker to monitor the disease severity and therapeutic response. In general, salivary IL-1$\beta$ and IL-6 and serum IL-6 and IL-8 maybe act as the significant markers for disease activity and monitoring the therapy of OLP (Table 1).

More importantly, it has been suggested that T-cell activation and cytokine production act locally and are not reflected in peripheral blood of OLP patients.[7] In other words, it seems acceptable that the pathogenesis of OLP does not clearly induce a systemic change but mainly mediate immunologically at local milieu.[7] Whole saliva is a highly versatile biological fluid that contains local vasculature-derived blood constituents, serum, and desquamated epithelial cells. Especially after topical treatments, the changes of the cytokines often were of significance not in sera but in saliva (Table 1). For these reasons, salivary cytokines may be produced from local cells of the inflammatory infiltration and by the oral keratinocytes themselves. With the nature of noninvasive collection, salivary cytokines offer distinctive advantages in the diagnosis and monitoring of OLP.

Taken together, we propose that salivary cytokines, which could be superior to serum ones, may serve as noninvasive biomarkers for monitoring the disease activity and therapeutic response of OLP. Further clinical trials with a large sample size and saliva samples collected with a standardized protocol at different time points, should be carried out to confirm the roles of the various cytokines during different therapies in diagnosis and monitoring of OLP.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2022.08.007.

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