The relationship between levels of salivary and serum interleukin-6 and oral lichen planus

A systematic review and meta-analysis

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ABSTRACT

Background. The relationship between levels of salivary and serum interleukin (IL)-6 and oral lichen planus (OLP) is not understood fully. The authors conducted a systematic review and meta-analysis to compare levels of salivary and serum IL-6 among people with OLP and healthy control participants.

Methods. The authors searched the literature for studies whose investigators had evaluated the relationships between IL-6 and OLP before treatment. The authors used meta-analysis to compare the standardized mean differences (SMD) of the levels of salivary and serum IL-6 between people who had OLP and people who did not have OLP and between patients with erosive OLP and patients with nonerosive OLP.

Results. The results of separate meta-analyses, which included 5 studies each, indicated that the levels of salivary and serum IL-6 were significantly higher among patients with OLP than among healthy control participants (SMD, 2.35; 95% confidence interval [CI], 0.50 to 4.19; $P = .01$; and SMD, 2.03; 95% CI, 0.74 to 3.33; $P = .002$; respectively). The results of a meta-analysis of 4 studies indicated that the levels of IL-6 were not significantly different between patients with erosive OLP and patients with nonerosive OLP (SMD, 1.37; 95% CI, −0.26 to 3.00; $P = .10$). There was significant heterogeneity among the studies ($P < .00001$).

Conclusions. Through the results of this meta-analysis, the authors found significant differences in the levels of IL-6 in saliva and serum between patients with OLP and healthy control participants. The authors found no differences in the levels of serum IL-6 between patients with erosive OLP and patients with nonerosive OLP. These results should be considered with caution because there was a high degree of heterogeneity among studies.

Practical Implications. Levels of IL-6 in saliva and serum may be potential biomarkers for OLP. However, additional research is needed to confirm findings of this meta-analysis.

Key Words. Oral lichen planus; interleukins; oral diagnosis.
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In 1869, Wilson[1] first described lichen planus (LP). LP is an inflammatory disorder that often occurs in the skin and mucosa, and the disease also can affect the nails, scalp, urinary tract, conjunctival mucosae, and other sites in the body.[2,3] LP is an inflammatory mucocutaneous condition that is mediated by means of a complex immune pathogenesis.[4] Oral lichen planus (OLP), which is an oral variant of LP, is a chronic inflammatory disease that affects oral mucosa tissues, such as buccal mucosa, dorsum of the tongue, and gingiva, with characteristically chronic, nonremissive, and possibly malignant degeneration.[5] Investigators have reported that there are 6 clinical variants[6]: reticular, papular, plaquelike, atrophic, erythematous, and erosive. Investigators also have categorized OLP into 2 broad categories—erosive and nonerosive—according to the clinical symptoms.[7] Nonerosive OLP, which includes the reticular, papular, plaquelike, atrophic, and erythematous forms, often is not associated with obvious symptoms, whereas erosive OLP, which

Supplemental material is available online.

includes the ulcerative and other erosive forms, commonly is sensitive and painful.

Although investigators have not elucidated fully the pathogenesis of OLP, they have found evidence that immunologic disease, mediated by means of a complex cytokine network, plays an important role in the exacerbation and perpetuation of OLP.[8] Interleukin (IL)-6 is a multifunctional cytokine involved in the immune and inflammatory responses. The production of IL-6 derives from activated T and B cells, activated monocytes, macrophages, endothelial cells, fibroblasts, and keratinocytes and is controlled by means of using nuclear factor–κB, which is reported to play an important role in the exacerbation of inflammatory processes.[9] Clinicians can detect the level of IL-6 in the saliva and serum and consider it to be a promising biomarker for monitoring disease activity.[10,11] In the past decade, the investigators of several studies have researched the levels of IL-6 in the saliva and serum of patients with OLP compared with the levels in healthy control participants.[12-14] Among these studies, some investigators reported a significant difference in the levels of IL-6 between patients with OLP and healthy control participants, but other investigators found no significant difference. The purpose of this meta-analysis was to determine whether there is a difference in the levels of serum and salivary IL-6 between patients with OLP and healthy control participants and to determine whether there is difference in the level of serum IL-6 between patients with erosive OLP and patients with nonerosive OLP.

METHODS

Guidelines and registration. We implemented the meta-analysis in accordance with the guidelines in the Cochrane Handbook[15] and in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] We did not register the meta-analysis.

Information sources and search. In November 2016, we performed a literature search to identify relevant studies for English- and Chinese-language articles by means of using the PubMed, Embase, Cochrane Library, and Chinese Biomedical Literature (CBM) databases. We developed a search strategy by means of combining Medical Subject Heading words and key words. We used appropriate alternatives for the key words of IL-6 and LP in the search. We used the following search terms: "interleukin-6," "interleukin 6," "IL-6," "IL 6," "lichen planus," "lichen ruber planus," and "lichen rubra planus." eTable 1 (available online at the end of this article) shows the details of the electronic database search. In addition, we searched the reference lists of the identified studies and consulted experts in the field to identify any additional studies. We consulted a senior medical librarian to develop the search strategy. Two authors (L.J., S.Q.) independently searched the electronic databases.

Inclusion and exclusion criteria. In this systematic review, we included studies whose authors evaluated the relationship between IL-6 and OLP before treatment. We included studies for which the investigators made the diagnosis of OLP according to its clinical manifestation and pathologic characteristics, on the basis of the definition of OLP by the World Health Organization.[17] We required that included studies have a sample size of at least 10 patients who had not received any treatment for OLP within 90 days before specimen collection. We excluded studies in which the investigators did not provide data related to levels of IL-6 or in which the study participants had other infections, allergies, autoimmune diseases, or any systematic disease that may have influenced the evaluation of IL-6. We also excluded animal studies, case reports, review articles, interviews, commentaries, and conference abstracts. eTable 2 (available online at the end of this article) shows the criteria in detail for included and excluded studies.

Study selection method. Two independent, blinded authors (L.J., S.Q.), conducted the study selection. If there was any discrepancy, the 2 authors discussed it, and if they could not compromise, they asked a third author (X.J.) for help drawing a final conclusion. These 2 authors screened the blinded titles and abstracts by means of marking studies as "1," "2," or "3," on the basis of the information provided. They gave a score of 1 to titles and abstracts that conformed to the eligibility criteria, a score of 2 to titles or abstracts that did not provide sufficient information or if there was no abstract available, and a score of 3 to titles or abstracts that did not conform with the eligibility criteria. They located the full texts of all of the articles that received scores of 1 or 2. They rigorously applied the inclusion and exclusion criteria to the full-text articles, and in situations for which they had questions they made efforts to contact the authors of the study.

Quality assessment. The 2 authors (L.J., S.Q.) independently assessed the quality of the included studies. If there was any discrepancy, they discussed it, and if they could not compromise, they asked a third author (X.J.) for help to draw a final conclusion. They used a modified Newcastle-Ottawa Scale[18] to assess the quality of each study. They used this scoring system to assess all of the studies to determine whether the content of each study was in accordance with the inclusion criteria. eTable 3 (available online at the end of this article) shows

ABBREVIATION KEY. **CBM:** Chinese Biomedical Literature. **ELISA:** Enzyme-linked immunosorbent assay. **IL:** Interleukin. **LP:** Lichen planus. **OLP:** Oral lichen planus. **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses.