Serum and salivary interleukin-4 levels in patients with oral lichen planus: A systematic review and meta-analysis

Hamid Reza Mozaffari, DDS, MSc,[a,b] Elisa Zavattaro, MD, PhD,[c] Mina Saeedi, DDS,[d] Pia Lopez-Jornet, DDS, MSc,[e] Masoud Sadeghi, MSc,[b,d] Mohsen Safaei, PhD,[f] Mohammad Moslem Imani, DDS, MSc,[g] Reza Nourbakhsh, DDS,[f] Hedaiat Moradpoor, DDS, MSc,[h] Amin Golshah, DDS, MSc,[g] and Roohollah Sharifi, DDS, MSc[i]

Objective. Cytokines have an important role in keratinocyte immune damage and can act in the pathogenesis of different cutaneous diseases. Accordingly, in the literature, interleukin 4 (IL-4) concentration has been previously investigated in patients affected by oral lichen planus (OLP).

Study design. The present meta-analysis evaluated the serum and salivary levels of IL-4 in connection with several OLP variants. The search was performed from 1995 in Cochrane Library and 1983 in Scopus, PubMed, and Web of Science to September 2018. The quality of the studies included in the meta-analysis was assessed using the Newcastle-Ottawa Scale assessment. The analyses were done by Review Manager 5.3 using mean difference (MD) and 95% confidence intervals (CIs).

Results. Out of 108 studies retrieved in the databases, only 10 were included and analyzed in quantitative synthesis. The pooled MD of the serum and salivary IL-4 levels in OLP patients compared with the controls was 6.36 picograms/milliliter (pg/mL) (95% CI: 1.47, 11.24; $P = .01$) and 2.67 pg/mL (95% CI: 2.66, 2.68; $P < .00001$), respectively. In addition, the pooled MD of serum and salivary IL-4 level was 1.30 pg/mL (95% CI: −0.35, 2.95; $P = .12$) and 1.83 pg/mL (95% CI: 0.26, 3.40; $P = .02$), respectively, in patients with erosive, erythematous, bullous, and ulcerative variants of OLP compared with patients with reticular OLP.

Conclusions. This meta-analysis found that OLP patients present elevated serum and salivary IL-4 levels, thus indicating that IL-4 may represent a potential salivary biomarker for the disease. By contrast, clinicians must be aware that even other factors (e.g., secondary infection) may influence its concentration. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:123−131)

Oral lichen planus (OLP) is known to be a chronic inflammatory disease associated with various other systemic disorders.[1] Its prevalence ranges from 1%−2% among the general population.[2] It often involves middle-aged patients and is more common in women than men.[3] Although the cause of OLP is unclear, various mechanisms have been hypothesized to be involved in its pathogenesis (antigen-specific cell-mediated immune response, autoimmune, humoral immunity, and nonspecific mechanisms).[4] Among them, the autoimmune mechanism postulates the disease to be a T-cell−induced autoimmune disorder in which $CD8^+$ T cells can induce oral epithelial cells apoptosis.[5] T helper (Th) cells have been traditionally divided into two subtypes (Th1 and Th2), according to cytokine production.[6] Accordingly, dysregulation of the immune system has been involved in the OLP etiology.[7] Cytokines can play an intermediate role between keratinocytes and inflammatory cells and also have an important role in keratinocyte immune damage.[8] In such a scenario, interleukin-4 (IL-4) is an important cytokine responsible for the secretion of other cytokines but is also necessary for the differentiation of Th2 cells[9,10] and plays a pivotal role in antibody production regulation and humoral immune response.[10,11] In regard to the connection between the immune system and OLP, meta-analyses have checked the salivary or serum levels of several cytokines such as tumor necrosis factor α,[12] IL-6,[13] and IL-8[14] in OLP patients and found that they were all significantly higher than in healthy controls. In a recent meta-analysis,[15] we

Statement of Clinical Relevance

This meta-analysis found that oral lichen planus patients compared with controls present elevated serum and salivary interleukin 4 levels, thus indicating that interleukin 4 may represent a risk factor for oral lichen planus development and also may be a good salivary biomarker for the disease.

[a]Department of Oral and Maxillofacial Medicine, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[b]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[c]Dermatology Unit, Department of Translational Medicine, University of Eastern Piedmont "Amedeo Avogadro," Novara 28100, Italy.
[d]Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[e]Facultad de Medicina y Odontologia Universidad de Murcia, Hospital Morales Meseguer, Clinica Odontologic Adv Marques Velez s/n, Murcia 30008, Spain.
[f]Oral and Dental Sciences Research Laboratory, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[g]Department of Orthodontics, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[h]Department of Prosthodontics, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[i]Department of Endodontics, School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran.
Received for publication Jan 6, 2019; returned for revision Apr 7, 2019; accepted for publication Apr 8, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.04.003

checked the correlation between salivary and serum immunoglobulins in OLP patients and the results indicated that the levels of immunoglobulins were higher in salivary than in serum samples. Therefore this is a further confirmation that the immune system, and namely cytokines, can affect the pathogenesis of OLP. On this basis, the present meta-analysis aims to evaluate the serum and salivary levels of IL-4 in connection with OLP based on case-control studies.

MATERIALS AND METHODS

This meta-analysis was performed according to the Preferred Reporting Guidelines for Systematic Reviews and Meta-Analyses guidelines.[16]

Search strategies

The studies were retrieved by searching the key terms "oral lichen planus" or "OLP" and "interleukin-4" or "IL-4" in Scopus, PubMed, Web of Science, and Cochrane Library databases up to September 2018. In detail, the search in Cochrane Library was started from 1995, whereas in the other databases the search started from 1983.

Study selection and selection criteria

The studies on the impact of OLP on serum and salivary IL-4 levels were selected without restrictions of language, period, gender, age, severity, and variants of OLP. The studies were analyzed if they (1) were case-control subtype reporting median or mean (± standard deviation) of serum and/or salivary IL-4 levels, (2) included OLP patients without any treatment, (3) reported OLP diagnosis in accordance with the World Health Organization's clinicopathologic diagnostic criteria,[17] (4) reported control patients without systematic and/or dental diseases, and (5) reported unstimulated saliva samples.

Data extraction

The studies were checked by one author (M.S.) to extract all the relevant data. Another author (H.R.M) reevaluated the data. Disagreements were resolved with the third author's discussion (E.Z.).

Quality assessment

The quality of the studies was evaluated by one author (M.S.) using the Newcastle-Ottawa Scale assessment[18] with a maximum score of 9 for each study that scored ≥7, meaning it was found to be a good-quality study.

Statistical analyses

The analyses were done by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, UK) with a random-effects model using mean difference (MD) and 95% confidence intervals (CIs), which, in the lack of heterogeneity, lead to use of the fixed-effects model. The heterogeneity percentage between the studies was evaluated by the Cochrane Q test and I^2 statistic; if $P < .1$ or $I^2 > 50\%$, there was a heterogeneity. A P value (2-sided) $<.05$ was considered statistically significant. The funnel plot analysis with Begg's and Egger's tests (for the evaluation of the publication bias across the studies) and sensitivity analysis with 1 removed study and cumulative analysis (for confirming stability of the results) were done by Comprehensive Meta-Analysis 2.0 (CMA 2.0) software. The unit of IL-4 level in this meta-analysis was picograms per milliliter (pg/mL).

RESULTS

Study selection

Out of 108 studies retrieved in the mentioned databases, 43 studies were screened (Figure 1). Out of 43 studies, 23 studies were not relevant and were excluded. The full texts of the remaining 20 studies were assessed for eligibility and half were excluded with reasons (3 studies were review/systematic review, 3 reported the polymorphisms of IL-4, 1 had duplicate data, and 3 had no relevant data). Finally, 10 studies were analyzed in quantitative synthesis (meta-analysis).

Baseline features

Out of 10 studies involved in the meta-analysis, 7 studies reported data from China,[19-25] 1 from Turkey,[26] 1 from the United States,[27] and 1 from Iran.[28] The studies were published from 2008 to 2018 (Table I). Together the studies included 502 OLP patients and 367 controls, except 1 study,[25] which did not report IL-4 level in controls and therefore did not allow comparing the level between the OLP patients and controls (117 patients and 100 controls). This study just compared the IL-4 level in patients affected by different OLP subtypes. Considering all the patients in the meta-analysis, the mean age of OLP patients and controls ranged from 41.5 to 56.3 years and 26.9 to 54 years, respectively. Among the 10 articles, 4 studies reported only the salivary IL-4 level,[19,20,21,28] 5 studies evaluated only serum IL-4 concentration,[21,23,25-27] and 1 study[22] reported both salivary and serum levels. When considering IL-4 concentrations among patients affected by different OLP variants, 4 studies reported the salivary IL-4 levels[19,20,22,28] and 4 studies the serum IL-4 levels.[22,25-27] In detail, the salivary IL-4 levels were from 103 patients with erosive and other OLP variants (erythematous, ulcerative) and 75 reticular OLP cases, whereas the serum levels were from 137 patients affected by erosive and other OLP variants (bullous, ulcerative, erythematous) and 106 reticular OLP patients. Most of the studies measured the IL-4 levels by enzyme-linked immunosorbent assay

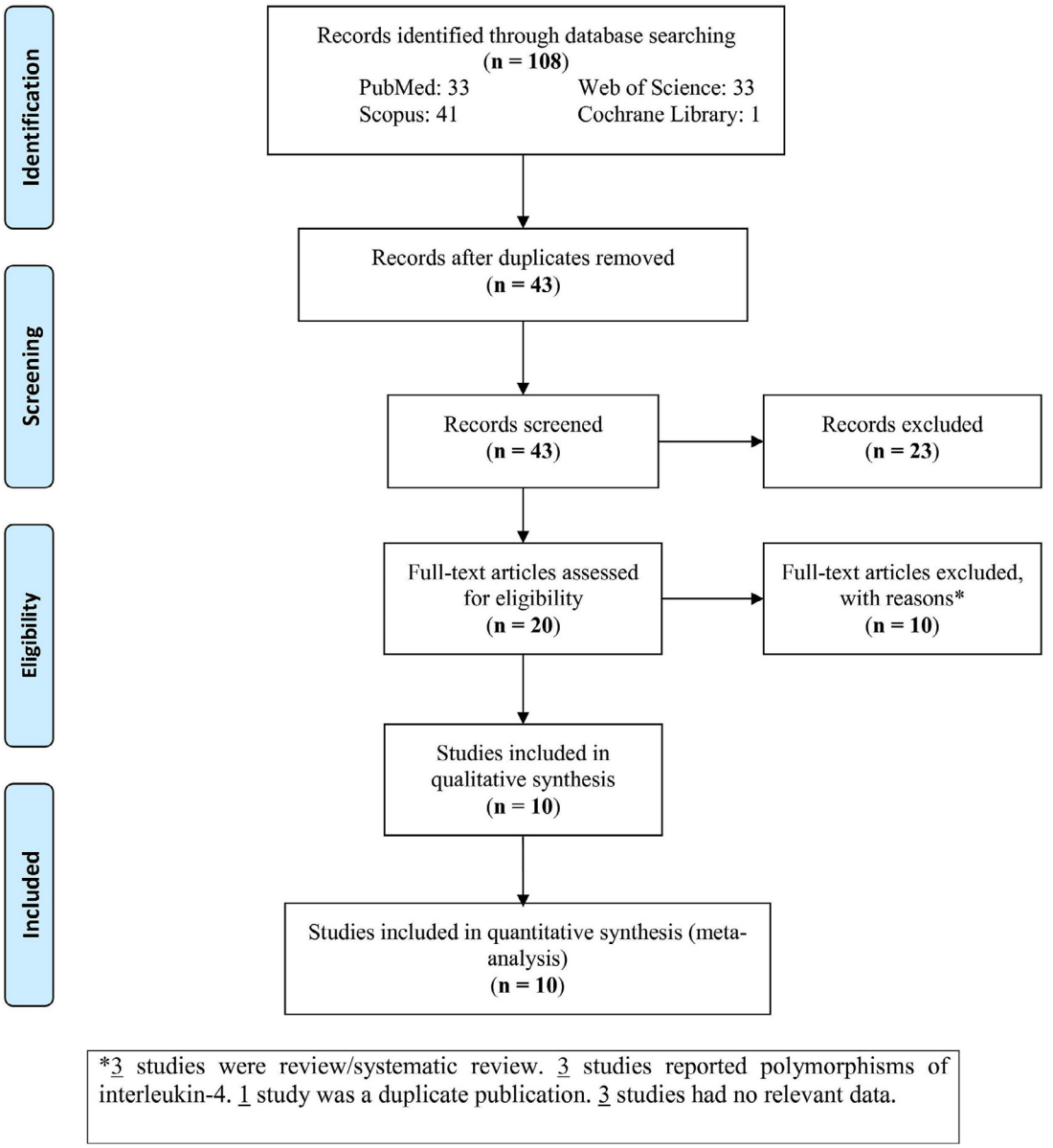

Fig. 1. The PRISMA flowchart of the study selection.

(ELISA) method, except 2 studies[24,26] that used the cytometric bead array method.

Meta-analysis

The pooled analysis indicated that the MD of serum IL-4 levels in OLP patients compared with the controls was 6.36 pg/mL (95% CI: 1.47, 11.24; $P = .01$; $I^2 = 97\%$ [$P_{\text{heterogeneity}}$ (P_h) < .00001]). The serum IL-4 level in OLP patients was significantly higher than in controls (Figure 2).

The pooled analysis of the salivary IL-4 level in OLP patients compared with the controls is shown in Figure 3. The MD was 2.67 pg/mL (95% CI: 2.66, 2.68; $P < .00001$; $I^2 = 0\%$ [$P_h = .59$]). The salivary IL-4 level in OLP patients was significantly higher than in controls.

The pooled analysis of serum IL-4 level based on the subtype of OLP is shown in Figure 4. The MD was 1.30 pg/mL (95% CI: −0.35, 2.95; $P = .12$; $I^2 = 79\%$ ($P_h = .003$)] in patients affected by erosive and other OLP variants compared with patients with reticular OLP. The result was not significant.

The pooled analysis of salivary IL-4 level based on the subtype of OLP is shown in Figure 5. The MD was 1.83 pg/mL (95% CI: 0.26, 3.40; $P = .02$; $I^2 = 80\%$ ($P_h = .002$)] in patients affected by erosive and other OLP variants compared with patients with reticular OLP. The salivary IL-4 level in patients with erosive and other subtypes was significantly higher than in reticular OLP patients.

Table I. Baseline features of the studies included in the analysis (N = 10)

First author, y	*Country*	*No. of participants (OLP/control)*	*Mean age of participants (OLP/control), y*	*Male participants (OLP/control), (n)*	*Sample*	*Subtype of OLP (n)*	*Method*
Tao, 2008[19]	China	19/7	46.5/26.9	7/3	Saliva	Atrophy-erosive (10), reticular (9)	ELISA kit (eBioscience Inc., San Diego, CA, USA)
Liu, 2009[20]	China	79/41	46/41	37/20	Saliva	Erythematous/ulcerative (20), reticular (16)	ELISA kit (R&D Systems Inc., Minneapolis, MN, USA)
Pekiner, 2012[26]	Turkey	30/30	51.10/48.09	9/12	Serum	Bullous/erosive (12), reticular (18)	Cytometric Bead Array Th1/Th2 Human kit (BD BioSciences, San Jose, CA, USA).
Zhou, 2012[21]	China	22/8	42/49	10/3	Serum	—	ELISA kit (R&D Systems Inc, Minneapolis, MN, USA).
Ding, 2014[27]	USA	36/19	45/43	21/12	Serum	Erythematous/erosive (20), reticular (16)	ELISA kit (BioLegend, Inc., San Diego, CA, USA)
Liu, 2014[22]	China	60/40	45/42	25/19	Serum & saliva	Erythematous/ulcerative (40), reticular (20)	ELISA kit (R&D Systems, Minneapolis, MN, USA)
Malekzadeh, 2015[28]	Iran	63/63	41.5/37	25/30	Saliva	Erythematous/ulcerative (33), reticular (30)	ELISA kit (eBioscience, San Diego, USA).
Wang, 2015[23]	China	35/35	53/54	31/31	Serum	—	ELISA kit (R&D Systems Inc., Minneapolis, MN, USA)
Wei, 2018[24]	China	41/14	56.3/51.2	9/6	Saliva	—	Cytometric Bead Array Th1/Th2 Human kit (BDBioSciences, USA).
Zhang, 2018[25]	China	117/110	Median: 52/52	37/45	Serum	Atrophy-erosive (65), Reticular (52)	ELISA kits (R&D Systems, Inc., Minneapolis, MN, USA)

OLP, oral lichen planus; *ELISA,* enzyme-linked immunosorbent assay.

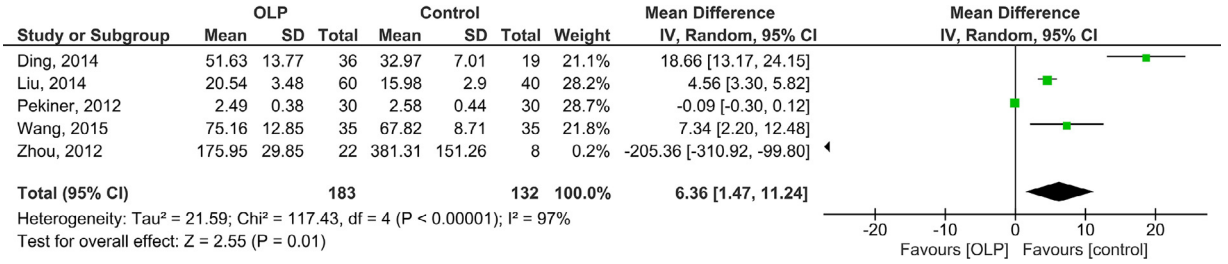

Fig. 2. The forest plot of serum interleukin 4 level (unit: pg/mL) in oral lichen planus patients versus controls. *OLP,* oral lichen planus; *SD,* standard deviation; *CI,* confidence interval; *IV,* instrumental variable; *df,* degrees of freedom.

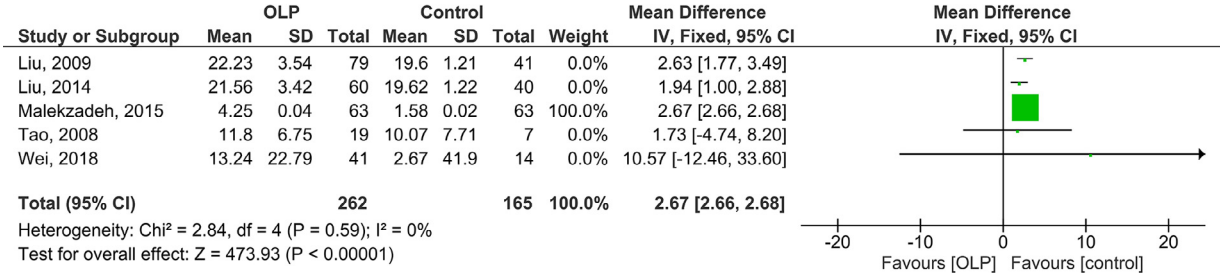

Fig. 3. The forest plot of salivary interleukin 4 level (unit: pg/mL) in oral lichen planus patients versus controls. *OLP,* oral lichen planus; *SD,* standard deviation; *CI,* confidence interval; *IV,* instrumental variable; *df,* degrees of freedom.

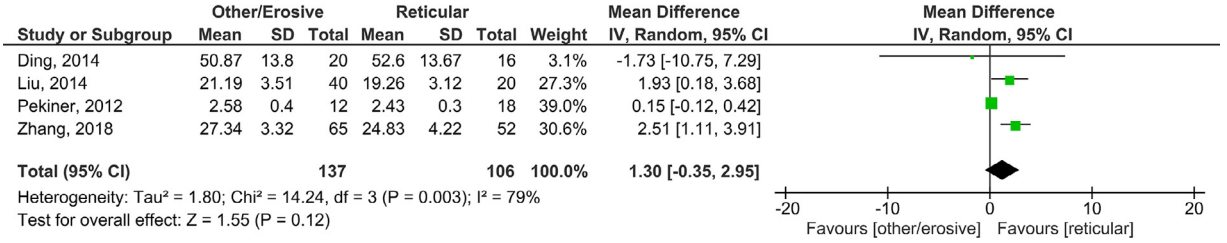

Fig. 4. The forest plot of serum interleukin 4 level (unit: pg/mL) based on subtype of OLP (erosive/other vs reticular). *OLP,* oral lichen planus; *SD,* standard deviation; *CI,* confidence interval; *IV,* instrumental variable; *df,* degrees of freedom.

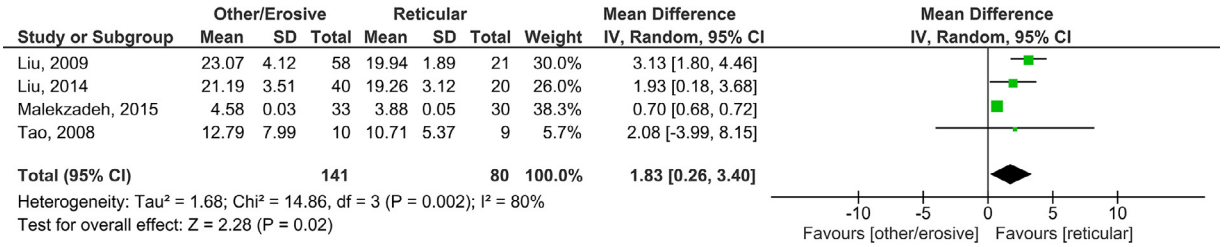

Fig. 5. The forest plot of salivary interleukin 4 level (unit: pg/mL) based on subtype of OLP (erosive/other vs reticular). *OLP,* oral lichen planus; *SD,* standard deviation; *CI,* confidence interval; *IV,* instrumental variable; *df,* degrees of freedom.

Quality assessment

The quality of the studies included in the present meta-analysis had a mean score of 6.6, with half of the studies having good quality (Table II).

Publication bias

The *P* values of Egger's and Begg's tests were >.05 in all analyses; therefore no publication bias was identified in the analyses (Figure 6)

Sensitivity analysis

We tested "one study removed" and "cumulative analysis" on each analysis and they did not change the previous results; therefore the pooled MD of each analysis was stable.

DISCUSSION

The results of the present meta-analysis found that serum and salivary IL-4 levels in OLP patients were

Table II. The quality score based on the Newcastle-Ottawa Scale (NOS) of each study included in the meta-analysis (N = 10)

First author (y)	Selection				Comparability		Outcome			Total score	Quality‡
	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Main factor*	Additional factor†	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate		
Tao, 2008[19]	+	+	—	+	—	+	+	+	—	6	Fair
Liu, 2009[20]	+	+	+	+	+	+	+	+	—	8	Good
Pekiner, 2012[26]	+	+	+	+	+	+	+	+	—	8	Good
Zhou, 2012[21]	+	+	—	—	+	+	+	+	—	6	Fair
Ding, 2014[27]	+	+	—	+	+	+	+	+	—	7	Good
Liu, 2014[22]	+	+	—	+	+	+	+	+	—	7	Good
Malekzadeh, 2015[28]	+	+	—	+	+	+	+	+	—	7	Good
Wang, 2015[23]	+	+	—	—	+	+	+	+	—	6	Fair
Wei, 2018[24]	+	+	—	—	+	—	+	+	—	5	Fair
Zhang, 2018[25]	+	+	—	—	+	+	+	+	—	6	Fair
Mean score										6.6	

*Age was matched between 2 groups.
†Sex was matched between 2 groups.
‡Good quality (score: ≥7) and fair quality (score: 5–7).

significantly higher than in controls. In addition, the serum and salivary IL-4 levels in patients with reticular OLP subtype were lower than in those suffering from other subtypes, although the difference was significant only for the salivary level.

OLP is a chronic inflammatory disease in which a Th1/Th2 cell imbalance is involved, thus favoring a Th2 predominance. IL-4 is a cytokine whose level may represent the activation of Th2 cell immune response. Moreover, some studies have also reported the interferon γ (IFN-γ) and/or its ratio with IL-4 in OLP, thus indicating the cell imbalance.[21,24,27] Hence, a high level of IL-4, indicating the Th2 activation, represents a further element favoring the autoimmune mechanism in the pathogenesis of OLP.

In the present meta-analysis, out of 5 studies reporting serum IL-4 level[21-23,26,27] in the OLP patients compared with healthy controls: In 3 studies[22,23,27] a higher level of IL-4 in patients was detected, whereas in one[21] a lower concentration was reported, and in the other one[26] no difference was identified. Indeed, Zhou et al.[21] described the pathway of programmed death 1 and its ligand B7-H1, which may be implicated in OLP and play a pivotal role in the negative modulation of T-cell−mediated immune response, thus reducing the serum IL-4 level in OLP. In addition, Pekiner et al.[26] reported lack of difference in serum IL-4 concentrations between patients and controls, and they concluded that this could be due to the low ratio of reticular/other-erosive OLP variants in patients compared with other studies.

On the other hand, 5 studies[19,20,22,24,28] reported higher salivary IL-4 concentration in OLP patients than in controls, but the difference was significant only in 3 studies.[20,22,28] Wei et al.[24] reported that salivary IFN-γ/ IL-4 ratio can negatively affect the salivary IL-4 and this ratio in OLP patients was significantly higher than controls.

OLP has numerous different clinical subtypes that are characterized either by various clinical features or possible malignant transformation, and only some studies investigating IL-4 level in OLP have considered the different variants of the disease. Indeed, 4 studies[22,25-27] reported the serum IL-4 levels and another 4 studies[19,20,22,28] reported the salivary IL-4 levels between different subtypes of OLP (erosive/other vs reticular), and the serum and salivary IL-4 levels in erosive/other subtypes were significantly higher than reticular in 2 studies[22,25] and in 3 studies,[20,22,28] respectively. It should be added that among 8 studies reporting the serum and/or salivary IL-4 levels based on the disease subtypes, only 1 study[27] reported low serum level of IL-4, but without reaching significant difference. Because the erythematous and erosive OLP subtypes can cause severe symptoms (i.e., bleeding and pain) and they have been reported, rarely, to undergo malignant

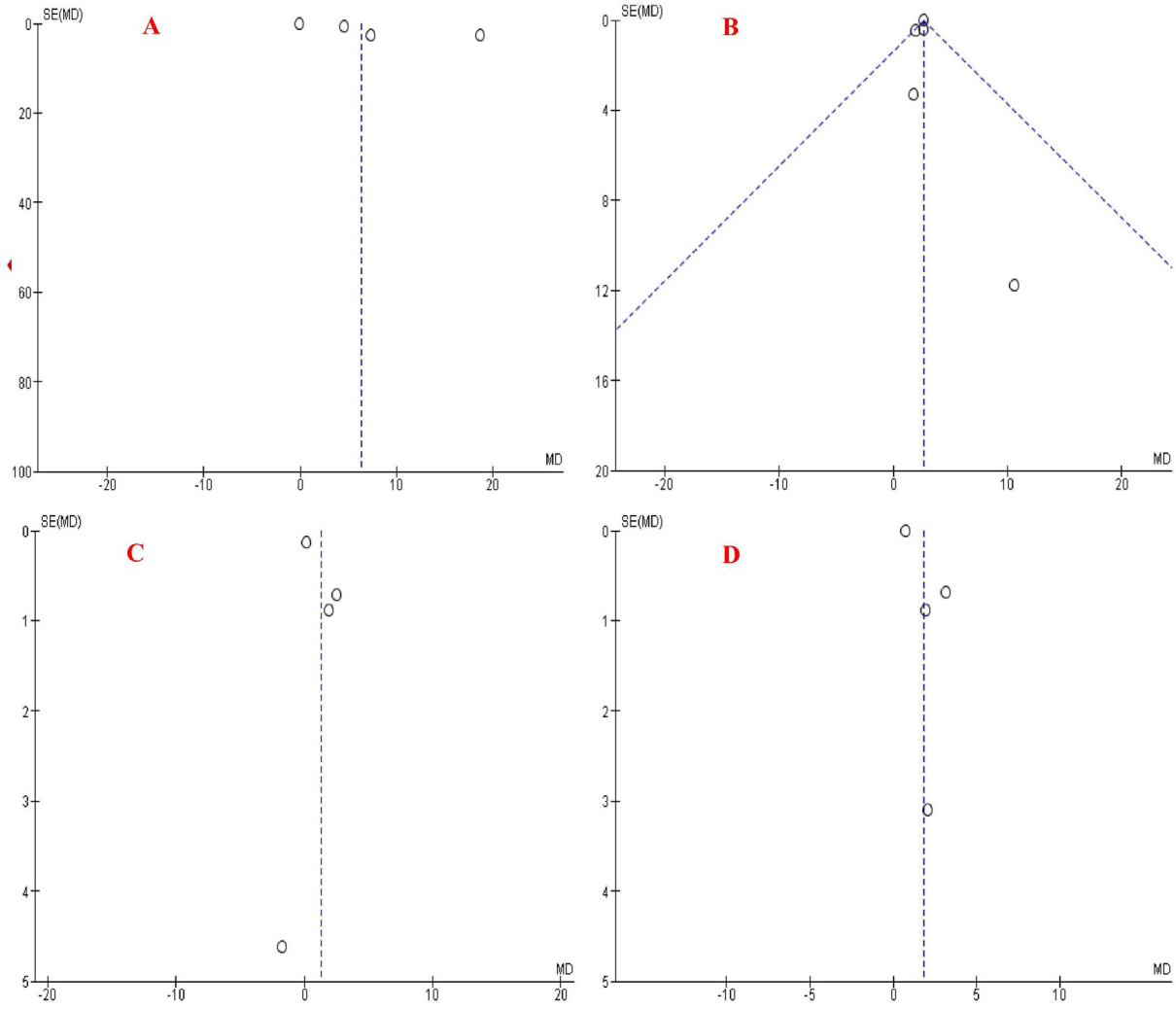

Fig. 6. The funnel plot of interleukin 4 levels: **(A)** serum and **(B)** salivary levels in oral lichen planus compared with controls; **(C)** serum and **(D)** salivary levels in other/erosive compared with reticular patients (y-axes, standard error [SE], and x-axes, mean difference [MD], with units of pg/mL).

transformation, several studies[29-33] have suggested that such factors may help explain the differences in IL-4 levels among various OLP variants. Another study[22] found a lower serum and salivary ratio of IFN-γ/IL-4, mainly in the erythematous and erosive subtypes compared with the reticular subtype; these data were in contrast with the serum and salivary IL-4 levels. Therefore it is clear that imbalance between Th1 and Th2 cells may influence OLP pathogenesis and cause elevated levels of IL-4 in OLP patients.[26,28] On the other hand, it can also be argued that IL-4 concentration may be influenced, either in serum or mainly in saliva, by the presence of a local inflammatory process, which is expected to be stronger in the erosive, ulcerative, and erythematous variants. Moreover, the presence of a possible secondary infection in the erosive and ulcerative OLP subtypes may represent a further cause of higher IL-4 salivary level.

Another important factor to be considered is represented by the interaction between genes and cytokines and also the effect of gene polymorphisms on the cytokine production. Indeed, a cohort study[34] on Chinese ethnicity found that IL-4 gene polymorphism seems to have a positive influence on OLP susceptibility and prognosis. Therefore this may explain the differences between the results in numerous studies. Additionally, considering the studies included in the present meta-analysis, none of them investigated the effect of age and gender on IL-4 levels, although we believe that these factors should also be considered in future studies.

Our meta-analysis presents some limitations: (1) To date, only a few studies on this topic have been reported and examined, (2) some studies reported

different number of patients in each OLP subtype, (3) different detection methods have been used in the studies, (4) there is a high heterogeneity among studies, and (5) only half of studies were of good quality.

On the other hand, the strengths of the meta-analysis are that (1) no publication bias was detected and (2) the results of each analysis were stable.

CONCLUSIONS

According to the present meta-analysis, OLP patients present elevated serum and salivary IL-4 levels, thus indicating that IL-4 may represent a potential and easy to collect salivary biomarker for the disease. On the other hand, as stated earlier, because the presence of either a more severe inflammation or secondary infection in erosive, ulcerative, and erythematous OLP variants may influence the IL-4 levels, it is clear that its use in clinical practice is not currently recommended. Moreover, because of the low number of studies reported, it is recommended that further studies with larger samples of patients be conducted, considering age, gender, genetic polymorphisms, and disease severity.

ACKNOWLEDGEMENTS

The authors sincerely and gratefully thank Kermanshah University of Medical Sciences for providing the financial support.

REFERENCES

1. Gupta S, Jawanda MK. Vulvovaginal gingival lichen planus: report of two cases and review of literature. *Indian J Dermatol*. 2015;60:222-229.
2. Lucchese A, Dolci A, Minervini G, et al. Vulvovaginal gingival lichen planus: report of two cases and review of literature. *Oral Implantol (Rome)*. 2016;9:54-60.
3. Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: a literature review and update. *Arch Dermatol Res*. 2016;308:539-551.
4. Roopashree MR, Gondhalekar RV, Shashikanth MC, George J, Thippeswamy SH, Shukla A. Pathogenesis of oral lichen planus—a review. *J Oral Pathol Med*. 2010;39:729-734.
5. Lavanya N, Jayanthi P, Rao UK, Ranganathan K. Oral lichen planus: an update on pathogenesis and treatment. *J Oral Maxillofac Pathol*. 2011;15:127-132.
6. Rhodus NL, Cheng B, Ondrey F. Th1/Th2 cytokine ratio in tissue transudates from patients with oral lichen planus. *Mediators Inflamm*. 2007;2007:19854.
7. Farhi D, Dupin N. Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies. *Clin Dermatol*. 2010;28:100-108.
8. Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Thongprasom K. Current controversies in oral lichen planus: report of an international consensus meeting. Part 1. Viral infections and etiopathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;100:40-51.
9. Kidd P. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. *Altern Med Rev*. 2003;8:223-246.
10. Neurath MF, Finotto S, Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. *Nat Med*. 2002;8:567-573.
11. Elser B, Lohoff M, Kock S, et al. IFN-gamma represses IL-4 expression via IRF-1 and IRF-2. *Immunity*. 2002;17:703-712.
12. Mozaffari HR, Ramezani M, Mahmoudiahmadabadi M, Omidpanah N, Sadeghi M. Salivary and serum levels of tumor necrosis factor-alpha in oral lichen planus: a systematic review and meta-analysis study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;124:e183-e189.
13. Mozaffari HR, Sharifi R, Sadeghi M. Interleukin-6 levels in the serum and saliva of patients with oral lichen planus compared with healthy controls: a meta-analysis study. *Cent Eur J Immunol*. 2018;43:103-108.
14. Mozaffari HR, Sharifi R, Mirbahari S, Montazerian S, Sadeghi M, Rostami S. A systematic review and meta-analysis study of salivary and serum interleukin-8 levels in oral lichen planus. *Adv Dermatol Allergol*. 2018;35:599-604.
15. Mozaffari HR, Zavattaro E, Abdolahnejad A, et al. Serum and salivary IgA, IgG, and IgM levels in oral lichen planus: a systematic review and meta-analysis of case-control studies. *Medicina (Kaunas)*. 2018;54. pii: E99.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
17. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncol*. 2009;45:317-323.
18. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed January 12, 2016.
19. Tao XA, Li CY, Rhodus NL, Xia J, Yang XP, Cheng B. Simultaneous detection of IFN-gamma and IL-4 in lesional tissues and whole unstimulated saliva from patients with oral lichen planus. *J Oral Pathol Med*. 2008;37:83-87.
20. Liu W, Dan H, Wang Z, et al. IFN-gamma and IL-4 in saliva of patients with oral lichen planus: a study in an ethnic Chinese population. *Inflammation*. 2009;32:176-181.
21. Zhou G, Zhang J, Ren XW, Hu JY, Du GF, Xu XY. Increased B7-H1 expression on peripheral blood T cells in oral lichen planus correlated with disease severity. *J Clin Immunol*. 2012;32:794-801.
22. Liu WZ, He MJ, Long L, et al. Interferon-γ and interleukin-4 detected in serum and saliva from patients with oral lichen planus. *Int J Oral Sci*. 2014;6:22-26.
23. Wang Y, Zhou J, Fu S, Wang C, Zhou B. A study of association between oral lichen planus and immune balance of Th1/Th2 cells. *Inflammation*. 2015;38:1874-1879.
24. Wei W, Sun Q, Deng Y, et al. Mixed and inhomogeneous expression profile of Th1/Th2 related cytokines detected by cytometric bead array in the saliva of patients with oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;126:142-151.
25. Zhang ZR, Chen LY, Qi HY, Sun SH. Expression and clinical significance of periostin in oral lichen planus. *Exp Ther Med*. 2018;15:5141-5147.
26. Pekiner FN, Demirel GY, Borahan MO, Ozbayrak S. Cytokine profiles in serum of patients with oral lichen planus. *Cytokine*. 2012;60:701-706.
27. Ding M, Zeng J, Sroussi H, Yu J, Xu J, Cheng X, Fan Y. Interactions between Golli-MBP and Th1/Th2 cytokines in patients with oral lichen planus. *Oral Dis*. 2014;20:205-211.
28. Malekzadeh H, Robati M, Yousefimanesh H, Ghafourian Boroujerdnia M, Nadripour R. Salivary interferon gamma and Interleukin-4 levels in patients suffering from oral lichen planus. *Cell J*. 2015;17:554-558.

29. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J Am Acad Dermatol*. 2002;46:207-214.
30. Al-Hashimi I, Schifter M, Lockhart PB, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;103:25-31.
31. Dan H, Liu W, Wang J, et al. Elevated IL-10 concentrations in serum and saliva from patients with oral lichen planus. *Quintessence Int*. 2011;42:157-163.
32. Sun Y, Liu N, Guan X, Wu H, Sun Z, Zeng H. Immunosuppression induced by chronic inflammation and the progression to oral squamous cell carcinoma. *Mediators Inflamm*. 2016;2016:5715719.
33. Giuliani M, Troiano G, Cordaro M, et al. Rate of malignant transformation of oral lichen planus: a systematic review. *Oral Dis*. 2019;25:693-709.
34. Bai J, Lin M, Zeng X, et al. Association of plymorphisms in the human IFN-gamma and IL-4 gene with oral lichen planus: A study in an ethnic Chinese cohort. *J Interferon Cytokine Res*. 2008;28:351-358.

Reprint Requests:

Masuod Sadeghi, MSc
Medical Biology Research Center
Kermanshah University of Medical Sciences
Kermanshah
Iran.
Sadeghi_mbrc@yahoo.com