JOURNAL OF CRITICAL REVIEWS

ISSN- 2394-5125 VOL 7, ISSUE 15, 2020

EVALUATE THE SALIVARY AND SERUM TNF-A LEVELS IN PATIENTS WITH ORAL LICHEN PLANUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Homeira Saebnoori[1], Roohallah Safarpour[2*], Elham Sadat Afraz[3]

[1]Post Graduated Student of Oral and Maxillofacial Pathology, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2]Post Graduated Student of Oral and Maxillofacial Pathology, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[3]Assistant professor, Department of Oral medicine, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran

Email: [2]Iran,fanoos1979@yahoo.com

Received: 01 May 2020 Revised: 23 June 2020 Accepted: 04 July 2020

ABSTRACT: Oral lichen planus (OLP) (LIE-kun PLAY-nus) is a chronic inflammatory disease that can affect the skin and any lining mucosa .High serum levels of TNF-a were detected in all patients with OLP in comparison with its hardly detectable levels in control subjects. The aim of present systematic review and meta-analysis was Evaluate the salivary and serum TNF-α levels in patients with PLP. From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform a systematic literature between 2010 and May 2020. Therefore, a software program (Endnote X8) has been utilized for managing the electronic titles. Searches were performed with mesh terms. The quality of the studies included was assessed using the Newcastle-Ottawa Scale (NOS) (1). mean differences between two groups (OLP and control) with 95% confidence interval (CI), random effects model and restricted maximum-likelihood (REML) method were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. The Meta analysis and forest plots have been evaluated with the use of a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).A total of 406 potentially relevant titles and abstracts were found during the electronic and manual search. Finally, a total of ten publications fulfilled the inclusion criteria required for this systematic review. Mean difference of TNF-a levels of saliva in patients with OLP was 48.98 pg/mL (MD, 48.98 95% CI 20.26, 77.69 P= 0.00). The present study showed the salivary and serum levels of TNF α were significantly increased in oral lichen planus patients to compared healthy patients.

KEY WORDS: salivary, serum, TNF-α, oral lichen planus

I. INTRODUCTION

Oral lichen planus (OLP) (LIE-kun PLAY-nus) is a chronic inflammatory disease that can affect the skin and any lining mucosa (oral, esophageal, vaginal mucosa as well as the skin) and affect the mucous membranes inside the mouth with greater incidence in women(2). The prevalence of this disease around the world is about 1% to 2%(3). The exact cause of OLP has not been determined, but the immunologic system plays an important role(4), as does the nuclear factor kB (NF-kB) as a primary transcription factor for the expression of a number of cytokines, including tumor necrosis factor-a (TNF-a) controls(5). TNF is a major mediator of inflammation stimulating both tissue destruction and repair(6), also TNF is a critical component of cell death and inflammation(7). Tumor necrosis factor (TNF)-alpha was recognized in the 1970s as an intrinsic immune serum capable of induction and had several stimulatory activities activated in T cells, including increasing the proliferation, interleukin-2 receptor (IL-2R) expression, and the response to IL-2 stimulus(8). It has been identified as an important mediator of cancer development and a powerful activator not only of apoptotic, but also anti-apoptotic signaling cascades(8, 9). Data collected during the past decade have pointed to TNF-a as a key cytokine in cutaneous lichen planus, as well as in OLP(9). High serum levels of TNF-a were detected in all patients with OLP in comparison with its hardly

ISSN- 2394-5125 VOL 7, ISSUE 15, 2020

detectable levels in control subjects. Simultaneously with the expression of other pro-inflammatory and anti-inflammatory cytokines mRNAs, all the OLP lesions have been shown to contain cells with mRNA for TNF-a(9, 10). The aim of present systematic review and meta-analysis was Evaluate the salivary and serum TNF-α levels in patients with oral lichen planus.

II. METHOD

Search strategy

From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform a systematic literature between 2010 and May 2020. Therefore, a software program (Endnote X8) has been utilized for managing the electronic titles. Searches were performed with mesh terms:

((((("Lichen Planus, Oral"[Mesh]) AND "Tumor Necrosis Factor Inhibitors"[Mesh]) AND "Tumor Necrosis Factor-alpha"[Mesh]) AND "Saliva"[Mesh]) AND "Serum"[Mesh]. This systematic review has been conducted on the basis of the key consideration of the PRISMA Statement–Preferred Reporting Items for the Systematic Review and Meta-analysis(11), and PICO or PECO strategy (table1).

Selection criteria

Inclusion criteria

1. Randomized controlled trials studies, controlled clinical trials, and prospective and retrospective cohort studies, case-control.

2. Patients with OLP

3. Any treatment modality for depression

4. Assessed TNF-a levels in the serum or saliva

6. in English

Exclusion criteria

1. In vitro studies, case studies, case reports and reviews.

Table1. PICO OR PECO strategy

PICO OR PECO strategy	Description
P	Population/ Patient: Patients with OLP
E	Exposure/ Intervention: assessed TNF-a levels in the serum or saliva
C	Comparison: compared OLP group with control group (healthy Patients)
O	Outcome: TNF-a levels of saliva and serum in OLP groups compared with healthy controls

Data Extraction and method of analysis

The data have been extracted from the research included with regard to the study, years, study design, Intervention group, control group, sample size, mean/ range of age. The quality of the studies included was assessed using the Newcastle-Ottawa Scale (NOS) (1). The scale scores range from 0 (lowest grade) to 9 (highest grade). For Data extraction, three reviewers blind and independently extracted data from abstract and full text of studies that included. Moreover, mean differences between two groups (OLP and control) with 95% confidence interval (CI), random effects model and restricted maximum-likelihood (REML) method were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. The Meta analysis and forest plots have been evaluated with the use of a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).

ISSN- 2394-5125 VOL 7, ISSUE 15, 2020

III. RESULTS

According to the research design, 406 potentially important research abstracts and titles have been discovered in our electronic searches. At the first phase of the study selection, 356 research have been with regard to the topics and abstracts. Therefore, we fully assessed the complete full-text papers of the rest 50 studies in the second stage so that we excluded 40 publications due to the lack of the defined inclusion criteria. Then, ten papers remained in agreement with our inclusion criteria required (Figure 1). Table 2 reports the individual studies in this meta-analysis.

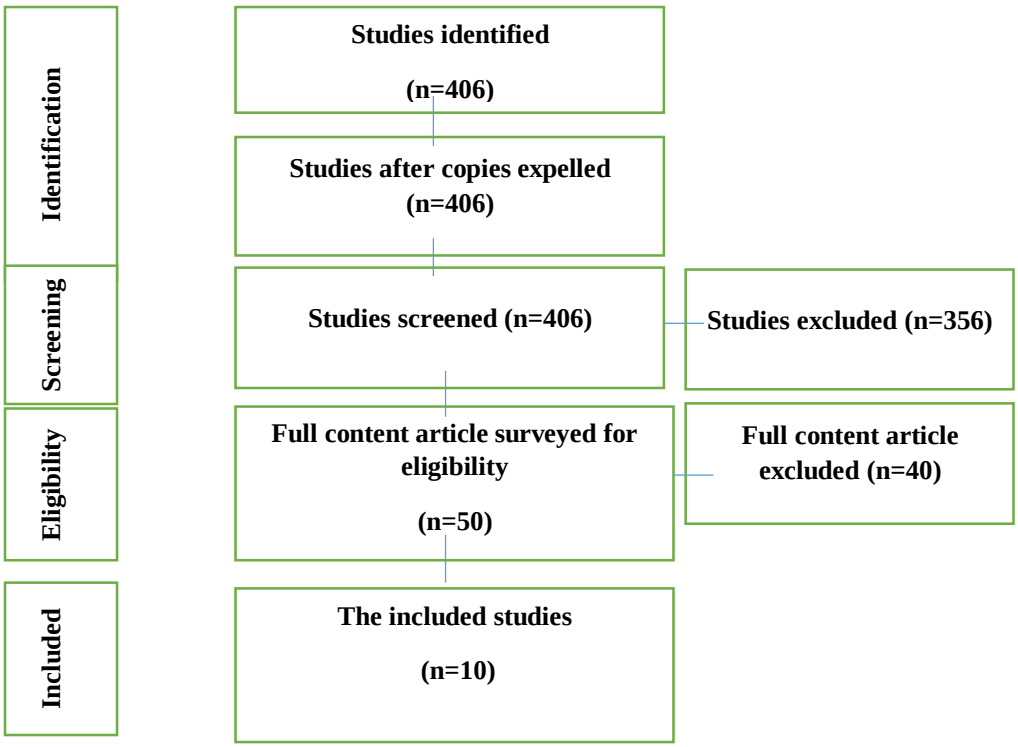

Figure 1. Study Attrition

Sample size

Therefore, ten studies have been included. The Number of patients in OLP group was 304 and in control group (healthy patients) was 267 a total was 571. The range of age in OLP group and control group was 15-75 with mean 41.1 years and 15-75 with mean 38.14 years, respectively (table2).

Table2. Studies selected for systematic review and meta-analysis.

N	Study. Year	Number of Patient				Mean/ Range of age (years)	
		OLP group		Control group		OLP group	Control group
		Male	Female	Male	Female		
1	Gupta et al.2019 (12)	30				36.50	26.75
		15		15			
		5	10	9	6		

ISSN- 2394-5125 VOL 7, ISSUE 15, 2020

2	Nandhini et al.2019(13)	44				15-75	15-75
		22		22			
		12	10	12	10		
3	Kara et al.2018 (14)	54				18-82	21-52
		34		20			
		14	20	8	12		
4	Ali et al. 2018 (15)	65				46.26±8.56 30--60	47.23±9.02 30—60
		35		30			
		15	20	13	17		
5	Kara et al.2017 (16)	54				42.85	35.85
		34		20			
		14	20	8	12		
6	Robati et al.2016 (17)	60				42±0.8	39±0.5
		30		30			
		12	18	15	15		
7	Malarkodi et al.2015(18)	60				43.5 18-75	42 23-61
		30		30			
		14	16	14	16		
8	Kaur et al.2015 (19)	104				41-65	42-65
		54		50			
		NA	NA	NA	NA		
9	Pekiner et al.2012 (20)	60				51.10 ± 12.25	48.09 ± 11.92
		30		30			
		9			18		
10	Ghallab et al. 2010 (21)	40				46.3 ± 4.99 40–55	42 ± 7.2 39–55
		20		20			
		2	18	3	17		

TNF-a levels of saliva in patients with oral lichen planus:

Mean difference of TNF-a levels of saliva in patients with oral lichen planus was 48.98 pg/mL (MD, 48.98 95% CI 20.26, 77.69 P= 0.00) among the 7 studies (Figure2). There was statistically significant difference between OLP group and control group (p=0.00). Heterogeneity found (I2 = 99.77%; P =0.00), However, significant statistical heterogeneity was found across studies.

TNF-a levels of serum in patients with oral lichen planus:

Mean difference of TNF-a levels of serum in patients with oral lichen planus was 30.35 pg/mL (MD, 30.35 95% CI 11.90, 48.80 P= 0.00) among the 6 studies (Figure3). There was statistically significant difference between OLP group and control group (p=0.00). Heterogeneity found (I^2 = 97.23%; P =0.00), However, significant statistical **heterogeneity was found across studies.**

Bias assessment

According to Newcastle-Ottawa Scale (NOS), the mean of score was 6.9, this outcome showed moderate risk of bias (table3).

ISSN- 2394-5125 VOL 7, ISSUE 15, 2020

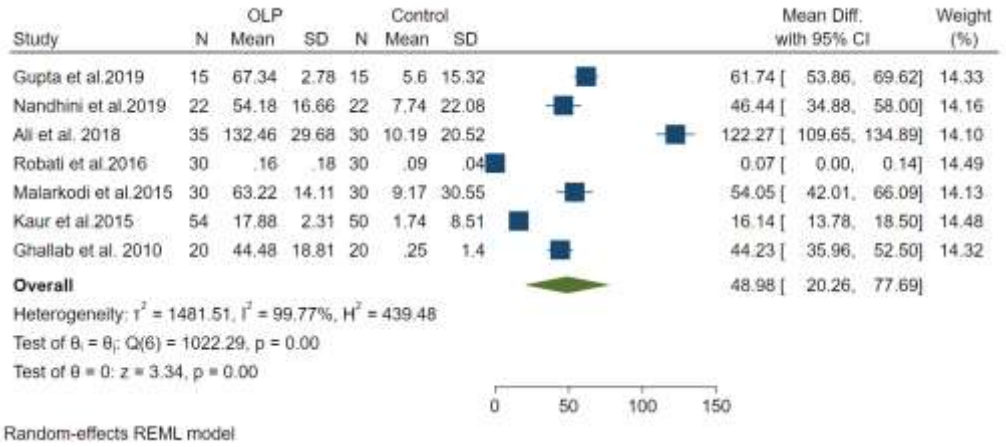

Figure2. Forest plots showed mean difference of TNF-a levels of saliva in patients with oral lichen planus vs heathy patients.

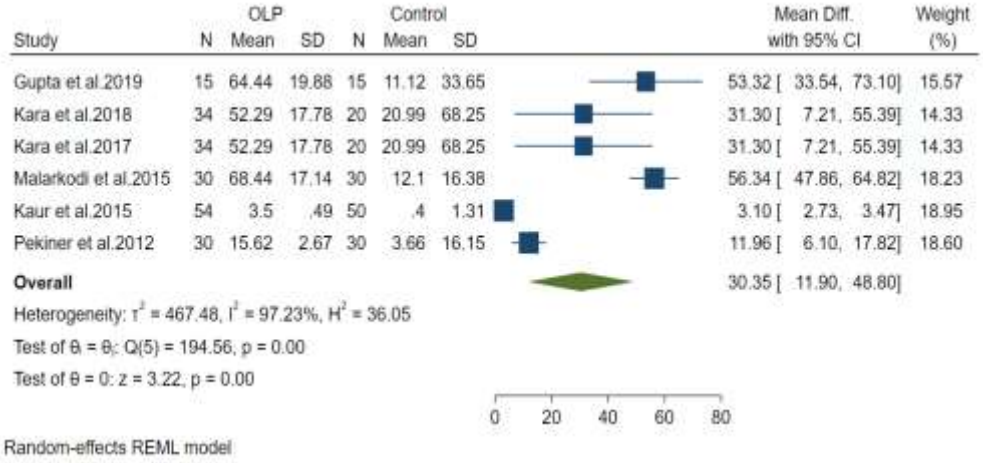

Figure3. Forest plots showed mean difference of TNF-a levels of serum in patients with oral lichen planus vs heathy patients.

Table3. Risk of bias assessment

study	Selection	Comparability	Exposure outcome	Total
Gupta et al.2019 (12)	2	1	3	6
Nandhini et al.2019(13)	2	1	2	5
Kara et al.2018 (14)	2	3	3	8
Ali et al. 2018 (15)	2	1	2	5
Kara et al.2017 (16)	1	1	3	5
Robati et al.2016 (17)	2	3	3	8
Malarkodi et al.2015(18)	2	3	3	8
Kaur et al.2015 (19)	3	2	3	8

Pekiner et al.2012 (20)	4	1	3	8
Ghallab et al. 2010 (21)	4	1	3	8
Mean of score	6.9			

High quality (total score: 7-9), moderate quality (total score: 4-6), low quality (total score: 0-3).

IV. DISCUSSION

The present systematic review and Meta-analysis findings shows the mean difference of TNF-a levels of saliva and serum between patients with oral lichen planus and healthy patients was 48.98 pg/mL and 30.35 pg/mL, Respectively. There was statistically significant difference between OLP patients and healthy patients (p=0.00). The meaning of the sentence was Saliva and serum TNF-a levels were significantly increased in patients with OLP compared with healthy patients. The immunologic system plays a significant role in OLP(22). These results show that the level of TNF-a in saliva is higher than serum, so using TNF-a in saliva is more beneficial and has more benefits than serum, also this method can be used by people with moderate education and to Indirectly collected and analyzed, it shows different values of biochemical and immunological parameters(23). Saliva is body fluid, it is important to recognize and can be used in tests measuring biologic markers and systemic and especially oral pathologies(24). In a recent meta-analysis by Mozaffari et al. (8) showed The mean difference of salivary TNF-a levels in patients with OLP versus healthy controls was 25.90 pg/mL and serum TNF-a levels was 1.65 pg/mL. These results are close to the present study and are consistent. Gupta et al. (12) showed The serum and salivary TNF-a level was significantly higher in lichen planus patients than in patients with normal oral mucosa. Also the result pf Nandhini et al. (13) study showed The salivary TNF-α level was significantly higher ($P < 0.001$) in patients than in controls. Kara et al.2018 reported TNF-α, a proinflammatory cytokine, may have an important role in the pathogenesis of lichen planus. According to Ali et al. (15) study, higher levels of TNF- in saliva compared to healthy individuals play an important role in oral lichen planus. Robati et al.2016 (17) showed The salivary levels of TNF-α and IL-6 were significantly increased in the group with OLP. However Malarkodi et al. (18) suggests that saliva can be a good alternate to serum to analyze TNF-*α* in oral lichen planus patients. Research also shows that TNF-a levels in saliva and serum can be affected by age, type of OLP, stress, alcohol consumption, smoking and genetics (25-28). One of the limitations of the present study is the inconsistency between the study population and the variable timing of saliva collection, various TNF-a measurement kits and methods, changes in healthy control group selection criteria, type and severity of OLP during studies, and non-uniform compliance. Age and sex between patients with OLP and the control group were noted.

V. CONCLUSION

The present study showed the salivary and serum levels of TNF-α were significantly increased in oral lichen planus patients to compared healthy patients. Also the level of TNF-a in saliva is higher than serum. Factors such as age, OLP type, stress, alcohol consumption, smoking, and genetics are suggested to be considered in future research.

VI. REFERENCES

[1] Stang a. Critical evaluation of the newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010;25(9):603-5.

[2] Lodi g, manfredi m, mercadante v, murphy r, carrozzo m. Interventions for treating oral lichen planus: corticosteroid therapies. Cochrane database of systematic reviews. 2020.(2)

[3] González-moles má, warnakulasuriya s, gonzález-ruiz i, gonzález-ruiz l, ayén á, lenouvel d, et al. Worldwide prevalence of oral lichen planus: a systematic review and meta-analysis. Oral diseases. 2020\.

[4] Agha-hosseini f, barati h, moosavi m-s. Aquaporin3 (aqp3) expression in oral epithelium in oral lichen planus. Experimental and molecular pathology. 2020:104441.

[5] Shen n, wang z, wang c, zhang j, liu c. Methane alleviates inflammation and apoptosis of dextran sulfat sodium-induced inflammatory bowel diseases by inhibiting toll-like receptor 4 (tlr4)/myeloid differentiation factor 88 (myd88)/nuclear translocation of nuclear factor-κb (nf-κb) and endoplasmic reticulum stress pathways in mice. Medical science monitor. 2020;26.

[6] Okuda-hanafusa c, uchio r, fuwa a, kawasaki k, muroyama k, yamamoto y, et al. Turmeronol a and turmeronol b from curcuma longa prevent inflammatory mediator production by lipopolysaccharide-

ISSN- 2394-5125 VOL 7, ISSUE 15, 2020

stimulated raw264. 7 macrophages, partially via reduced nf-κb signaling. Food & function. 2019;10(9):5779-88.
[7] Parameswaran n, patial s. Tumor necrosis factor-α signaling in macrophages. Critical reviews™ in eukaryotic gene expression. 2010;20.(2)
[8] 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 surgery, oral medicine ,oral pathology and oral radiology. 2017;124(3):e183-e9.
[9] Pezelj-ribaric s, prso ib, abram m, glazar i, brumini g, simunovic-soskic m. Salivary levels of tumor necrosis factor-α in oral lichen planus. Mediators of inflammation. 2004;13(2):131-3.
[10] Lv k-j, chen t-c, wang g-h, yao y-n, yao h. Clinical safety and efficacy of curcumin use for oral lichen planus: a systematic review. Journal of dermatological treatment. 2019;30(6):605-11.
[11] Moher d, liberati a, tetzlaff j, altman dg, altman d, antes g ,et al. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement (chinese edition). Journal of chinese integrative medicine. 2009;7(9):889-96.
[12] Gupta s, ahuja n, nadaf a. Measurement of serum and salivary tnf-α in oral lichen planus patients. International journal of research and review. 2019;6(3):174-7.
[13] Nandhini j, ramasamy s, kaul rn, sakthivel s, munshi ma, sunil s. Estimation of the level of salivary proinflammatory cytokine in oral lichen planus–a case–control study in cuddalore-based population. Journal of indian academy of oral medicine and radiology. 2019;31(2):128.
[14] Kara ya. The measurement of serum tumor necrosis factor-alpha levels in patients with lichen planus. Indian journal of dermatology. 2018;63.297:(4)
[15] Ali vs, abd st, abdulla wl. The salivary concentration of tumor necrosis factor alpha and transforming growth factor beta in iraqi patients with oral lichen planus.
[16] 1Kara ya. The measurement of serum tnf-α levels in patients with lichen planus. 2017.
[17] Robati m, yousefimanesh h, maleki r, brujerdnia mg. Salivary tumor necrosis factor alpha and interleukin 6 levels in oral lichen planus patients. Indian j oral sci. 2016;7:79-82.
[18] Malarkodi t, sathasivasubramanian s. Quantitative analysis of salivary tnf-α in oral lichen planus patients. International journal of dentistry. 2015;2015.
[19] Kaur j, jacobs r. Proinflammatory cytokine levels in oral lichen planus, oral leukoplakia, and oral submucous fibrosis. Journal of the korean association of oral and maxillofacial surgeons. 2015;41(4):171-5.
[20] Pekiner fn, demirel gy, borahan mo, özbayrak s. Cytokine profiles in serum of patients with oral lichen planus. Cytokine. 2012;60(3):701-6.
[21] Ghallab na, el-wakeel n, shaker og. Levels of salivary ifn-gamma, tnf-alfa, and tnf receptor-2 as prognostic markers in (erosive) oral lichen planus. Mediators of inflammation. 2010;2010.
[22] Mozaffari hr, ziaei n, nazari h, amiri sm, sharifi r. Oral lichen planus treatment by co 2 laser: a systematic review. Asian journal of scientific research. 2017;10(1):1-9.
[23] Freudenreich o. Dual diagnosis. Psychotic disorders: springer; 2020. P. 351-8.
[24] Barhoumi l, bellagambi fg, vivaldi fm, baraket a, clément y, zine n, et al. Ultrasensitive immunosensor array for tnf-α detection in artificial saliva using polymer-coated magnetic microparticles onto screen-printed gold electrode. Sensors. 2019;19(3):692.
[25] Tanni se, pelegrino nr, angeleli ay, correa c, godoy i. Smoking status and tumor necrosis factor-alpha mediated systemic inflammation in copd patients. Journal of inflammation. 2010;7(1):29.
[26] Singh p, gupta nd, bey a, khan s. Salivary tnf-alpha: a potential marker of periodontal destruction. Journal of indian society of periodontology. 2014;18(3):306.
[27] Petrescu f, voican sc, silosi i. Tumor necrosis factor-α serum levels in healthy smokers and nonsmokers. International journal of chronic obstructive pulmonary disease. 2010;5:217.
[28] Gavala a, venetsanou k, kittas c, manolis e, yiambides a, myrianthefs p, et al. Decreased whole blood tnfα production capacity after acute alcohol exposure and lps stimulation ex vivo. Critical care. 2010;14(1):p13.