Archives of Oral Biology 140 (2022) 105445

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

Review

A systematic review and meta-analysis on serum and salivary levels of total antioxidant capacity and C-reactive protein in oral lichen planus patients

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ARTICLE INFO

Keywords:
lichen planus, oral
C-reactive protein
antioxidants
systematic review
meta-analysis

ABSTRACT

Objective: Oral lichen planus (OLP) is an inflammatory disease that total antioxidant capacity (TAC) and C-reactive protein (CRP) play an important role in its pathogenesis. In this meta-analysis, we compared the salivary and serum levels of TAC and CRP between OLP patients and controls.
Design: A comprehensive search was performed in four databases (PubMed, Scopus, Web of Science, and Cochrane Library). Standardized mean difference (SMD) and 95% confidence intervals (CI) were computed by the RevMan 5.3. Sensitivity analysis, subgroup analysis, meta-regression, and publication bias were analyzed by the CMA 2.0.
Results: Nineteen articles were included in the meta-analysis. The pooled SMDs were -1.80 μmol/L (95%CI: -2.75, -0.85; $p = 0.0002$) and -2.56 μmol/L (95%CI: -4.40, -0.72; $p = 0.006$) for the salivary and serum levels of TAC, respectively. The SMDs for salivary and serum levels of CRP were 0.64 μg/L (95%CI: 0.35, 0.94; $p < 0.0001$) and 0.97 mg/L (95%CI: 0.56, 1.338; $p < 0.00001$), respectively. Geographical area based on the country was a significant factor in the subgroup analysis for salivary TAC level. There was adequate evidence supporting the occurrence of less salivary and serum TAC levels in OLP patients than controls, but the amount of information was inadequate to make valid conclusions for salivary CRP level.
Conclusions: In OLP patients, salivary and serum levels of TAC is significantly lower while the salivary and serum levels of CRP is significantly higher than controls.

1. Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease or an oral potentially malignant disorder of unknown cause that is more common in females than males, histological changes can affect the pathogenesis and progression of the disease and the malignancy risk in OLP patients (Mozaffari, Mirbahari, & Sadeghi, 2018). OLP is linked with other systemic diseases such as high blood pressure and diabetes mellitus (Mozaffari et al., 2016) and could significantly impair quality of life (Tadakamadla et al., 2018). The pooled prevalence of OLP is 0.89% and 0.98% among the general population and clinical patients, respectively (Li et al., 2020), that recently a meta-analysis reported the worldwide prevalence of OLP was approximately 1%, with a marked geographical difference that the highest prevalence was in Europe (1.43%) and the lowest in India (0.49%) (González-Moles, Warnakulasuriya, et al., 2021). The OLP prevalence increases significantly and progressively from the age of 40 years (González-Moles, Warnakulasuriya, et al., 2021). In addition, the highest prevalence of OLP was observed in non-Asian countries at the age of 40 years and older (Li et al., 2020). A review and two systematic reviews reported that OLP is associated with an elevated risk of occurrence of oral cancers (Warnakulasuriya et al., 2021; González-Moles, Ramos-García, et al., 2021; Ramos-García et al.,

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https://doi.org/10.1016/j.archoralbio.2022.105445

Available online 10 May 2022
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Several recent meta-analyses showed an association between serum/salivary level of proinflammatory cytokines and OLP pathogenesis, which recommended using these as markers for diagnossis and therapeutic efficacy (Mozaffari et al., 2017; Mozaffari, Sharifi, Mirbahari, et al., 2018; Mozaffari, Sharifi, & Sadeghi, 2018; Mozaffari et al., 2019; Pekiner et al., 2012). Several recent meta-analyses also showed a link between the proinflammatory cytokine polymorphisms and the risk of OLP (Mozaffari et al., 2020; Shi et al., 2017; Zhou & Vieira, 2018). In addition, a significant role of serum/salivary levels of immunoglobulins (Mozaffari, Zavattaro, et al., 2018) and hormones such as cortisol (Lopez-Jornet et al., 2019) on the OLP pathogenesis is suggested. Therefore, these findings demonstrate the significance of the immune response in OLP and suggest that OLP can be a chronic T cell-mediated inflammatory disease (Kurago, 2016; Roopashree et al., 2010), as well as the role of genetics in development and pathogenesis of OLP (Pan et al., 2020). Some literature also indicates that behavioral and environmental factors (Kats et al., 2019; Mester et al., 2018; Amin et al., 2020; Agha Hosseini et al., 2016) such as smoking, infections, and stress play an important role in the pathogenesis of OLP.

C-reactive protein (CRP) is an inflammatory marker that is synthesized by hepatocytes and synthesis of this factor is regulated by proinflammatory cytokines (Kruse et al., 2010). Adipocytokines are closely related to CRP (Maachi et al., 2004). Higher salivary CRP levels are observed in OLP patients compared to the controls (Honarmand et al., 2021). It has been suggested that antioxidant imbalances can have a main role in OLP development (Agha-Hosseini et al., 2012; Aly & Shahin, 2010). Total antioxidant capacity (TAC) is used to assess the antioxidant status of salivary and serum samples and can assess the antioxidant response to free radicals produced in a particular disease (Rubio et al., 2016). Some studies reported an association between salivary/serum levels of TAC and CRP (Azizi & Farshchi, 2012; Upadhyay et al., 2010; Shiva et al., 2020) with OLP development and others did not find any association (Honarmand et al., 2021; Lopez-Jornet et al., 2014; Shiva & Arab, 2016). To the best of our knowledge, there is no meta-analysis of the association of salivary/serum levels of TAC and CRP with OLP development, so we aimed to conduct a meta-analysis, meta-regression, and trial sequential analysis (TSA) of the association of salivary and serum levels of TAC and CRP with OLP development.

2. Materials and methods

2.1. Study design

The reporting of the present meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols (Moher et al., 2010). The PECO (Population, Exposure, Comparator, and Outcome) question (Morgan et al., 2016; Morgan et al., 2018) was: Are serum and salivary TAC and CRP levels different in OLP patients compared to controls? (humans with and without OLP at any age and sex: P; OLP disease, E; OLP patients compared to controls: C; and changes in the serum and salivary TAC and CRP levels: O).

2.2. Identification of articles

A comprehensive search was performed by one author (M.S) in four databases of PubMed/Medline, Web of Science, Scopus, and Cochrane Library until June 16, 2021, without any restrictions to retrieve the relevant articles. The search strategy was ("C-reactive protein" or "CRP" or "total antioxidant capacity" or "TAC") and ("oral lichen planus" or "OLP"). Moreover, the citations of the retrieved articles linked to the subject were examined to ensure that no study was missed and then the titles and abstracts of the relevant articles were evaluated by the same author (M.S); subsequently, the full-texts of the articles following the eligibility criteria were downloaded. Another author (H.R.M) rechecked the process of the retrieved articles. A lack of agreement among the two authors was resolved by a third author (J.T).

2.3. Inclusion and exclusion criteria

The included inclusion criteria were: 1) case-control studies without any restrictions, 2) studies reporting salivary and serum TAC and CRP levels in OLP patients and controls, 3) OLP patients were diagnosed clinically and pathologically, 4) unstimulated saliva were collected in the studies, 5) salivary samples were gathered in the morning, and 6) OLP patients had no other systemic diseases. On the contrary, review articles, studies with incomplete data, studies without a control group, studies including patients with a mix of oral diseases, conference papers, book chapters, and comment papers were removed.

2.4. Data collection

Two authors (M.S and H.R.M) separately extracted the data of the articles involved in the meta-analysis. Extracted data were included first author, publication year, the country and continent of participants, sample size of OLP patients and controls, type of OLP, and the mean levels of salivary and serum of TAC and CRP in two groups.

2.5. Quality evaluation

The quality of the studies was evaluated using the Newcastle-Ottawa Scale (NOS) scale (Wells et al., 2011). The maximum score of each study was nine and a high-quality study had a score $\geq$ of 7. The quality assessment was done by one author (M.S).

2.6. Statistical analysis

The effect sizes were computed using the Review Manager 5.3 (RevMan 5.3) presenting the standardized mean difference (SMD) along with 95% confidence interval (CI) of serum and salivary levels of TAC and CRP between the OLP patients and controls. To estimate the pooled SMD significance, the Z-test was applied with a *p*-value (two-sided) less than 0.05 considered significant. When I^2 statistic ($P_{heterogeneity} < 0.1$ or $I^2 > 50\%$) represented a significant heterogeneity; a random-effects model (DerSimonian & Laird, 2015) was performed, and if when the heterogeneity was insignificant, a fixed-effect model (Mantel & Haenszel, 1959) was utilized.

A subgroup analysis was performed according to the country and continent of origin of the studies, and type of OLP. A random-effects meta-regression analysis was conducted based on the publication year and sample size of the included studies. Bootstrap method for meta-regression was estimated by IBM SPSS 22.0 software. The degree of publication bias was determined using a funnel plot and Egger's regression test and therefore, Egger's test is commonly used to assess potential publication bias in a meta-analysis via funnel plot asymmetry. Egger's test assesses a linear regression of the intervention effect estimates on their standard errors weighted by their inverse variance (Egger et al., 1997) and Begg's test evaluates if there is a significant relationship between the ranks of the effect estimates and the ranks of their variances (Begg & Mazumdar, 1994){Egger, 1997 #128}{Egger, 1997 #128}. The potential publication bias was examined in a Begg's funnel plot by Begg's test and the degree of asymmetry was examined by Egger's test. The *p*-values of Egger's and Begg's tests were extracted and a *p-value* (two-sided) less than 0.10 demonstrated existence of the publication bias. To evaluate the stability of pooled SMDs, both "one-study-removed" and "cumulative" analyses were used. These analyses (publication bias and sensitivity analyses) were carried out using the Comprehensive Meta-Analysis version 2.0 (CMA 2.0) software.

To address false-positive or negative conclusions from meta-analyses (Imberger et al., 2016), TSA was conducted using TSA software (version 0.9.5.10 beta) (Copenhagen Trial Unit, Centre for Clinical Intervention

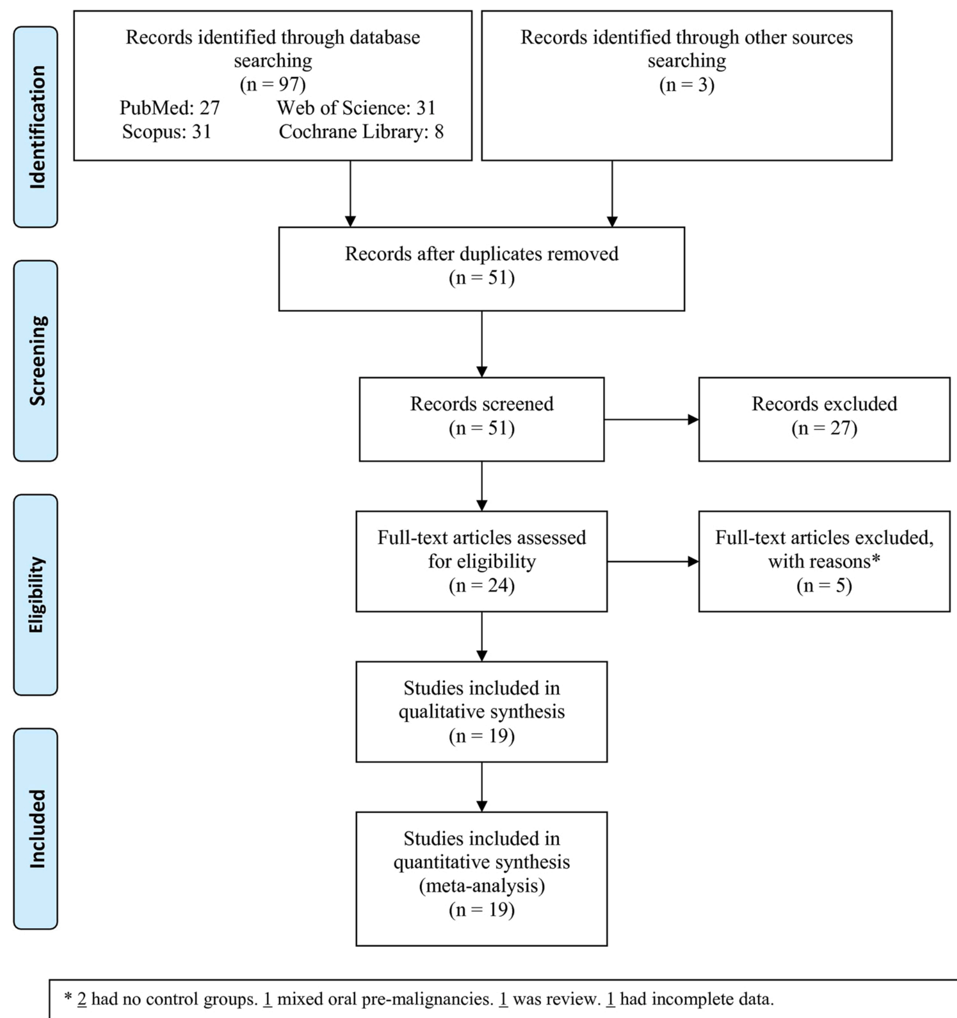

Fig. 1. Flowchart of the study selection.

Research, Rigshospitalet, Copenhagen, Denmark) (Wetterslev et al., 2017). A futility threshold could be examined by TSA to achieve a result of no impact before achieving the information size. The required information size (RIS) with an alpha risk of 5%, a beta risk of 20%, and a two-sided boundary type was computed. We estimated D^2 as 100% for the salivary level and 99% for the serum level of TAC, and the MD and

Table 1
Characteristics of the articles included in the meta-analysis.

The First author, publication year	Country	Ethnicity	Number of cases	Number of controls	Type of OLP	Outcome	Sample
(Battino et al., 2008)	Romania	Caucasian	20	20	Mixed	TAC	Saliva
(Agha-Hosseini et al., 2009)	Iran	Caucasian	30	30	Mixed	TAC	Saliva
(Upadhyay et al., 2010)	India	Asian	32	15	Unknown	TAC	Serum
(Miricescu et al., 2011)	Romania	Caucasian	20	20	Mixed	TAC	Saliva
(Agha-Hosseini et al., 2012)	Iran	Caucasian	32	30	Mixed	TAC	Saliva
(Azizi and Farshchi, 2012)	Iran	Caucasian	48	44	Erosive	TAC	Saliva
(Abdolsamadi et al., 2014)	Iran	Caucasian	36	36	Erosive	TAC	Saliva
(Lopez-Jornet et al., 2014)	Spain	Caucasian	40	30	Mixed	TAC	Saliva
(Shirzad et al., 2014)	Iran	Caucasian	30	30	Erosive	TAC	Saliva
(Totan et al., 2015)	Romania	Caucasian	30	30	Mixed	TAC	Saliva & Serum
(Darczuk et al., 2016)	Poland	Caucasian	62	30	Mixed	TAC	Saliva
(Hashemy et al., 2016)	Iran	Caucasian	25	23	Mixed	TAC	Serum
(Shiva and Arab, 2016)	Iran	Caucasian	22	22	Mixed	TAC	Saliva & Serum
(Shahidi et al., 2017)	Iran	Caucasian	32	15	Mixed	CRP	Saliva
(Tunali-Akbay et al., 2017)	Turkey	Caucasian	20	20	Mixed	TAC	Saliva
(Tvarijonaviciute et al., 2017)	Spain	Caucasian	20	31	Unknown	CRP	Saliva
(Shiva et al., 2020)	Iran	Caucasian	22	22	Unknown	CRP	Saliva & Serum
(Honarmand et al., 2021)	Iran	Caucasian	20	20	Unknown	CRP	Saliva
(Uppal et al., 2021)	India	Asian	30	30	Unknown	CRP	Saliva & Serum

Abbreviations: OLP, Oral lichen planus; TAC, Total antioxidant capacity; CRP, C-reactive protein. Note: Mixed type includes two or more types of OLP (plaque, reticular, erosive, and ulcerative, atrophic, and keratotic lesions).

Table 2
Quality score of each study were entered to the meta-analysis.

The First author, publication year	Selection (0-4)				Comparability (0-2)		Exposure (0-3)			Total score
	Case definition adequate	Representativeness of the case	Selection of the control	Definition of the control	Main factor	Additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
(Battino et al., 2008)	*	*	*	*	-	-	*	*	*	7
(Agha-Hosseini et al., 2009)	*	*	*	*	*	-	*	*	*	8
(Upadhyay et al., 2010)	*	*	*	*	*	-	*	*	*	8
(Miricescu et al., 2011)	*	*	-	*	-	-	*	*	*	6
(Agha-Hosseini et al., 2012)	*	*	-	*	-	*	*	*	*	7
(Azizi & Farshchi, 2012)	*	*	*	*	*	-	*	*	*	8
(Abdolsamadi et al., 2014)	*	*	*	*	*	*	*	*	*	9
(Lopez-Jornet et al., 2014)	*	*	*	*	*	*	*	*	*	9
(Shirzad et al., 2014)	*	*	*	*	*	*	*	*	*	9
(Totan et al., 2015)	*	*	*	-	-	-	*	*	*	6
(Darczuk et al., 2016)	*	*	-	*	-	*	*	*	*	7
(Hashemy et al., 2016)	*	*	*	*	*	*	*	*	*	9
(Shiva & Arab, 2016)	*	*	*	*	*	*	*	*	*	9
(Shahidi et al., 2017)	*	*	*	*	*	*	*	*	*	9
(Tunali-Akbay et al., 2017)	*	*	*	*	*	*	*	*	*	9
(Tvarijonaviciute et al., 2017)	*	*	*	*	-	*	*	*	*	8
(Shiva et al., 2020)	*	*	*	-	*	*	*	*	*	8
(Honarmand et al., 2021)	*	*	*	*	*	*	*	*	*	9
(Uppal et al., 2021)	*	*	*	*	*	*	*	*	*	9

variance based on empirical assumptions that were autogenerated by the software. If the Z-curve reached the RIS line or monitored the boundary line or futility area, enough cases were involved in the studies, and the conclusions were reliable. Otherwise, the amount of information was not large enough and there was a requirement for further evidence. The units of the salivary and serum levels of TAC were μmol/L, the salivary level of CRP was μg/L, and the serum level of CRP was mg/L. The salivary level of CRP in one study was presented on a graph (Tvarijonaviciute et al., 2017) was extracted for this meta-analyses using GetData Graph Digitizer 2.26 software. All authors examined the final statistical analyses and any concerns were resolved by a discussion.

3. Results

3.1. Study selection

On searching electronic databases and other sources, 100 records were identified. After removing irrelevant and duplicate records, 24 full-text articles were evaluated (Fig. 1). Then, 5 full-text articles were excluded with reasons (two had no control groups, one mixed oral premalignancies, one was review, and one had incomplete data). At last, 19 articles {Abdolsamadi, 2014 #1;Agha-Hosseini, 2012 #3;Agha-Hosseini, 2009 #2;Azizi, 2012 #4;Battino, 2008 #5;Darczuk, 2016 #6; Hashemy, 2016 #7;Honarmand, 2021 #8;Lopez-Jornet, 2014 #10; Miricescu, 2011 #9;Shahidi, 2017 #11;Shirzad, 2014 #12;Shiva, 2016 #13;Shiva, 2020 #15;Totan, 2015 #16;Tunali-Akbay, 2017 #17; Tvarijonaviciute, 2017 #18;Upadhyay, 2010 #19;Uppal, 2021 #20} were included in the qualitative and quantitative synthesis (meta-analysis).

3.2. Study characteristics

Out of nineteen articles analyzed, ten studies (Agha-Hosseini et al., 2012; Azizi & Farshchi, 2012; Lopez-Jornet et al., 2014; Battino et al., 2008; Agha-Hosseini et al., 2009; Miricescu et al., 2011; Abdolsamadi et al., 2014; Shirzad et al., 2014; Darczuk et al., 2016; Tunali-Akbay et al., 2017) reported the salivary level of TAC, two (Upadhyay et al., 2010; Hashemy et al., 2016) reported the serum level of TAC, three (Honarmand et al., 2021; Tvarijonaviciute et al., 2017; Shahidi et al., 2017) reported the salivary level of CRP, two (Shiva & Arab, 2016; Totan et al., 2015) reported both the salivary and serum levels of TAC, and two (Shiva et al., 2020; Uppal et al., 2021) reported both the salivary and serum levels of CRP (Table 1).

3.3. Quality score

The mean of quality score for all articles was 8.1 that seventeen articles had high quality (Table 2).

3.4. Pooled analyses

The pooled analyses for the salivary and serum levels of TAC and the

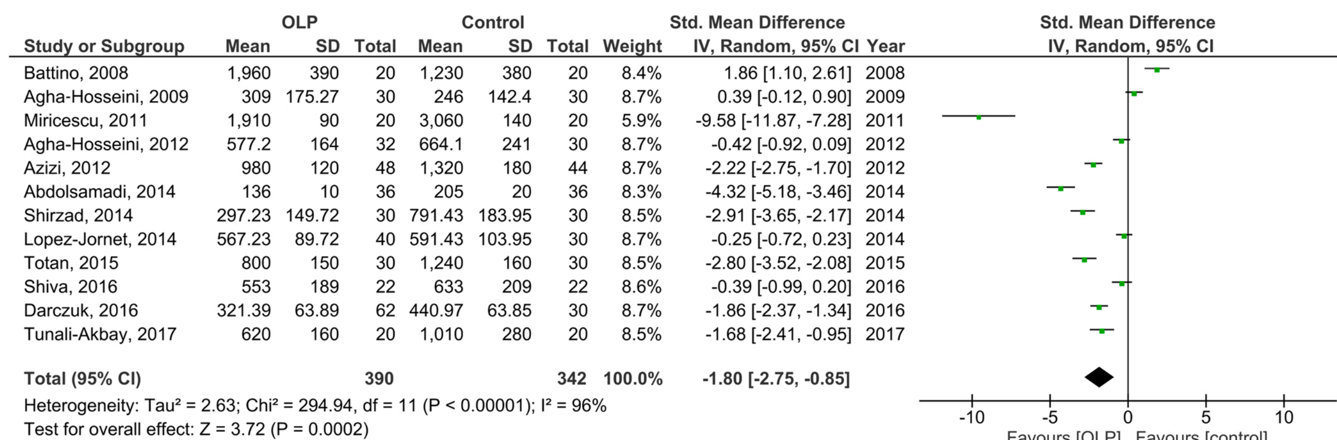

Fig. 2. Random-effects forest plot analysis of salivary level of total antioxidant capacity between the OLP patients and controls. Standardized mean difference was represented by the green square and 95% CI was represented by horizontal line. The area of the green square is proportional to the specific study weight to the overall meta-analysis. The center of the diamond illustrates the pooled mean difference and its width shows the pooled 95% CI. *Abbreviations*: OLP, Oral lichen planus; CI, Confidence interval.

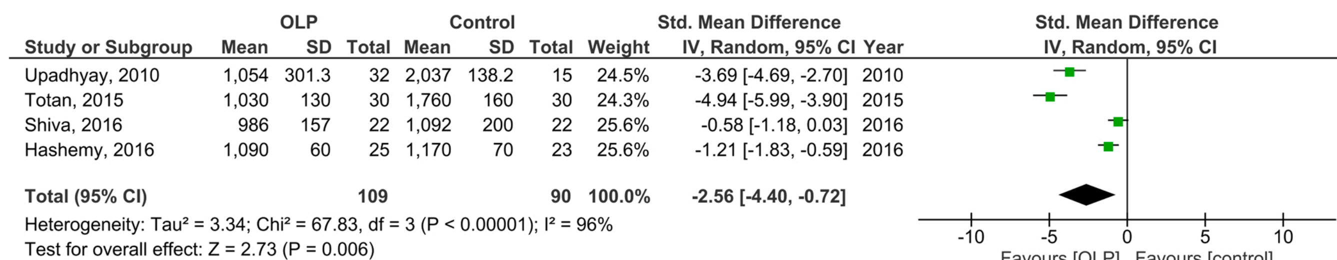

Fig. 3. Random-effects forest plot analysis of serum level of total antioxidant capacity between the OLP patients and controls. Standardized mean difference was represented by the green square and 95% CI was represented by horizontal line. The area of the green square is proportional to the specific study weight to the overall meta-analysis. The center of the diamond illustrates the pooled mean difference and its width shows the pooled 95% CI. *Abbreviations*: OLP, Oral lichen planus; CI, Confidence interval.

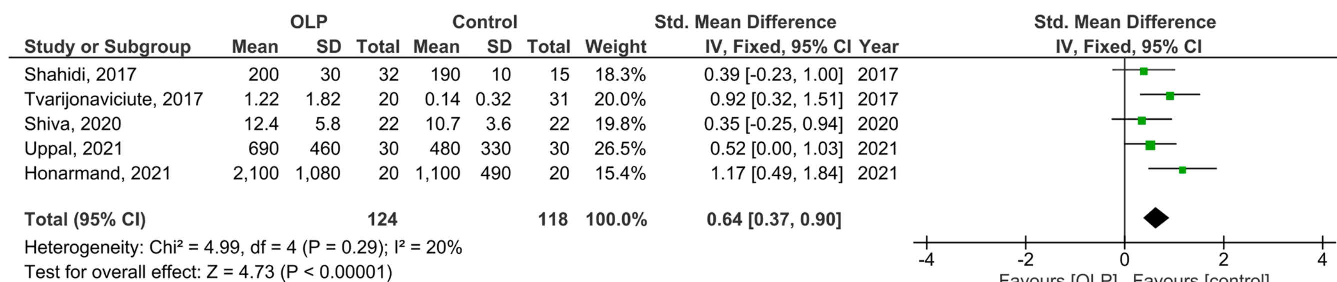

Fig. 4. Random-effects forest plot analysis of salivary level of C-reactive protein in OLP patients and controls. Standardized mean difference was represented by the green square and 95% CI was represented by horizontal line. The area of the green square is proportional to the specific study weight to the overall meta-analysis. The center of the diamond illustrates the pooled mean difference and its width shows the pooled 95% CI. *Abbreviations*: OLP, Oral lichen planus; CI, Confidence interval.

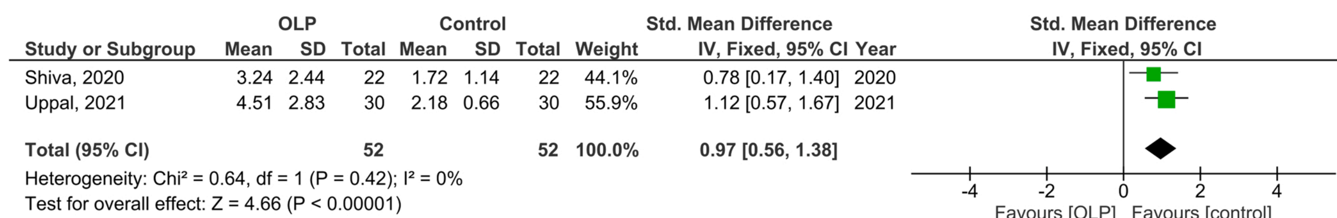

Fig. 5. Random-effects forest plot analysis of serum level of C-reactive protein between the OLP patients and controls. Standardized mean difference was represented by the green square and 95% CI was represented by horizontal line. The area of the green square is proportional to the specific study weight to the overall meta-analysis. The center of the diamond illustrates the pooled mean difference and its width shows the pooled 95% CI. *Abbreviations*: OLP, Oral lichen planus; CI, Confidence interval.

Table 3
Subgroup analyses based on country, continent, and type of disease for evaluation of salivary level of total antioxidant capacity in oral lichen planus patients compared to controls.

Variable	Subgroup (N)	SMD	95%CI	*p*-value	I^2	P_h
Country	Iran (6)	-1.62	-2.90, -0.34	0.01	96%	<0.00001
	Romania (3)	-3.36	-7.99, 1.26	0.15	98%	<0.00001
	Spain (1)	-0.25	-0.72, 0.23	0.30	-	-
	Poland (1)	-1.86	-2.37, -1.34	<0.00001	-	-
	Turkey (1)	-1.68	-2.41, -0.95	<0.00001	-	-
Continent	Asia (7)	-1.63	-2.74, -0.51	0.004	96%	<0.00001
	Europe (5)	-2.21	-4.12, -0.29	0.02	97%	<0.00001
Type of OLP	Erosive (3)	-3.11	-4.28, -1.95	<0.00001	00%	0.0002
	Mixed (9)	-1.30	-2.30, -0.30	0.01	96%	<0.00001

Abbreviations: N, Number of studies; SMD, Standardized mean difference; CI, Confidence interval; OLP, Oral Lichen Planus; Ph, Pheterogeneity.

salivary and serum levels of CRP are shown in Figs. 2, 3, 4, and 5, respectively. The pooled SMDs were -1.80 µmol/L (95%CI: -2.75, -0.85; $p = 0.0002$; $I^2 = 96\%$) for the salivary level of TAC, -2.56 µmol/L (95% CI: -4.40, -0.72; $p = 0.006$; $I^2 = 96\%$) for the serum level of TAC, 0.64 µg/L (95%CI: 0.37, 0.90; $p < 0.00001$; $I^2 = 20\%$) for the salivary level of CRP, and 0.97 mg/L (95%CI: 0.56, 1.38; $p < 0.00001$; $I^2 = 0\%$) for the serum level of CRP. The difference of the salivary and serum levels of TAC and the salivary and serum levels of CRP between the OLP patients and controls was statistically significant. Salivary and serum levels of TAC were significantly lower and the salivary and serum levels of CRP were significantly higher in the OLP patients than the controls.

3.5. Subgroup analysis

The results of the subgroup analyses showed that geographical area based on the country was a factor that significantly influenced the pooled estimate of the salivary level of TAC (Table 3). But geographical area (based on the continent) and the type of OLP were not effective factors on the pooled estimate of the salivary level of TAC.

3.6. Meta-regression

An increase in the sample size could significantly change the serum level of TAC (Table 4). With an increase in the sample size, the serum levels of TAC reduced. However, an increase in the publication year could not significantly change the salivary levels of TAC and CRP and the serum level of TAC. Also, an increase in the sample size could not significantly change the salivary levels of TAC and CRP. We didn't estimate the meta-regression for the salivary and serum levels of CRP and the serum level of TAC because they included less than 10 studies (https://training.cochrane.org/handbook/current), therefore bootstrap method (with 1000 replications per meta-regression analysis) was implemented. The 95%CI of bootstrap was (-1.000, 1.000) for the correlation of the serum level of TAC with the publication bias, (-1.000, -0.478) for the correlation of the serum level of TAC with the sample size, (-1.000, 1.000) for the correlation of the salivary level of CRP with the publication bias, (-0.635, 0.623) for the correlation of the salivary level of CRP with the sample size. The 95%CIs of bootstrap on the two sides had same signs (negative, negative) for the correlation of the serum level of TAC with the sample size and therefore the bootstrapped correlation could be significant. Our findings suggested that there was a relationship between the serum level of TAC with the sample size. But for others, there was no significant correlation. For the serum level of CRP, the correlation couldn't calculate because it included two studies.

3.7. Sensitivity analysis

"one-study-removed" and "cumulative analysis" showed the pooled data stability for the salivary/serum levels of TAC and the salivary level of CRP (Supplementary file).

3.8. Publication bias

Egger's and Begg's tests reveal any publication bias for the salivary and serum levels of TAC (*p*-values of both tests < 0.10), but there was no publication bias for the salivary level of CRP (*p*-values of both tests > 0.10). Fig. 6 shows the Begg's funnel plots. We did not calculate the publication bias for the serum level of CRP because it included less than three studies.

3.9. 3.9. Trial sequential analysis

The results illustrated that the cumulative Z-curve (blue line) has successfully crossed both conventional boundary (Z-statistic above 1.96) and the trial sequential monitoring boundary (concave red line) for the salivary and serum levels of TAC (Fig. 7). The TSA showed sufficient evidence supporting the finding of lower salivary and serum levels of TAC in the OLP patients compared to controls (the conclusion is reliable) and therefore further relevant studies are unnecessary. In contrast, the Z-curve did not reach the RIS line or monitored the boundary line or futility area for the salivary level of CRP and therefore, the amount of information was not large enough needing more studies. We could not calculate the TSA for the serum level of CRP because it included less than three studies and for the salivary level because the variance was zero.

4. Discussion

OLP is a chronic inflammatory disease that affects the oral mucosa and its cause or etiology is unclear (Lu et al., 2015). The main results showed that the serum and salivary levels of TAC in the OLP patients were significantly lower than the controls. In addition, the salivary and serum levels of CRP in OLP patients were significantly higher than the controls.

One research reported that the salivary antioxidant vitamin levels (vitamins A, C, and E) in erosive OLP patients were significantly lower than the controls (Abdolsamadi et al., 2014), the possible protective effect of these vitamins in decreasing the OLP risk may be associated with the role of antioxidants in eliminating free radical damage and

Table 4
Meta-regression of salivary levels of total antioxidant capacity (TAC) in oral lichen planus (OLP) patients compared to controls based on publication year and sample size.

Variable (N)			Point estimate	Standard error	Lower limit	Upper limit	Z-value	*p*-value
Salivary TAC level (12)*	Publication year	Slope	-0.19757	0.16956	-0.52990	-0.13476	-1.16517	0.24395
	Sample size	Slope	-0.00347	0.02781	-0.05797	-0.05104	-0.12468	0.90078

Abbreviation: N, Number of studies.
* Including 390 OLP cases and 342 controls.

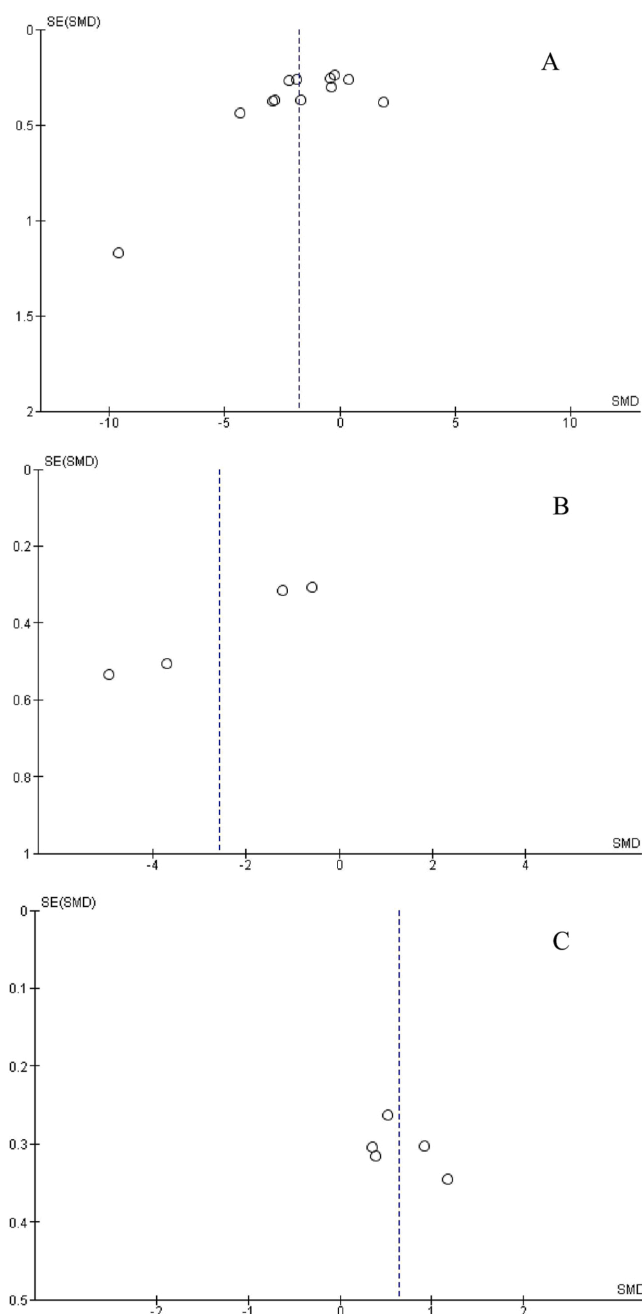

Fig. 6. Funnel plots of serum and salivary outcomes in oral lichen planus patients compared to controls. A) salivary level of total antioxidant capacity, B) serum level of total antioxidant capacity, and C) salivary level of C-reactive protein. *Abbreviations*: SMD, Standardized mean difference; SE, Standard error.

single oxygen (Jacob & Burri, 1996). A possible link between the inflammatory process and the metabolism of free radicals has been reported (Cimen et al., 2003). It has been suggested that an imbalance in free radical levels with antioxidants can play an important role in initiating and causing inflammatory lesions in the mouth (Mashayekhi et al., 2005; Battino et al., 1999). Therefore, decreased antioxidant capacity may indicate cell damage by oxidative processes (Azizi & Farshchi, 2012). OLP as a T cell-mediated mucocutaneous inflammatory disease involves the damaged epithelial cells (Mignogna et al., 2004). In confirmation of these results, our meta-analysis showed significantly decreased salivary and serum levels of TAC in the OLP patients compared to the controls. In addition, geographical area and type of OLP affected the salivary level of TAC as one study reported that oxidative stress in the erosive form of OLP is higher than in the reticulate form (Darczuk et al., 2016). In addition, Wang et al. (2001) indicated a role of genetics on total antioxidant status; genetics can be related to geographical area.

CRP is believed to have strong proinflammatory properties (Dasu et al., 2007) and the main function of this protein is to defend the host (Pepys & Hirschfield, 2003). CRP has been found to be increased in patients with several cancers (Szkandera et al., 2014; Graff & Beer, 2013; Wang & Sun, 2009) and systemic inflammation such as cardiovascular disease (Out et al., 2012). CRP is an acute-phase protein whose levels can increase by several environmental factors and diseases (Mengji et al., 2015). Kathiresan et al. (2006) showed that baseline CRP levels are affected by a variety of environmental and genetic factors. Our meta-analysis reported higher salivary serum levels of CRP in the OLP patients compared to the controls.

Low volume of saliva along with reduced accuracy in its processing compared to serum can make it difficult for these markers to be detected in saliva (Uppal et al., 2021), as our meta-analysis illustrates. However, there was a positive correlation between the serum and salivary CRP levels in oral potentially malignant disorders (Uppal et al., 2021). This suggests that researchers should use highly sensitive methods to determine the salivary level of CRP. The difference between the results of studies can be due to the differences in the sensitivity of the methods for detection or measurement of the salivary CRP level and even the difference in sampling as one study reported that CRP is a protein with changeable levels on daily basis (Mengji et al., 2015).

There were some limitations to this meta-analysis; the small number of studies prevented the conduction of subgroup analyses, meta-regression, TSA, sensitivity analysis, and publication bias assessment for all the outcomes, in addition to the high heterogeneity. In addition, our meta-analysis was not registered in any database and we could not use Embase database that these problems can increase the bias in our meta-analysis. Despite these limitations, this is the first meta-analysis to provide synthesized evidence on the association of salivary and serum levels of TAC and CRP and OLP. Further, we used TSA analysis to control the likelihood of false positives and negatives.

4.1. Conclusions

Low salivary and serum levels of TAC were observed in OLP patients compared to the controls while the salivary and serum levels of CRP were higher in OLP patients. Salivary levels of TAC were different based on the country of individuals. More studies with a higher number of participants are required, particularly, those assessing the CRP levels, to confirm the results of the present meta-analysis. Also, researchers should consider environmental and genetic factors which could significantly influence the serum and salivary levels of TAC and CRP. Therefore, well-designed studies with emphasis on risk factors in various ethnicities and with the more number of participants are needed in the future to confirm the result of the meta-analysis. In addition, future primary-level studies -not only meta-analyses- should pay attention to our limitations to reduce the bias.

Financial support and sponsorship

This study was funded by the Research Council of Kermanshah University of Medical Sciences, Kermanshah, Iran (Grant Number: 980991).

CRediT authorship contribution statement

Masoud Hatami: Conceptualization, Resources, Supervision, Writing – review & editing. **Mahya Rezaei**: Data curation, Writing – review & editing. **Masoud Sadeghi**: Formal analysis, Investigation, Methodology, Software, Writing – review & editing. **Jyothi Tadakamadla**: Validation, Visualization, Writing – review & editing. **Filiz**

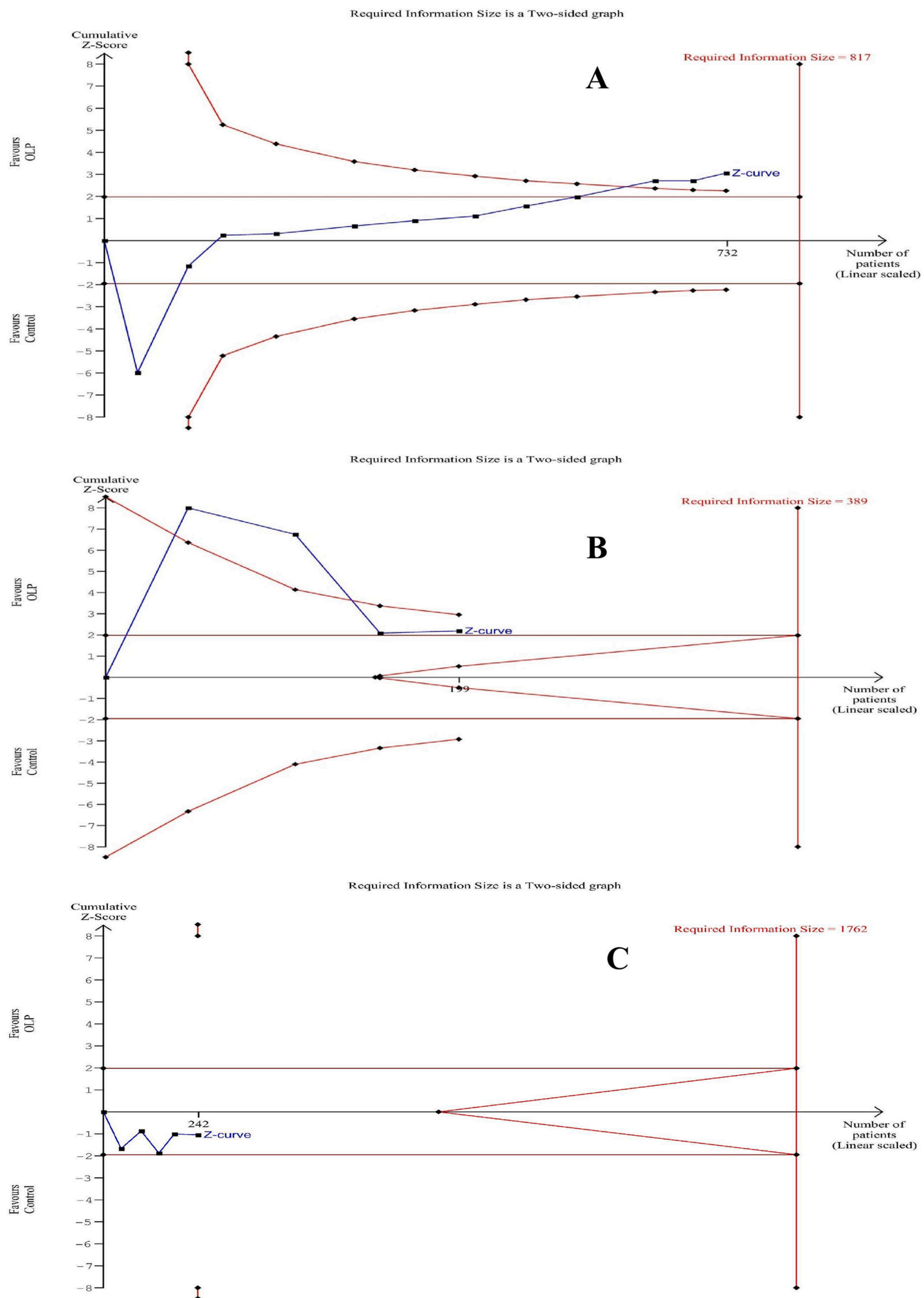

Fig. 7. Trial sequential analysis of serum and salivary factors in oral lichen planus patients compared to controls. A) salivary total antioxidant capacity level and (the required information size was calculated to 817), B) serum total antioxidant capacity level (the required information size was calculated to 389), and C) salivary C-reactive protein (the required information size was calculated to 1762).

Namdar Pekiner: Validation, Visualization, Writing – review & editing. **Hamid Reza Mozaffari**: Funding acquisition, Project administration, Writing – original draft.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgments

This work was performed in partial fulfillment of the requirements for a doctorate degree in General Dentistry (Mahya Rezaei), in Faculty of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.archoralbio.2022.105445.

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