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Evaluation of antioxidant-oxidant status of saliva in recurrent aphthous stomatitis: A systematic review

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Review Article

Abstract

BACKGROUND AND AIM: Recurrent aphthous stomatitis (RAS) as a common oral lesion may be created due to oxidative stress. In this study, we intend to examine the salivary antioxidant-oxidant status in patients with RAS.

METHODS: In this review study, all English and Persian articles were searched by relevant keywords from the PubMed, ScienceDirect, Cochrane, Scopus and SID databases from 1995 to 30 March 2020. Two independent reviewers performed the study selection using the specified eligibility criteria. Finally, Newcastle-Ottawa Scale (NOS) method was used for the quality evaluation of studies.

RESULTS: A systematic search on the references led to the identification of 87 articles, of which 68 were excluded and finally, 19 articles were included in the study. The majority of the studies (86%) showed no significant decrease in the total antioxidant capacity (TAC). In 71% of the studies, the malondialdehyde (MDA) levels exhibited an increasing trend and in all studies, Glutathione peroxidase (GPx) had a decreasing trend; the results in relation to uric acid were contradictory.

CONCLUSION: Beyond the need for more extensive research in this area, it can be concluded that since RAS has multifactorial etiology, changes in the body's antioxidant-oxidant status are considered as an effective factor along with other factors.

KEYWORDS: Saliva; Aphthous; Stomatitis; Antioxidants; Oxidative Stress

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Recurrent aphthous stomatitis (RAS) is one of the oral lesions in which 10-20 percent of the world's population is affected.[1] RAS is characterized by repeated ulceration with defined borders, which might be single or multiple and very painful. The healing of these ulcers is slow compared to traumatic lesions.[2] various factors have been reported as predisposing factors or related to RAS. However, the etiopathogenesis of the condition is still unknown and no definitive medication is available for its treatment and treatment of the affected individuals consists of symptomatic treatment modalities.[3] Several parameters including allergies, genetic predisposition, hormonal effects and immune factors, blood disorders, infective agents, malnutrition, stress, and trauma are often considered in the RAS occurrence.[4] The balance of the body's antioxidant-oxidant system and speeding up of the formation of free radicals are influenced by these parameters.[5] It is noted that the relationship between oxidative stress and RAS has been illustrated in the past studies.[6-8] Serum antioxidants levels are low in patients with RAS, as noted in previous studies.[9,10] There is also a deficiency in serum antioxidant enzymes in these patients, which is mentioned in the study by Gupta et al.[11]

Saliva as a combination of gingival crevicular fluid (GCF) and salivary glands secretions is at the forefront of the fight with oxidative stress.[12] Saliva contains antioxidants such as uric acid and albumin

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that are diffused to saliva from the plasma and GCF. Catalase (CAT) positive organisms are other sources of oral antioxidants.[12]

Conflicting results have been reported in the past studies on the status of salivary antioxidant-oxidant in patients with RAS. The purpose of this study is to review the status of salivary antioxidant-oxidant in patients with RAS.

Methods

This systematic review study was accepted by the ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran (ethical code: IR.TBZMED.REC.1398.167). A focused question was produced according to the participants, intervention, control, and outcomes (PICO) principles.[13] The focused question for this review was "Is there an association between salivary oxidant/antioxidant status and RAS?"

For gathering the data, English and Persian articles were searched for in PubMed, ScienceDirect, Cochrane, Scopus, and SID databases from 1995 to 30 March 2020. The searches were combined with the Medical Subject Heading (MeSH) terms and keywords of "recurrent aphthous stomatitis" or "recurrent aphthous ulcers" or "recurrent oral ulcers" and "saliva" and "antioxidant" and "oxidant" or "oxidative stress". The inclusion criteria were all the case-control studies that evaluated antioxidant-oxidant status of saliva in patients with RAS. The exclusion criteria were articles that evaluated these factors amongst patients who had another disease beside RAS. In the initial phase, the titles and abstracts of the articles were reviewed by two individuals separately based on the inclusion and exclusion criteria. Disagreements were resolved with the third author's comments. Next, the full text of the selected articles was reviewed. Newcastle-Ottawa Scale (NOS) method was used for the quality evaluation of studies with a maximum score of 9 for each study that scored > 7, meaning it was found to be a good-quality study.[14] Endnote X5 resource management software was used to organize the study titles and abstracts as well as identify duplicates. Microsoft Excel was used to extract the characteristics of studies. The details of the selected studies included the following: the name of the first author, the year of publication, number of patients in case group, number of people in control group, salivary antioxidant and oxidative stress levels.

Results

A systematic search of references led to the identification of 87 articles. Of these, 53 articles were excluded due to duplication and 13 ones after reviewing the title and abstracts. After reviewing the full text articles, 2 articles were excluded. Finally, 19 papers were selected for this study. The flow chart for the identified and imported articles is shown in figure 1.

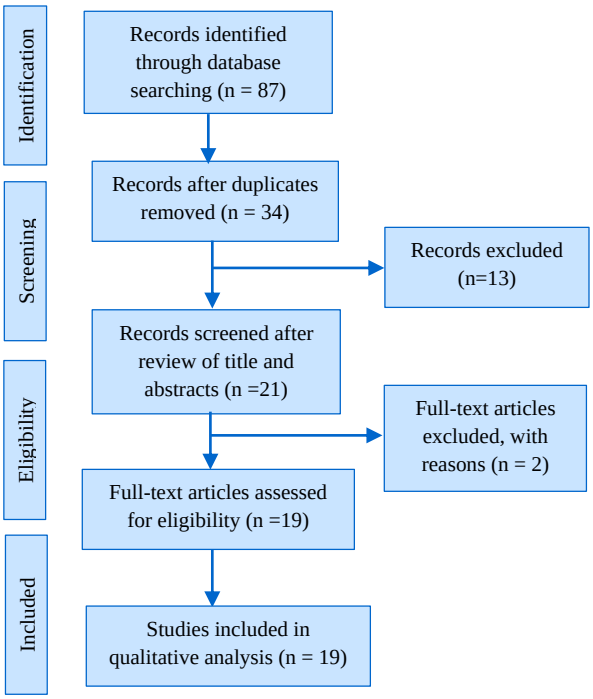

Figure 1. Flowchart of searching strategy

Table 1 shows the antioxidant and oxidative stress levels in patients with RAS.[15-33] In 71% of the studies, the malondialdehyde (MDA) levels exhibited an increasing trend,[17,18,22,23,25] and in all studies, glutathione peroxidase (GPx) had a decreasing trend;[16,17,27,28] the results in relation to uric acid were contradictory.[16,17,27,28]

Table 1. Salivary oxidant/antioxidant status in patients with recurrent aphthous stomatitis (RAS)

Authors	No. of Cases	No. of controls	Salivary antioxidant levels	Salivary oxidative stress levels
Rezaei et al.[15]	28	28	TAC: no significant difference in active phase ($P \leq 0.640$), increase in healing phase ($P \leq 0.034$)	
Jesija et al.[16]	40	40	SOD ($P \leq 0.0150$)*, CAT activity and UA ($P < 0.001$)*, GPx activity ($P < 0.001$)#	
Ziaudeen et al.[17]	30	30	SOD activity ($P < 0.005$)*, GPx activity and UA ($P < 0.005$)#	MDA ($P < 0.005$)*
Babaee et al.[18]	28	28	TAC ($P \leq 0.042$)#	MDA ($P < 0.001$)*
Kiran et al.[19]	30	30		SPOX ($P \leq 0.041$)#
Momen-Beitollahi et al.[20]	31	32	TAC: no significant difference ($P \leq 0.100$)	
Caglayan et al.[21]	25	50	TAC: no significant difference ($P > 0.050$)	TOS, OSI, MPO activity: no significant difference ($P > 0.050$)
Saral et al.[22]	30	20	A, E, C, vitamins ($P < 0.050$)#	MDA ($P < 0.005$)*
Farhad Mollashahi et al.[23]	30	30	TAC: no significant difference ($P \leq 0.055$)	MDA ($P < 0.001$)*
Khademi et al.[24]	25	24	A, E, C, vitamins: no significant difference ($P > 0.050$)	MDA: no significant difference ($P > 0.050$)
Al-Essa and Zaidan[25]	30	30	TAC: no significant difference ($P > 0.050$)	MDA ($P < 0.050$)*
Azizi et al.[26]	25	25	TAC: no significant difference ($P > 0.050$)	
Saxenal[27]	40	40	SOD and CAT activity ($P < 0.001$)*, UA ($P < 0.050$)*, GPx activity ($P < 0.001$)#	
Karincaogl et al.[28]	22	30	SOD ($P < 0.001$)*, CAT activity ($P < 0.0500$)*, GPx activity ($P < 0.001$)#, UA: no significant difference ($P > 0.050$)	
Prihanti et al.[29]	16	16		MDA: no significant difference ($P > 0.050$)
Kaliamoorthy et al.[30]	30	30	Albumin: in active stage of RAS ($P < 0.001$)*	
Ohashi et al.[31]	18	19		NO ($P \leq 0.010$)*
Sunitha and Shanmugam[32]	20	20		NO ($P < 0.001$)*
Jagtap and Baad[33]	20	30		NO ($P < 0.001$)

*Significant increase, #Significant decrease
TAC: Total antioxidant capacity; MDA: Malondialdehyde; SOD: Superoxide dismotase; GPx: Glutathione peroxidase; CAT: Catalase; SPOX: Salivary peroxidase; TOS: Total oxidant status; OSI: Oxidative stress index; MPO: Myeloperoxidase; NO: Nitric oxide

The majority of the studies (86%) showed no significant decrease in total antioxidant capacity (TAC).[15,20,21,23,25,26] Superoxide dismutase (SOD) and CAT activity (antioxidant enzymes) in all studies indicated significant increases.[16,17,27,28] The levels of salivary nitric oxide (NO), which is a gaseous free radical, were higher in all studies compared to the healthy individuals.[31-33]

Discussion

Saliva is at the forefront of the fight with free radicals which exhibits antioxidant capacity.[16] Researchers showed a disturbance in the balance of antioxidant-oxidant in patients with RAS, which accelerates the release of free radicals and increases salivary oxidative stress.[15-18]

Salivary oxidative stress can be considered as a criterion to diagnose, follow up, and treat certain diseases.[34] TAC as a diagnostic indicator of saliva includes enzymatic and non-enzymatic antioxidants.[35] Although some studies have shown a reduction in salivary levels of TAC in the RAS group compared to the healthy individuals, no important changes have been observed in many studies, suggesting that reactive oxygen species (ROS) has not an important role in creating RAS. The source of

contradictory results in various studies can be due to multiple factors including evaluation techniques, sample size, genetic differences in the study groups, effect of nutrition, and exposure to oxidative factors.

Oral cells are uniquely susceptible to free radical damage because the mucus membranes allow rapid absorption of substance across their surfaces. The increase in the free radicals from oxidative stress leads to further breakdown of cell walls and oral tissue.[16-19] The influence of oxidative stress on RAS pathophysiology has been reported due to upper levels of salivary NO in RAS group. Therefore, it is believed that NO results in cellular injuries, followed by erosion and ulceration.[31-33]

The reason for the increased activity of salivary antioxidant enzymes in RAS group can be explained by the fact that when creating RAS, defense mechanisms of saliva make the whole body send stored antioxidants to the required area.[28] The increase in salivary TAC levels from the stage of active lesions to the stage of recovery in the study by Rezaei et al.[15] may be due to two possible reasons. The first reason is that high TAC levels are a defense mechanism via inflammatory alterations in the tissue. The second reason is that due to pain in the mouth, patients alter their diet to consume more liquid foods and nectars which are commonly rich in vitamins and antioxidant agents which improve the condition of antioxidants throughout the body and saliva. The effect of diet on salivary antioxidant levels in support of this hypothesis has been shown in some studies.[36] However, alterations in the salivary antioxidant-oxidant levels depend on many factors which make it difficult to interpret the changes occurred. This issue could be considered as one of the limitations of this study.

Conclusion

It can be concluded that since RAS has multifactorial etiology, changes in the body's oxidant/antioxidant status are considered as a factor in line with other factors. In the future, to achieve more consistent results, more studies on the etiology and pathogenesis of the oxidant/antioxidant status of patient with RAS are needed.

Conflict of Interests

Authors have no conflict of interest.

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