Original Article

Serum prolidase and oxidative stress levels in patients with recurrent aphthous stomatitis: a prospective, controlled study

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Abstract

Background: Recurrent aphthous stomatitis is a common disease characterized by single or multiple, self-healing, well-circumscribed, periodic ulcers occurring in the oral cavity. Although the relationship between recurrent aphthous stomatitis and oxidative stress has been extensively reviewed in the past, its relationship with prolidase enzyme levels has not been previously investigated.

Aim: The aim of this study is to investigate plasma antioxidant status and prolidase enzyme levels in patients with recurrent aphthous stomatitis.

Methods: The serum total oxidant status, total antioxidant status, oxidative stress index, prolidase and paraoxonase levels of 34 recurrent aphthous stomatitis patients (mean age 35.1) and 34 healthy controls (mean age 37.7) were compared in this study.

Results: Total oxidant status was significantly higher in the recurrent aphthous stomatitis group ($P < 0.005$). The mean total oxidant status value was 5.19 mmol/L in the recurrent aphthous stomatitis group, while it was 2.90 mmol/L in the control group. Oxidative stress index was significantly higher in the recurrent aphthous stomatitis group ($P = 0.016$*). The mean oxidative stress index level was 0.28 AU in the recurrent aphthous stomatitis group, while it was 0.18 AU in the control group. When control and patient groups were compared, there was no significant difference between groups with regard to the total antioxidant status ($P = 0.343$). The total antioxidant status levels were 1.09 and 1.14 mmol/L in control and patient groups, respectively. There was no statistically significant difference between PON1 levels of recurrent aphthous stomatitis and control groups ($P = 0.218$). Mean PON1 levels were 326 U/L in the recurrent aphthous stomatitis group and 381 U/L in the control group. Prolidase levels were not significantly different between recurrent aphthous stomatitis and control groups ($P = 0.955$). The mean prolidase level was 219.79 U/L in the recurrent aphthous stomatitis group and 219.26 U/L in the control group.

Limitations: The limitation of this study is the small size of both patient and control groups and exclusion of pediatric patients., Similar studies performed in pediatric patient populations with a comparison to adults may be useful in providing meaningful results.

Conclusions: We detected that the total oxidant status and oxidative stress index was higher in patients with recurrent aphthous stomatitis as compared to healthy controls. We could not demonstrate a significant difference in total antioxidant status, PON1 and prolidase values.

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Key words: Oxidative stress index, paraoxonase, prolidase, recurrent aphthous stomatitis, total antioxidant status, total oxidant status

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Introduction

Recurrent aphthous stomatitis is a common disease characterized by a single or multiple, self-healing, well-circumscribed, periodic ulcers occurring in the oral cavity.[1-3] The prevalence of recurrent aphthous stomatitis among populations varies between 5 and 66%, and it is more common among women.[4] Recurrent aphthous stomatitis is generally more frequent in the 10–19 age group.[5] There are many etiological factors postulated for recurrent aphthous stomatitis, of which the most important ones are mechanical, chemical or thermal injury to the oral mucosa with other causes like psychological stress, systemic disease, immunological disorders, smoking, various drugs, allergic diseases and genetics also being implicated.[6,7] It is known that 10–20% of recurrent aphthous stomatitis patients have deficiency of iron, folic acid and vitamin B12.[8,9] There is no specific test to diagnose recurrent aphthous stomatitis, and thus the diagnosis is a clinical one. A meticulous medical history and examination are the keys to diagnosis. A detailed blood analysis can be performed and oral cultures can be taken for excluding other causes of oral ulceration. A biopsy should be performed in cases of doubt.[10]

Prolidase is a metalloenzyme within the group of hydroxylases that is found in many tissues and activated by Mn^{2+}.[11] It is thought that changes in the levels of prolidase may be involved in the pathogenesis of many diseases. Prolidase deficiency causes a rare autosomal recessive hereditary condition. In this condition, chronic recurrent infections, mental retardation, splenomegaly and skin lesions are seen.[12] Common skin lesions of prolidase deficiency are telangiectasia, purpura, hyperkeratosis, recurrent ulcers of the lower extremities, eczematous lesions and lymphedema.[13]

Reactive oxygen species are reactive molecules that contain one or more unpaired electrons in their outer atomic orbitals.[14] Excessive production of reactive oxygen species plays a role in the pathogenesis of many diseases e.g., diabetes mellitus, cancer, rheumatoid arthritis systemic lupus erythematosus, Behçet's syndrome and atherosclerosis. Shifting of the balance between oxidant and antioxidant molecules toward the oxidants creates oxidative stress.[15] Instead of measuring oxidant and antioxidant molecules separately in the plasma, measurements of the total antioxidant status and total oxidant status have been developed.[16] It has been shown in various studies that decrease in total antioxidant status levels and increase in reactive oxygen species levels may be important in the pathogenesis of recurrent aphthous stomatitis.[17] PON1, which works as a strong antioxidant, is a high-density lipoprotein-associated hydroxylase that can hydroxylase paraxone which is a potent inhibitor of cholinesterases.[18]

In our study, we aimed to compare serum total oxidant status, PON1, oxidative stress index and prolidase levels between recurrent aphthous stomatitis patients and a healthy control group. Although we found that the relationship between recurrent aphthous stomatitis and oxidative stress has been extensively documented, we could not find any articles in which the relationship between recurrent aphthous stomatitis and prolidase has been studied. We believe our study is the first in literature to investigate prolidase and oxidative stress in recurrent aphthous stomatitis.

Methods

This study was conducted between March 31, 2016 and April 15, 2017 in Hitit University School of Medicine's Ear, Nose and Throat Surgery Department. Ethical approval was obtained from Hitit University Clinical Research Ethics Committee (project number 2016-29). A total of 34 patients with recurrent oral ulcers and 34 healthy controls, aged between 18 and 50, were included in the study. The study protocol was formulated in accordance with the Helsinki Declaration 2000, and an informed consent form was obtained from the patients and control groups participating in the study.

The diagnosis of recurrent aphthous stomatitis was made by evaluating the patient's history, clinical and physical examination findings. Patients with single or multiple painful, round or ovoid, recurrent ulcerations in the oral mucosa were included in the study. Patients who were diagnosed to have recurrent aphthous stomatitis at least three times during the year were included in the study. Pregnant women, pediatric patients, alcohol users, smokers, antioxidant users and intravenous drug abusers were excluded from the study. In addition, patients with coronary heart disease, chronic pulmonary or liver diseases, neoplasia and dermatological rheumatologic and endocrine diseases which could affect the oxidative balance in the body were excluded from the study. None of the patients were treated with corticosteroids during the period of the study or for 3 months before the study. None of them had an an active infection. Routine blood counts and biochemical tests were done on the participants in the study and only patients with normal results were included.

Healthy controls consisted of persons who had not experienced any recurrent aphthous stomatitis symptoms before and during the study. There were no systemic, metabolic, neoplastic, rheumatologic, dermatological and inflammatory diseases that could cause oxidative stress in the control group. Smokers, vitamin, steroid, antioxidant and alcohol users were also excluded from the control group.

An informed consent was obtained from all patients in both groups as an indication of their voluntary participation in the study. Ten ml of venous blood was collected from each patient between 08:00 and 10:00 in the morning and placed in a vacuum biochemistry tube. After waiting for 30–45 min, the samples were centrifuged for 10 min at 4000 rpm, and the serum was separated and then stored at −80°C until the day of analysis.

Total oxidant status, total antioxidant status, PON1, oxidative stress index and prolidase measurements

The method developed by Erel, for total oxidant status and total antioxidant status measurements, was used.[16] Determination of total oxidant status was performed by using a kit developed by Erel (RelAssay® Diagnostics kit, Mega Tıp, Gaziantep, Turkey), which measures this calorimetrically by an autoanalyzer (VitalScientific, Selectra/Flexor E, Dieren, The Netherlands). The results were displayed as micromolar hydrogen peroxide equivalent per liter (μmol H2O2 equivalent/L). Measurement of total antioxidant status was by means of a commercial kit (RL0031 Rel Assay) and analyzed in an Abbott Architect® c16000 autoanalyzer, the results being expressed as micromolar trolox/litre. In a study conducted by Erel, serum reference intervals for total oxidant status were found to be 5.54–21.38 μmol H2O2 equiv./L for women and 6.31–24.38 μmol H2O2 equiv./L for men.[16]

Oxidative stress index: The ratio of total oxidant status levels to total antioxidant status levels is indicative of the degree of oxidative stress.[16] The mmol value in the unit of the total antioxidant status test is converted to μmol and the results are expressed as "arbitrary unit (AU)" and the following formula is used:

Oxidative stress index = Total oxidant status (mmol H2O2 equiv./L)/total antioxidant status (mmol trolox equiv./L) × 10

PON1 levels were measured using a full automatic RelAssay® commercial kit in an Abbott Architect® c16000 autoanalyzer. Results were given as units/mol. In a tris buffer, the calcium ion-activated PON1 enzyme, breaks paraoxane down to *p*-nitrofenole (diethyl-*p*-nitrophenylphosphate). Molar absorptivity of *p*-nitrofenole is 18.290 M^{-1} cm^{-1}, and one unit of PON1 activity equals to that of 1 mol product generated in 1 min at 37°C.

Serum prolidase enzyme activity levels were measured by ELISA (Cat. No. Cusabo Biotech Co. Ltd. CSB-E16196h). Intra-assay coefficient of variation (CV) and inter-assay coefficient were <8% and <10%, respectively. The test interval was between 93.75 and 6000 mU/mL with a sensitivity of 93.75 mU/mL Measurements were made using the Radim company ALİSEİ automatic ELISA device.

Statistical analysis

Statistical analyses were performed using the SPSS software package (version 22.0, SPSS Inc. Chicago, IL, USA). Distribution of normality was tested with the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation, the median (min–max) according to distribution hypotheses, and the categorical variables were presented as numbers and percentages. Continuous variables were analyzed by the Student's *t*-test to compare the means of two independent factors in case of normally distributed variables. Non-normally distributed independent samples were compared using the Mann–Whitney *U*-test. Receiver operating characteristic curve analysis was done to investigate the diagnostic validity of total oxidant status and oxidative stress index. The Youden index was used to determine the optimal cut-off point in receiver operating characteristic analysis. Sensitivity, specificity and predictive values were calculated to determine the prediction success of the cutoff point after receiver operating characteristic analysis. The significance level was accepted as $P < 0.05$.

Results

The study and the control groups were similar in terms of age and gender ($P > 0.05$ for both). The mean total oxidant status value was 2.90 ± 6.06 mmol/L and the median (min–max) was 1.87 (0.14–36.10) mmol/L in the control group, and it was 5.19 ± 8.26 mmol/L and median (min–max) 2.61 (0.49–36.45) mmol/L in the recurrent aphthous stomatitis group. Serum total oxidant status levels in the recurrent aphthous stomatitis group were significantly higher than in the control group ($P = 0.004$) [Table 1]. Oxidative stress index was significantly higher in the recurrent aphthous stomatitis group ($P = 0.016$*). The mean oxidative stress index level was 0.28 AU in the recurrent aphthous stomatitis group, while it was 0.18 AU in the control group. The mean total antioxidant status level was 1.09 ± 0.17 mmol/L and median (min–max) was 1.10 (0.71–1.52) mmol/L in the control group and 1.14 ± 0.19 mmol and median (min–max) 1.12 (0.79–1.70) mmol/L in the recurrent aphthous stomatitis group. There was no significant difference between the groups in terms of total antioxidant status values ($P = 0.343$) [Table 1]. There was no statistically significant difference between PON1 levels of recurrent aphthous stomatitis and control groups ($P = 0.218$) [Table 1]. The mean PON1 level was 381 ± 23 U/L and median (min–max) was 344.50 (94–1087) U/L in the control group and 326.47 ± 254.19 U/L and median (min–max) 210.50 (88–1193) U/L in the patient group. The mean prolidase level was 219.26 ± 32.53 U/L and median (min–max) 219 (138–273) U/L in the control group and 219.79 ± 43.58 U/L and median (min–max) 222 (140–325) U/L in the patient group. There was no significant difference between groups in terms of prolidase values ($P = 0.955$) [Table 1]. The receiver operating characteristic curve analysis was performed for total oxidant status and oxidative stress index. The cut-off value for total oxidant status is 1.835 and for oxidative stress index is 0.285 [Table 2].

Discussion

In the present study, we found a statistically significant difference between the groups in terms of the total oxidant status values, with the serum total oxidant status levels being significantly higher in patients with reactive oxygen species when compared with the control group. There was no significant difference between the patients with recurrent aphthous stomatitis and the control group in terms of the

Table 1: Comparison of recurrent aphthous stomatitis and control groups in terms of total antioxidant status, total oxidant status, paraoxonase, prolidase and oxidative stress index

Biochemical Parameter	Group	*n*	Mean±SD	Median (minimum-maximum)	*P*
TOS	Control	34	2.90±6.06	1.87 (0.14-36.10)	0.004*,[b]
	RAS	34	5.19±8.26	2.61 (0.49-36.45)	
TAS	Control	34	1.09±0.17	1.10 (0.71-1.52)	0.343[a]
	RAS	34	1.14±0.19	1.12 (0.79-1.70)	
PON1	Control	34	381.00±236.32	344.50 (94-1087)	0.218[b]
	RAS	34	326.47±254.19	210.50 (88-1193)	
Prolidase	Control	34	219.26±32.53	219 (138-273)	0.955[a]
	RAS	34	219.79±43.58	222 (140-325)	
OSI	Control	34	0.28±0.63	0.18 (0.01-3.72)	0.018*,[b]
	RAS	34	0.48±0.81	0.21 (0.05-3.72)	

[a]Student's *t*-test, [b]Mann-Whitney *U*-test, *Statistically significant (*P*<0.01). SD: Standard deviation, TOS: Total oxidant status, TAS: Total antioxidant status, PON1: Paraoxonase, OSI: Oxidative stress index, RAS: Recurrent aphthous stomatitis

Table 2: Receiver operating characteristic curve analysis results and sensitivity, specificity and predictive values

Statistical parameter	TOS	OSI
AUC (95% CI)	0.702 (0.579-0.825)	0.667 (0.539-0.796)
P	0.004	0.018
Cut-off	≥1.835	≥0.2857
Sensitivity	0.794 (0.616-0.907)	0.412 (0.251-0.592)
Specificity	0.500 (0.328-0.672)	0.882 (0.716-0.962)
PPV	0.614 (0.455-0.753)	0.778 (0.519-0.926)
NPV	0.708 (0.488-0.866)	0.600 (0.452-0.733)

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, TOS: Total oxidant status, OSI: Oxidative stress index, CI: Confidence interval

prolidase, total oxidant status, total antioxidant status and PON1 values. The association between prolidase deficiency and some dermatologic diseases, such as Behçet's and lichen planus has been investigated earlier but this has not been previously studied in recurrent aphthous stomatitis. For this reason, we decided to investigate prolidase levels together with oxidative parameters in this group of patients.

Normal serum prolidase levels are below 1000 U/L.[19] The prolidase enzyme can be found in many tissues, such as the small intestine, uterus, brain, muscle tissue, erythrocytes and serum. Changes in prolidase enzyme activity are thought to be responsible for the development of many diseases.[20] Prolidase is a metalloenzyme within the group of hydroxylases[11] and is highly specific, because it is the only enzyme that catalyzes the compounds which have a peptide bond harboring proline or hydroxyproline amino azote in their C terminals.[20] Proline and hydroxyproline amino acids that are released after prolidase enzyme action are important for the maintenance of healthy connective tissues, and additionally, they constitute approximately 25% of the collagen tissue.[21] Proline is used in protein synthesis, whereas hydroxyproline is excreted in the urine. Prolidase enzyme deficiency causes an increase of urinary excretion of the dipeptides proline and hydroxyproline.[22] The prolidase enzyme has also been implicated in delayed wound healing, because it plays a vital role in inflammatory and angiogenic signaling pathways that regulate matrix degradation and collagen turnover.[23]

In their study performed on patients with oral ulcers due to Behçet's disease, Bozkurt *et al*. have found higher serum prolidase activity in patients with Behçet's disease as compared to the controls. Despite the fact that total oxidant status levels in Behçet's patients were significantly higher than the control group, total antioxidant status levels were reported to be generally low.[24]

Tugrul *et al*. compared total antioxidant status, total oxidant status and oxidative stress levels in 42 recurrent aphthous stomatitis patients and 39 healthy subjects. They found that total antioxidant status and oxidative stress were increased and total antioxidant status was decreased in the recurrent aphthous stomatitis group.[25] Bagan *et al*., in their study, analyzed patients with recurrent aphthous stomatitis oxidative stress in the presence and absence of active ulcers. They included 28 active diseases and 29 control groups in the study. They reported increased oxidative stress in recurrent aphthous stomatitis patients.[26]

In our study, we found prolidase levels in cases and controls to be similar. Skin lesions and leg ulcers caused by prolidase deficiency are usually longstanding. We think that serum prolidase levels are normal in patients with reactive oxygen species in our study because the healing process is very rapid in patients with recurrent aphthous stomatitis.

Bilgili *et al*. performed a study where total antioxidant status, total oxidant status, PON1 and oxidative stress index levels were compared in 31 recurrent aphthous stomatitis patients and 31 healthy controls. Serum total antioxidant status, PON1 and aril esterase levels were significantly lower in recurrent aphthous stomatitis patients as compared to controls. while total oxidant status and oxidative stress index were significantly higher in cases.[27] It has been suggested that the increased oxidative stress plays a role in the development of recurrent aphthous stomatitis. Although we found high total

oxidant status levels in recurrent aphthous stomatitis patients in our study, we did not find a significant difference between cases and controls in terms of total antioxidant status, PON1 and prolidase levels. Our study demonstrated that recurrent aphthous stomatitis patients are exposed to oxidative stress.

Akoglu *et al*. investigated total antioxidant status, total oxidant status, PON1 and aril esterase activities in 44 recurrent aphthous stomatitis patients and 38 healthy controls. Total oxidant status and oxidative stress index in cases were found to be higher while total antioxidant status, PON1 and aril esterase levels were lower.[28] Çağlayan and Yılmaz measured total antioxidant status and glutathione peroxidase (GPx) activities in samples of the saliva of 50 recurrent aphthous stomatitis patients and 25 controls. Although they reported no significant difference between the salivary total antioxidant status levels between patient and control groups, GPx activity in salivary samples of patients with recurrent aphthous stomatitis was found to be lower when compared to the control group.[29] Avci *et al*. compared total antioxidant status, total oxidant status and nitric oxide levels in 25 recurrent aphthous stomatitis patients and 25 healthy subjects in their study. They found increased total oxidant status and decreased total antioxidant status levels in patients with recurrent aphthous stomatitis. They found that oxidative stress was increased in cases when compared to the control group.[30]

When we compared recurrent aphthous stomatitis and control groups in this study, we found significantly increased levels of total oxidant status in the former., whereas total antioxidant status, PON1 and prolidase levels were not significantly different. Receiver operating characteristic analysis was conducted to investigate whether total oxidant status and oxidative stress index could be used as diagnostic and prognostic markers in discriminating between recurrent aphthous stomatitis and non-recurrent aphthous stomatitis patients. The total oxidant status [area under the curve = 0.702 (0.579–0.825)] and oxidative stress index (area under the curve = 0.667) suggested its meaningful use when evaluated together.

If the total oxidant status is greater than 1.835, the patient will have a reactive oxygen species life of 79.4% sensitivity. The low selectivity of 0.500 (0.328–0.672) showed that total oxidant status could not be used for healthy separation. If the oxidative stress index value is >0.286, 88.2% will show selective reactive oxygen species again. A low sensitivity of 0.412 (0.251–0.592) indicates that oxidative stress index cannot be used in patient differentiation.

The limitation of this study is the small size of both patient and control groups and exclusion of pediatric patients. Similar studies performed in pediatric patient populations with a comparison to adult levels can provide meaningful results.

Conclusions

We found that total oxidant status and oxidative stress index levels were statistically higher in patients with reactive oxygen species than controls. There was no significant difference between recurrent aphthous stomatitis and control groups in terms of prolidase, total antioxidant status and PON1 levels. In this study, recurrent aphthous stomatitis patients were found to be exposed to more oxidative stress than the control group. There is a need for more extensive and comprehensive work in this area.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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