

Evaluation of Uric Acid, Total Antioxidant and Lipid Peroxidation Parameters in Serum and Saliva of Patients with Oral Lichen Planus

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Abstract

Background: Oral lichen planus (OLP) is a chronic and inflammation mucosal disease. Reactive Oxygen Species (ROS) and oxidative stress damage might be the cause. Malondialdehyd (MDA), one parameter of lipid peroxidation is appropriate for DNA damage in OLP disease.

Objective: To evaluate antioxidants and oxidative stress parameters in patients with oral lichen planus (OLP) diseases and healthy control group with compare on serum and salivary samples.

Material & Methods: The research population included 22 patients with OLP which recently diagnosed and 22 healthy controls matched for periodontal status. Total antioxidant activity (TAA), Malondialdehyde (MDA) or lipid peroxidation product and uric acid (UA) were evaluated in both serum and saliva. The t-tests were used for differences between the two groups in normal distributed variables and also Spearman's rho correlation coefficient for assessing association between serum and salivary fluids.

Results: TAA levels in OLP patients showed significant result and lower than healthy control group ($p=0.39$). Also, results in the saliva MDA concentration, was significantly higher in OLP patients than controls. In correlation test, inverse and significant correlation was observed between the MDA and UA values ($r=0.682$, $P=0.0001$) and a significant correlation was found between serum TAA and UA values.

Conclusion: This study showed that OLP groups have higher cellular lipid peroxidation in compare to healthy controls and low level of TAA than controls. Patients with OLP are believed to be more at risk of antioxidant-oxidative stress imbalance.

Keywords: uric acid, total antioxidant, lipid peroxidation, oral lichen planus

1. Introduction

Oral lichen planus (OLP) is common chronic, mucosal and also with inflammation background disease. It is classified into cell-mediated immune state with cellular degeneration (Mishra, 2014). The origin of this degeneration, have been shown to be sub epithelial infiltration of T-lymphocytes that produce this local production of cytokines which sequentially can cause oxidative damage to the tissues by stimulating formation of Reactive Oxygen Species (ROS) (Epstein et al., 2003; Mehdipour et al., 2014). There are different forms of clinical appearances of OLP including linear, annular, popular, reticular and plaque shape, also atrophic, erosive (ulcerative) and bullous lesions in oral spaces at different periods or similar (Scully, Carrozzo, & Cartan, 2008). There are many studies in oxidative state of biological systems including production of ROS, oxidative stress and antioxidant defense, inflammation and chronic diseases that have been studied in degenerative and carcinogenesis disease (Ergun et al., 2011; Chole et al., 2010; Agha-Hosseini et al., 2009). The first step of production of oxidative stress is the metabolic reactions that use oxygen and represent disturbance balance in pro-oxidant/antioxidant reactions in living organisms (Valko et al., 2009). It has been found ROS is produced by keratinocytes, fibroblasts and several inflammatory cells, could lead to imbalance between the pro-oxidants and antioxidants in the body (Fuchs et al., 2001). The metabolites of ROS cause damage to cell membranes by lipid peroxidation (Ergun et al., 2011). MDA is the major and the best study in lipid peroxidation of polyunsaturated fatty acid product (Mishra et al., 2014). MDA can react with several efficient groups of molecules including

lipoproteins, proteins, RNA and DNA (Cartan & Healy, 2008). During intracellular oxidative stress the endogenous MDA is formed and it can react with important macromolecules in biological systems including DNA, which results MDA-DNA adducts a suitable biomarker for DNA damage in the body (Saran et al., 2008). Determination of MDA is generally used for the recognition of lipid peroxidation parameters in body fluids (Edward et al., 2013). Results in several studies have been shown high concentration of MDA and also low antioxidant activities in salivary fluids seem to reveal increased free and oxygen radical activity during inflammation in periodontal diseases (Celecet et al., 2005; Canakci et al., 2009). Oxidative reactions may play a key role in the pathogenesis of periodontitis and it also is correlated with tissue damage. However, it is unclear that this result is the basis or a result of periodontitis (Akalin et al., 2007). Some studies on the capacity of the total antioxidant in saliva have provided important information that lack of antioxidants may lead to inflammation and increased risk of disorders including lichen planus (Diab-Ladki et al., 2003). The contribution of different antioxidants in our life style provides larger defense against injury by ROS than using any one compound alone (Ghiselli et al., 2000). It is very important to recognize about the mechanisms of main antioxidants and identify possibly synergistic interaction of all antioxidants in the body fluids. Therefore, understanding about specific information of total antioxidant may give more important biological information in turn than that achieved by determining levels of individual antioxidants (Serafini & Del Rio, 2004). In order to study about free radicals and its association with pathogenesis of precancerous disorders, some cancers such as leukoplakia, oral sub mucous fibrosis and oral cancer is clear and was studied (Rai et al., 2008; Gokul, 2010). Evaluation on Saliva can provide easy and reasonable documented in the process of diagnosing and monitoring general health and disease classifications. A small number of studies have been evaluated the antioxidant profile for these parameters in serum and salivary fluids of patients with OLP. In the current research the existence of oxidative stress was investigated in OLP patients. In this way, TAA and concentration of MDA were examined in the serum and saliva fluids in OLP and healthy controls. There is growing evidence indicating uric acid (UA) has a role as antioxidant in the body and it is believed that administration of UA could increase plasma antioxidant capacity (Glantzounis et al., 2005). Evidences from several studies suggest that UA has a specific role in inhibitor of radicals that is generated by the breakdown of peroxynitrite (ONOO-) in the production of NO with the superoxide anion (Glantzounis et al., 2005). UA may match to antioxidants with low molecular mass in the body fluids (Cao et al., 1998; Re et al., 1999). UA has key role as significant antioxidants in plasma that can scavenge ROS and it is important that it can chelate metal ions (Yasuda et al., 2013; Eberhardt et al., 2000). Thus, monitoring UA level in serum as an indicator of the antioxidant defense (oxidative balance) could be important for the clinicians' treatment strategy.

2. Patients and Methods

2.1 Subjects

In this research, 22 individuals (10 males and 12 females; mean age 48.7 ± 9.2 years) with OLP were recruited from Tooba clinic, Mazandaran University of Medical Sciences. The patients were categorized based on severity of disease and also was scored the based on ranged from 2 to 4 with the average of 2. In the category of lesions the score range were from 0 (no lesion) to 5 (large erosion) (Buajeeb et al., 2008). Twenty two healthy groups as controls who had no oral mucosal disease and were matched with the case groups about periodontal situations (mean range of age: 43.7 ± 6.9 years). The lesions in all OLP patients were detected on mouth or buccal mucosa location (14 reticular and 8 erosive), based on biopsy results with at least of two specific microscopic key factor including a sub epithelial lymphocytic band-like infiltrate and central signs of basal layer erosion were considered as inclusion criteria that confirmed lichen planus. Case subjects, untreated for the disease with the start of signs within 3 months were recruited in this study. Patients with lichenoid lesions related with drugs or restitutions (Al-Hashimi et al., 2007) and those with dermatological OLP were excluded in this study. Patients with history of any oral candidiasis proved by laboratory analyze and major systemic diseases were also excluded from the study. Also for a medical examination, all case groups and controls were examined by hematology and biochemical parameters (CBC, FBS, ESR, and liver profile). The patients on medication of non steroids inflammatory drugs, immunosuppressive mediators and prescribe vitamins supplementation medication during last three months were excluded in the study. Also, the use of oral site medication that could positively effect on results of research, record of surgery or trauma, smoking or alcohol consumption at least one month before the study were excluded.

2.2 Oral Examination

The diagnosis of oral lichen planus was confirmed by clinic pathological features. Oral sites examined by evaluation of lips and oral cavity and healthy control groups without signs of disease were identified. In the proof of disease, existence of papular and/or reticular lesions including the same lace-like or pinhead-size and white color, little high keratotic models in some position of the oral cavity were observed. Oral examination was

performed by person who was a professional in oral medicine and surgery.

2.3 Salivary and Serum Assays

About 10 ml fasting blood sample was taken from people with OLP and healthy controls. The serum was prepared and stored at -80°C until examined. The sample on salivary fluids were collected from patients and control group after an all night fasting. At the first step, For covering suitable collection of saliva sample, advised the mouth were washed with distilled water and also case and control groups were learned spit saliva sample into a suitable graded tub for sampling. As soon as saliva was collected, at the first step total whole salivary fluids were centrifuged at 12000g for 10 min at $+4^{\circ}\text{C}$, the superior parts were transferred in a tub and stored at -80°C until analyzed. All samples were examined two times.

2.4 Total Antioxidant Capacity

Total antioxidant capacity or activity in saliva and serum was determined by FRAP (Ferric reducing ability of plasma) assay. The mechanism of FRAP test was depends on the reduction of Fe^{3+} to Fe^{2+} (FRAP assay) as described previously (Kohen et al., 2002). At the working process, FRAP reagent was prepared by mixing 300mM acetate buffer (pH3.6), 10 mM 2,4,6-tripyridyl-s-triazine (TPTZ) solution and 20mM $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in a 10:1:1 ratio just before use and heated to 37°C . TPTZ solution was prepared with mixing of 10mM TPTZ in 40mM HCL. Ten micro liters of sample then was added to 300 μl fresh working reagent and warmed in 37°C . Finally the absorption of colored complex reagent was recorded at 593 nm by spectrophotometer (UV-1800 Shimadzu-Japan). The ranges of FRAP standard was 100-1000 μM that were organized and used in comparable with all samples.

2.5 Malondialdehyde (MDA)

MDA one parameter of lipid peroxidation was measured based on thiobarbituric acid (TBARS) method according to the Nurten *et al.* (2006). The standard solution was prepared in concentration of 1,1,3,3 tetraetoxypropane (TEP) and the results were expressed as nmol/ml in serum and saliva samples. The results in colored solution were recorded at 535 nm by UV-1800 Shimadzu spectrophotometer.

2.6 Uric Acid (UA)

Uric acid was examined in the one enzymatic method according to Fossati et al. (1980). In this way, uric acid was converted by uricase enzyme to allantoin and hydrogen peroxide. Hydrogen peroxide generated reacted with a phenol and 4-aminoantipyrine solutions in a reaction that named as trinder, and finally absorbance of a chromophoresolution were recorded at 660-80 nm by spectrophotometer (UV-1800 shimadzu).

2.7 Statistical Analyses

The results in the research were expressed as the means \pm SD, and for expression of significant differences between 2 or more groups but in normal variable were assessed by t-test and analysis of variance (ANOVA) and with non-Gaussian distribution variable were compared using Mann-Whitney test. The association between the dependent and independent variables in saliva and serum was determined by the correlation test.

3. Results

The study evaluated biochemical markers in 22patients with oral lichen plane which comprise 12women and 10 men, and mean \pm SD in age 48.7 ± 9.2 years, and 22 controls which comprise 9 men and 13 women; and mean \pm SD in age 43.7 ± 6.9 years, without statistically differences. Salivary and serum MDA levels were shown statistically significantly higher than healthy control group ($P < 0.03$) and TAA value in serum was significantly lower ($P < 0.01$) than in OLP cases. Results in serum uric acid in OLP patients were significantly lower than that in control groups (Table 1). In addition, a significant inverse correlation was found between serum UA and MDA values ($r = 0.682$, $P = 0.0001$) and a significant correlation was observed between serum TAA and UA values ($r = 0.586$, $P = 0.0001$). Moreover, there was a significant correlation but inverse result in MDA and TAA values in serum ($r = 0.677$, $p = 0.0001$) and saliva ($r = 0.475$, $P = 0.045$). The MDA and UA parameters were significantly associated with the tertiles of total antioxidant activity (Table 2).

Table 1. Total antioxidant activity, malondialdehyde and uric acid values of the patients with oral lichen planus (OLP-P) and healthy subjects (HS)

	OLP(n=)	HS(n=)	P
	Mean±SD	Mean±SD	
Total Antioxidant Activity in Salivary fluids (TAA-SA) ($\mu\text{mol/l}$)	553±189	633±209	0.338
Total Antioxidant Activity in Serum (TAA-SE) ($\mu\text{mol/l}$)	986±157	1092±200	0.041
Malondialdehyde in Salivary fluids(MDA-SA) (nmol/ml)	1.12±0.20	0.97±0.16	0.05
Malondialdehyde in Serum (MDA-SE) (nmol/ml)	4.49±0.38	3.90±0.51	0.001
Uric Acid in Salivary fluids (UA-SA) (mg/dl)	4.39±0.54	4.75±0.68	0.161
Uric Acid in Serum(UA-SE) (mg/dl)	5.8±0.46	6.25±0.68	0.043

Tests used: Ferric antioxidant power assay (FRAP) for total antioxidant activity (TAA), Malondialdehyde (MDA), Uricas, Enzymatically method for Uric acid levels (UA).

Table 2. Data for quintiles of total antioxidant activity (TAA) variability

	Group 1	Group 2	Group 3	P Value
Range SD (Total antioxidant activity)	<1000 $\mu\text{mol/l}$	1000-1200 $\mu\text{mol/l}$	>1200 $\mu\text{mol/l}$	
MDA (nmol/ml)	4.48±0.46	4.1±0.52	3.9±0.48	0.001
Uric Acid (UA) (mg/dl)	5.8±0.64	6.1±0.73	6.3±0.55	0.042

The cases were categorized into tertiles on the basis of antioxidant activity variability. The significants of differences as mean or median were tested using analyses of variance and Kruskal-Wallis tests respectively.

4. Discussion

Lichen planes in oral cavity, is a chronic, mucocutaneous and with reflect of inflammation disease. The pathophysiology of OLP is multifarious and in the microscopic evaluation, its features are associated with pathognomonic characteristics and degeneration of cells which is supposed to be certified to associate epithelial permeation of T-lymphocytes leading to local production of cytokines (Khan et al., 2003). Recently, it has been stated that the imbalance in levels of free radical and ROS with antioxidants may play an important role in the start of several inflammatory oral disease (Hosseini et al., 2009). ROS and tissues oxidative damage, following in extend a lack of antioxidants may result in appearance of this disease (Upadhyay et al., 2010; Batu et al., 2016). The age incidence of OLP as stated in selected articles suggests that this disease is most commonly seen in the fifth decade of life (Upadhyay et al., 2010; Ioana et al., 2011). Malonaldehyde, a small molecular weight that is one of the main and end product of lipid peroxidation reaction, has an important role on DNA damage in the body. Upadhyay et al. reported MDA levels were significantly in OLP patients higher than controls in serum and also saliva. In another study, MDA levels significantly increased and also TAA levels decreased in case group compared to the controls. Thus, the results indicated the presence of oxidative stress and its correlation with pathogenesis of OLP (Ioana et al., 2011). Researchers have confirmed the function of oxidative stress in the etiopathogenesis of OLP by estimating the levels of markers that act as oxidative damage like MDA in various samples, serum, saliva and tissue. There have been studied by Balwant & Ergun et al. (2010) which established the relative analysis of MDA levels in serum and salivary fluids in case group. Different studies suggest that such results with increasing level of oxidative parameters, low level of antioxidants, results showed that one protection system is necessary in biological fluids of OLP patients, thus process of oxidative stress has a key role in pathophysiology of disease (Aly & Shahin, 2010). Similarly, increased lipid peroxidation and super oxide radical anion O_2^- with decrease in antioxidants capacity has been examined and reported on serum in patients with oral cancer (Manoharan et al., 2005). Serafini et al. (2004) confirmed several antioxidants with enzymatic activity are decreased in the biopsy of patients with OLP especially epidermis one. In other study, Agha Hosseini et al., have also established significant differences in level of MDA in OLP and healthy control group which is in conformity with the current study. A study according to the Japans group reported low level of lycopene (nutrient antioxidant) in body fluids of OLP patients (Nagao et al., 2001). Some studies was preferred examining total antioxidant activity (TAA) as a substitute of individual antioxidants in blood and other body fluids, because TAA as an incorporated parameter may provide a better marker than one antioxidant. TAA value was significantly lower than healthy controls in OLP patients which this result was agreement with several researches (Celec et al., 2005; Canakci et al., 2009; Serafini et al., 2006). ROS play important roles in immunology and inflammatory effects,

and in the human body fluids, there are several antioxidants systems that have ability to maintain the stability of oxidation-reduction situation (Al-Hashimi et al., 2002; Kohen & Nayska, 2007). The imbalance in increased ROS production and decreased antioxidant activity could direct to improved injury. In fact, there are several diseases in this way that is produced by imbalance of oxidation-reduction reactions in body (Khan et al., 2003; Upadhyay et al., 2010; Ioana et al., 2011). Finding in this research showed high level of lipid peroxidation parameters in OLP patients but without significant increase in TAA levels. So, it seems that there is an imbalance of oxidative stress in patients with OLP. Uric acid is one compound of catabolism purine nucleotides is main significant antioxidants and also a powerful free radical scavenger in human biological fluids. Apart from its role as radical scavenger, UA can chelate metals ions, the same iron and copper, converting them to weakly reactive types that unable catalyze free radical reaction (Glantzounis et al., 2005; Pasalic et al., 2012). Some studies have revealed the role of antioxidants UA in other situations (Waring, 2006; Hooper et al., 2000). Battino et al. (2008) also evaluated UA in serum and saliva of OLP and healthy control, results of their study showed significant differences in UA levels between the case and control and was the most important antioxidant in salivary fluid. As our findings point to a decrease in the antioxidant UA, the problem of oxidative stress and free radicals in OLP should also be more examined in studies with larger number of patients, and other indicators of oxidative stress and antioxidants. Also, the results of this study propose that OLP may be related to decrease of UA concentration in serum and saliva. UA may be considered as a useful biomarker of antioxidant status for difficulty of treatment strategy and monitoring process in OLP patients. Low level of total antioxidant is known to disturb its balance to oxidative stress parameters (Serafini et al., 2006). But there is limited data regarding the correlation of total antioxidant activity with MDA and UA levels. The current results indicate that MDA and UA levels interact with total antioxidant capacity.

5. Conclusions

The results in the current research showed that case groups are more exposed lipid peroxidation than controls. It is suggested that OLP patients have more risk imbalance of oxidative stress-antioxidant situations. The findings of this study lead to the conclusion that if antioxidants protection mechanisms are decreased in oral lichen plane disease (as proposed in present and few other studies) the diminished oxidant/antioxidant balance may contribute to the pathology effects of OLP. Therefore, determining of MDA, TAA and UA in biological fluids may in attendance as a diagnostic indicator and also as a means to evaluate progress and monitoring process of disease.

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Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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