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Relationship between oxidative stress and "burning mouth syndrome" in female patients: a scientific hypothesis

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Abstract. – INTRODUCTION: Burning Mouth Syndrome (BMS) is characterized by burning sensation and pain in the mouth with or without inflammatory signs and specific lesions.

MATERIALS AND METHODS: Aim of the present study was to investigate about a possible correlation between the Burning Mouth Syndrome and oxidative stress. We recruited 18 healthy female patients between 54 and 68 years of age with a diagnosis of "Burning Mouth Syndrome".

Oxidative stress assessment was performed by means of an integrated analytical system composed of a photometer and a mini-centrifuge (FRAS4, H&D s.r.l., Parma, Italy). Samples of whole capillary blood were taken by a finger puncture in a heparinized tube and immediately centrifuged; a small amount of samples plasma (10 microL) were thereafter tested for total oxidant capacity (d-ROMs test) and biological antioxidant potential as iron-reducing activity (BAP test) (Diacron International s.r.l., Grosseto, Italy).

RESULTS: Our results indicate that female patients affected by Burning Mouth Syndrome show significantly different d-ROMs and BAP levels, similar to those present in oxidative stress condition with respect to the general population. It was also emphasized that, after the most painful phase, the levels representing the present oxidative stress, progressively return to normal, even if still significantly higher 7 days after, with respect to the normal population. No similar study was performed up to now.

CONCLUSIONS: This study confirms the effectiveness of antioxidant treatments in the patients affected by BMS, in order to prevent or decrease the onset of oxidative stress and the consequent increased risk of oxidative-related systemic diseases.

Key Words:
Oxidative stress, Burning mouth syndrome, d-ROM test, BAP test.

Introduction

"Burning Mouth Syndrome" (BMS) is characterized by burning sensation and pain in the mouth with or without inflammatory signs and specific lesions[1]. Synonyms found in scientific literature include glossodynia, oral dysesthesia, glossopyrosis, glossalgia, stomatopyrosis and stomatodynia[1-4]. It usually affects women aged between 40 and 60 years and the prevalence in the general population is 3.7%; BMS affects women in 65% of reported cases[5]. BMS generally shows three main aspects: mouth pain, alteration in taste and referred xerostomia in absence of visible mucosal lesions in the mouth[3]. Pain is from moderate to severe in burning sensation, mainly affecting the dorsum and the tongue tip and it may persist along years. Pain may also be present in the gums, lips and jugal mucosa, with no visible lesions following pharyngeal inspection. Pain increases, day by day, in states of anxiety, fatigue, excessive speaking and when ingesting hot and seasoned food; pain subsides with cold foods, work and recreation[3,6]. Burning in the mouth does not manifest clinically in the zones where the peripheral nerves branch off, in fact, it typically affects more than one site. The etiology of BMS is really difficult to assess; in fact, there may be more than one etiological factors. Patients seek help from a variety of medical specialists, including dentists and dermatologists and they often try a range of therapies, such as: corticosteroids, analgesics, antibiotics, estrogens, retinoids and psychotropic drugs. However, none of the listed treatments were found to be really effective[6].

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Hakeberg et al[1], focusing on psychological aspects of women with BMS, observed that all patients in their study had gone through situations of great stress or disappointment in their lives, culminating with the appearance of mouth pain.

Furthermore, a recent article proposes an hypothesis focused on a neurodegenerative cause of BMS: chronic anxiety or post traumatic stress, associated to menopause, leads to a dysregulation of the adrenal production of steroids[7]. One consequence is a decreased or modified production of some major precursors for the neuroactive steroid synthesis occurring in the skin, mucosa and nervous system. This results in neurodegenerative alterations of small nerves fibers of the oral mucosa and /or some brain areas involved in oral somatic sensations. These neuropathic changes become irreversible and precipitate the burning pain, dysgeusia and xerostomia associated with stomatodynia, all of which involve thin nerve fibers[8].

The aim of the present study is to assess the relationship between Burning Mouth Syndrome (BMS) and oxidative stress in female patients, supposing that stomatodynia may be caused by an imbalance between reactive chemical species (RCS) production and their elimination. In fact, oxidative stress represents an imbalance between the production and manifestation of reactive oxygen species (ROS) and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of tissues can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Some ROS can even act as messengers through a phenomenon called redox signaling. In the scientific literature, oxidative stress has been associated with several diseases, such as neurodegenerative diseases[9] or psychic impairments, such as ADHD (attention deficit hyperactivity disease)[10] and anxiety[11].

Materials and Methods

Eighteen female patients, aged between 54 and 68 years old, with diagnosis of primary Burning Mouth Syndrome in accordance with the "Headache Classification Committee of the International Headache Society (2004) criteria"[12], were evaluated between April 2009 and January 2011. All patients had primary BMS for more than 2 years and less than 5 years, and had no oral infections or other lesions and no diseases belonging to the exclusion criteria. A visual-analogue scale (V.A.S.)[13] was used in order to evaluate the intensity pain referred by patients during the first clinical evaluation and the subsequent follow-up (Table I).

Exclusion criteria included Sjögren syndrome, rheumatological diseases, diabetes, hyper- or hypothyroidism, generalized pain, history of surgery in the facial/oral region, trigeminal glossopharyngeal or vagus neuralgia and smoking habit; moreover, we excluded all patients suffering from other disorders and clinical conditions which could have caused "oxidative stress". Informed written consent was obtained from all patients recruited for this study.

Oxidative stress assessment was performed by means of an integrated analytical system composed of a photometer and a mini-centrifuge (FRAS4, H&D s.r.l., Parma, Italy). Samples of whole capillary blood were taken by a finger puncture in a heparinized tube and immediately centrifuged; a small amount of samples plasma (10 µL) were thereafter tested for total oxidant capacity (d-ROMs test) and biological antioxidant potential as iron-reducing activity (BAP test) (Diacron International s.r.l., Grosseto, Italy). The d-ROMs test is based on the ability of a plasma sample to oxidise the N,Ndiethylparaphenilendiamine (not coloured) to its radical cation (red colored); the reaction is monitored photo-

Table I. Visual-analogue scale.

No pain		Mild pain			Troublesome pain			Heavy pain		Unbearable pain
0	1	2	3	4	5	6	7	8	9	10
										

metrically at 37°C at 505 nm and the results are expressed as "Carratelli Units" (CARR U, ΔAbs5050 nm/min). The oxidant capacity of plasma against N, N-diethylparaphenilendiamine is mainly due to hydroperoxides, with the contribution of (ferr) oxidase activity of ceruloplasmin and mieloperoxidase.

Normal Values of d-ROMs Test Ranges Between 250 and 300 CARR Units

The BAP test is based on the ability of a plasma sample to reduce the iron of a coloured complex containing ferric ions to its ferrous derivative, not coloured; the reaction is monitored photometrically at 37°C at 505 nm and the results are expressed in mol/L of reduced iron (using ascorbic acid as standard reference). Such biological antioxidant potential is mainly due to vitamin C, uric acid, bilirubin, albumin and tocopherols hydroperoxides. Normal values of BAP test are assessed over 2200 μM.

BAP test values over 2200 μM were detected on the same machine using the same lot of kits; all tests were performed by the same operator and the analytical instrumentation was calibrated before the analytical session by means of plasma with known values of d-ROMs and BAP test. In order to further check the reliability of the analysis mean, we performed the same tests on samples of whole capillary blood taken from 5 healthy volunteers and we had values of d-ROMs and BAP test just like we expected to find in healthy subjects; our 5 healthy volunteers were 5: these Caucasian females were aged between 60 and 67 years old.

This Study Was Conducted in Two Different Times for Each Patients

First time (T_0)s: it was performed in the same day in which each individual patient came to one of the Authors, referring about her symptomatology consisting of stomatodynia and unbearable pain (according to VAS reported in Table I); a sample of capillary blood was then taken up and subjected to BAP-test (normal values > 2200 μM) and d-ROMs test (normal values between 250 and 300 U CARR).

Second time (T_1): it was performed among 7 and 10 days after the latest manifestation of pain.

Statistical Analysis

All data were expressed as mean value ± SD.

T_0 data were statistically compared to T_1 data performing the "paired *t*-test".

dROMs

Paired *t* test

t = 6.673; df = 17; Two-tailed *p* <0.001	
Number of pairs 18	
Mean of differences	65.11
95% confidence interval	44.52 to 85.70
R squared	0.7237
Correlation coefficient (r)	0.2269

BAP

Paired *t* test

t = 8.655; df = 17; Two-tailed *p* < 0.001	
Number of pairs 18	
Mean of differences -512.0	
95% confidence interval	-636.8 to -387.2
R squared	0.8150
Correlation coefficient (r)	0.09435

Results

On recruitment, the mean value of d-ROMs test data resulted 429 ± 65, while the mean value of BAP Test data resulted 1880 ± 154.

The first follow-up visit at 7 days after the latest manifestation of pain (T_1) revealed an average increase in BAP test of 14 ± 5% and an average reduction in d-ROM test of 28 ± 9%.

The ANOVA test showed high statistical significance ($p < 0.001$) between compared data.

The present study clearly demonstrated a significant correlation between "oxidative stress" and "Burning Mouth Syndrome" in female patients.

Discussion

The aim of the present study was to investigate about a possible correlation between the "Burning Mouth Syndrome" and oxidative stress. Up to now, no study, in the scientific literature, was performed in this light.

The analysis of results indicates that female patients, affected by Burning Mouth Syndrome, show significantly different d-ROMs and BAP levels, compatible with an oxidative stress condition, if compared to the general population. Moreover, after the most painful phase of BMS, the d-ROMs and BAP levels progressively return to normal, even if the oxidative stress appears still significantly higher 7 days after this first phase, compared to the normal values, as well as seen by our research team. We considered even

the possibility of an increasing of oxidative stress levels as direct consequence to the sensation of chronic pain affecting the patients with BMS.

Although the increased ROS and the consequential involvement of oxidative stress have been regarded as important mechanisms in the pathogenesis of pain, by reducing GABA inhibitory influence on SG neurons that are involved in pain transmission[14], the stability of measurements of biomarkers of oxidative stress in blood should remain valuable up to 36-48h after the active phase of oxidative damage[15]. However, this study clearly showed d-ROMs and BAP levels still significantly higher 7 days after this active phase of oxidative damage, compared to the normal values.

Conclusions

The present study underlines the high levels of oxidative stress in female patients affected by Burning Mouth Syndrome. This investigation confirms the importance and the effectiveness of immediate antioxidant treatments in the BMS in order to prevent or decrease the onset of oxidative stress and the consequent increased risk of oxidative-related systemic diseases. Due to the importance of this preliminary result, we are conscious to proceed in evaluating a much more number of patients, considering this study only as a pilot study, devoted to let people know, for the first time, the supposed and concretely demonstrated relationships.

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