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LETTER TO THE EDITOR

Salivary interleukin-6 and tumor necrosis factor-α in patients with burning mouth syndrome

Burning mouth syndrome (BMS) is characterized by burning symptoms on the clinically healthy oral mucosa. To date, etiology of BMS is still unknown. We hypothesized that maybe inflammation which is not clinically apparent might lead to burning symptoms which would then result in altered cytokine profile. In the 28 female patients with BMS (age range 48–80 years, mean 64.05 years) and 28 female controls (age range 40–75 years, mean 63.82 years) by use of enzyme-linked immunosorbent assay, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels were determined. Statistical analysis included use of independent sample *t*-test and $P < 0.05$ was considered as significant. Our results show no significant differences between patients and controls regarding salivary IL-6 and TNF-α.
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Keywords: Saliva, IL-6, TNF-α, burning mouth syndrome

Introduction

Burning mouth syndrome (BMS) is an unresolved disease both for the patient and the clinician, albeit large amount of the literature has been published in this area. It is a chronic pain syndrome that mainly affects middle-aged/old women with hormonal changes or psychologic disorders (Scala *et al*, 2003). BMS is usually characterized by symptoms of burning on the healthy appearance of the oral mucosa, most frequently on the tip of the tongue, followed by the palate and lips. Numerous local and systemic factors might contribute to the symptoms of burning in the mouth, but at this moment they are exclusion criteria for the diagnosis of BMS (Woda and Pionchon, 1999; Sardella and Carrassi, 2001). To date, in the majority of the patients the condition is idiopathic and its etiopathogenesis remains largely obscure (Scala *et al*, 2003). In recent years, neuropathic basis for BMS has been identified (Jaaskelainen *et al*, 2001; Forssell *et al*, 2002) as burning is a typical symptom of chronic neuropathic pain which is a result of nerve damage. More recently, Bartoshuk *et al* (2005) concluded that interactions between taste and oral pain are responsible for BMS, because in the absence of any visible clinical pathology they found severe taste damage. Throughout the literature, amongst other causes, it has been proposed that alterations in the quality and/or quantity of saliva might contribute to the symptoms of BMS.

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Patients and methods

Prior to the investigation written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. The patient group consisted of 28 female patients with BMS (age range 48–80 years, mean 64.05 years) diagnosed on the basis of burning symptoms and clinically healthy appearance of the oral mucosa and 28 female controls (age range 40–75 years, mean 63.82 years) who were healthy and were not taking any medications 1 month prior to this study. Prior to establishment of BMS diagnosis every patient underwent a series of local and systemic investigations. Local investigations were to exclude parafunctional activity such as tongue thrusting, candidal infection (swabs were taken), denture examination when present. Only patients with BMS who did not respond to salivary substitutes were included in the study. Blood tests were performed in all patients and they included complete blood count, iron and folate studies, vitamin B12 levels, liver function tests, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies and electrolytes. None of the patients had any systemic disease which might contribute to the symptoms of burning.

Saliva was collected by simple spitting method into calibrated containers from participants for 5 min between 9 and 11 AM (Wu-Wang *et al*, 1995). Salivary flow rates were determined for each participant. Periodontal status (CPI) was recorded (World Health Organisation, 1997) and only participants without periodontal disease were included in this study. Cytokine immunoassay kits (R&D Systems, Minneapolis, MN, USA) were used to determine the concentration of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in the whole-saliva samples both from patients and controls. The assays were conducted according to the manufacturer's directions and the assay is now performed everywhere.

Results

The results are expressed as mean ± SD. Statistical difference was tested with independent sample *t*-test. $p < 0.05$ was considered as statistically significant.

No significant differences in levels of salivary IL-6 and TNF-α were found in BMS patients when compared

Table 1 Salivary IL-6 and TNF-α levels in patients with burning mouth syndrome and control group

	Patients	*Controls*
IL-6 (pg ml^{-1})	8.64 ± 7.57	9.68 ± 9.06
TNF-α (pg ml^{-1})	8.07 ± 16.15	12.32 ± 18.41

IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

with the controls ($p < 0.05$) (Table 1). Significant differences in salivary flow rates were found between patients with BMS and controls.

Discussion

Xerostomia is a frequently concomitant symptom of BMS (Savage, 1996: Bergdahl and Bergdahl, 1999: Femiano *et al*, 2004). Regarding quality of saliva only few studies have investigated salivary constituents in patients with BMS. Hershkovich and Nagler (2004) found significantly increased levels of salivary sodium, total protein, albumin, lysozyme, amylase, immunoglobulin A (IgA), IgG, IgM and secretory IgA in 91 patients with BMS when compared with the healthy controls. They also found increased levels of the abovementioned variables in patients with xerostomia and taste disturbances, suggesting the underlying peripheral neurologic damage in these conditions. The results of Vučićević Boras *et al* (2001) show that secretory IgA and lysozyme levels were significantly decreased in the stimulated whole saliva of BMS patients when compared with the unstimulated whole saliva. Magnesium level did not change in the saliva stimulated in patients with BMS. Tammiala-Salonen and Soderling (1993) found no decrease in protecting and lubricating properties of saliva in patients with BMS, although they did find significantly lower total protein concentration in the stimulated saliva of women with BMS as well as higher concentration of sialic acid. Lundy *et al* (1997) could not find any difference in the major parotid glycoproteins between patients with BMS and controls. To our knowledge, this is the first report upon salivary cytokines in BMS patients. We have selected TNF-α because it has been implicated in the pathogenesis of many autoimmune and inflammatory diseases and inducers of its production are: endotoxins, certain viruses, immune complexes, substance P, ultraviolet light, hapten-induced irritant and contact hypersensitivity reactions, mucosal atrophy as well as other cytokines such as IL-1. Our results showed no significant differences between patients and controls regarding salivary IL-6 and TNF-α. However, some of the patients had xerostomia and thus may not be 'true' BMS patients. Xia *et al* (2003) found no differences in serum IL-2 and IL-6 levels between patients with BMS and controls. However, to our knowledge, there is only one published article upon correlation of salivary and serum cytokines in diseases affecting the oral cavity, i.e., in patients with oral squamous cell carcinoma showing that both salivary cytokines IL-6 and basic fibroblast growth factor were elevated while the same serum cytokines were not elevated (Vučićević Boras *et al*, 2004). Our hypothesis about subclinical inflammation in BMS patients needs further verification. However, it is still possible that other cytokines might play a role in BMS.

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