Original Article

JOMP
Journal of Oral Medicine and Pain

pISSN 2288-9272 eISSN 2383-8493
J Oral Med Pain 2017;42(4):116-124
https://doi.org/10.14476/jomp.2017.42.4.116

Antidiuretic Hormone Levels in Men with Burning Mouth Syndrome: A Pilot Study

Yeon-Hee Lee[1], Mi-Jin Hwang[1], Suk Chon[2], Q-Schick Auh[1]

[1]Department of Orofacial Pain and Oral Medicine, Kyung Hee University Dental Hospital, Seoul, Korea
[2]Department of Endocrinology and Metabolism, Kyung Hee University Hospital, Kyung Hee University College of Medicine, Seoul, Korea

Received October 14, 2017
Revised November 15, 2017
Accepted November 17, 2017

Correspondence to:
Yeon-Hee Lee
Department of Orofacial Pain and Oral Medicine, Kyung Hee University Dental Hospital, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea
Tel: +82-2-958-9454
Fax: +82-2-962-8124
E-mail: omod0209@gmail.com

Purpose: Burning mouth syndrome (BMS) is a disabling pain that mostly occurs in elderly women, but rarely in men. It is characterized by an unremitting oral burning sensation and pain without detectable oral mucosal changes. We investigated the clinical and hematologic features of middle-aged men with BMS, and compared the results to those of men with oral mucositis.

Methods: Five men with BMS (48.60±6.19 years) and five age-matched controls with oral mucositis (49.80±15.26 years) underwent clinical and psychological evaluations and blood tests. Psychological status was evaluated using the Symptom Checklist-90-Revised. Cortisol, estradiol, progesterone, testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), and antidiuretic hormone (ADH) levels and erythrocyte sedimentation rate (ESR) were determined from the blood samples.

Results: ADH level was significantly lower in men with BMS than in the controls. ADH levels correlated with testosterone ($p<0.01$), and ACTH levels strongly correlated with ESR ($p<0.05$). Progesterone level positively correlated with FSH and LH levels. Pain intensity on a visual analogue scale correlated with estradiol level only in men with BMS. Among psychological factors, the obsessive-compulsive disorder, interpersonal-sensitivity, and anxiety scores were higher in men with BMS than in the controls ($p<0.05$). However, no correlations were observed between the psychological and hematologic factors in both groups. The BMS symptoms presented only on the tongue, with the lateral border being the most prevalent area.

Conclusions: Men with BMS may experience dysregulated endocrinologic or psychoneuroendocrinologic interactions, which might affect oral BMS symptoms, aggravating the severity of the burning sensation.

Key Words: Antidiuretic hormone; Blood; Burning mouth syndrome; Estradiol; Gonadal hormone; Male

INTRODUCTION

Burning mouth syndrome (BMS) is defined by the International Headache Society (IHS) as an intraoral burning sensation without any medical or dental cause. It was first categorized as a distinct disease in 2004. IHS classifies BMS in the category of cranial neuralgias and central causes of facial pain.[1)] BMS is defined by the International Association for the Study of Pain as a burning pain in the tongue or other oral mucous membranes, without any pathologic mucosal changes and lasting at least 4 to 6 months.[2)] The main symptom of BMS is a burning sensation in the oral mucosa and perioral regions, and it is usually described as scalding, tingling, or numbing.[2,3)] BMS is

characterized by positive sensory symptoms, such as burning sensation, dysgeusia, and dysesthesia, and negative sensory symptoms, including taste loss and paresthesia. These characteristics and definitions seem clear. However, patients with BMS experience continuous burning pain without any obvious clinical signs, for which there are no definitive diagnostic or imaging tests;[1] clinicians have difficulty understanding, diagnosing, and managing BMS.

BMS probably has a multifactorial origin, and sometimes, it can be idiopathic, or unclear etiopathogenesis involving local, systemic, and psychological factors. Female gender, peri-menopause, aging, depression, anxiety, and chronic medical conditions including gastrointestinal and urogenital diseases are reported risk factors for BMS development.[4-6] BMS affects 1.5%-8% of the general population, mainly occurring in middle-aged to elderly women, and has a 90% higher incidence in women than in men.[7-9] In a previous cohort study, the prevalence of BMS was higher in women (5.5%) than in men (1.6%), and BMS was not found to occur before 40 years of age; nevertheless, the prevalence increased with age in both sexes.[4] The big difference in BMS prevalence between the sexes might be explained by the hormonal changes occurring around these middle ages. Women undergo endocrinological and physical changes during menopause, particularly a decrease in the levels of estradiol and increase in the levels of follicle-stimulating hormone (FSH) or luteinizing hormone (LH) that affect their health.[10] In middle-aged men, aging is associated with a significant decrease in the levels of testosterone, dehydroepiandrosterone sulfate, and estradiol, and an increase in the levels of LH and FSH.[11] According to Kim et al.,[12] female gonadal and stress hormones are dysregulated in patients with BMS. Although the results have not been consistent, the levels of female gonadal hormones such as estradiol, progesterone, and FSH have been shown to be altered in patients with BMS.[9,12,13] With regard to estradiol, altered levels of estrogen can affect the oral mucosal health, because the oral mucosa contains estrogen receptors.[14] Unfortunately, little research has been conducted into the relationship between the changes in endocrinal regulation and oral health.

Psychological factors are also considered major contributing factors to BMS. According to Kenchadze et al.,[15] patients with BMS in the age group of 46 to 70 years had depression, insomnia, neurologic disorders, phobic syndrome, and cancer-phobia. A previous psychological questionnaire survey of 184 patients with BMS showed that they had psychological conditions such as anxiety, depression, and neurotic tendencies. However, the authors emphasized that it was difficult to consider that psychological factors alone cause BMS.[3] Low sleep quality also contributes to the aggravation of BMS symptoms. According to a case-control study, patients with BMS had lower sleep quality than did healthy controls, and a depressed mood and anxiety were correlated with the existence of sleep disturbances in these patients with BMS.[16] In addition, antidiuretic hormone (ADH) or vasopressin has a crucial role in maintaining sleep quality.[17] Dysregulated or decreased ADH secretion can aggravate BMS symptoms. Almost all researchers agree and suggest complex interactions between psychological factors and other local and/or systemic factors. In addition, it is widely accepted that psychological factors play a crucial role in the genesis and maintenance of pain sensations.[15]

Various factors may simultaneously participate in the occurrence and development of BMS. Furthermore, since BMS occurs mainly in peri- or post-menopausal women,[4] many studies have overwhelmingly focused on the causes, development, and treatment of BMS in middle-aged women. Thus, studies focused on the etiopathology and symptoms of BMS in men have scarcely been reported in the neurological and dental literature. In this study, we investigated the psychologic and hematologic features of men with BMS by comparing their features with those of age-matched controls with chronic oral mucositis.

MATERIALS AND METHODS

1. Patients

We recruited 10 men who attended the Department of Orofacial Pain and Oral Medicine (Kyung Hee University Dental Hospital, Seoul, Korea) between January 1, 2016 and June 30, 2017. Five men diagnosed with BMS (48.60±6.19 years) without objective clinical abnormality, and five age-matched controls with oral mucositis (49.80±15.26 years) with a definite oral mucosal lesion were included. The inclusion criteria for the patients with BMS adhered to the

International Classification of Headache Disorders-3 classification suggested by IHS as follows: 1) superficial intraoral pain for more than 3 months; 2) a persistent (more than 2 h/day) and burning quality of the pain; 3) age between 30 and 68 years; and 4) no visible clinical changes in the oral mucosa. Since BMS has rarely been reported in men,[14,18] men with BMS were selected for the present investigation, and the measured values were compared with those of age-matched controls. All patients underwent clinical and psychological evaluations and blood tests. Their psychological status was evaluated using the Symptom Checklist-90-Revised (SCL-90R). The levels of cortisol, estradiol, progesterone, testosterone, FSH, LH, adrenocorticotropic hormone (ACTH), cortisol, ADH, and erythrocyte sedimentation rate (ESR) were determined from blood samples. Patients were also asked to complete inventories used for the analysis of duration, type, intensity, and area of BMS symptoms. The exclusion criteria for the patients were as follows: heavy smoker, having uncontrolled diabetes, having a history of a disease or/and a therapy that can cause secondary BMS symptoms.

2. Study Design

All patients in both the BMS and oral mucositis groups underwent a physical examination, laboratory screening tests, and psychiatric assessment using the SCL-90R. The obtained data were analyzed and compared statistically. The research protocol was reviewed for compliance with the Helsinki Declaration and was approved by the Institutional Review Board of the University Hospital (KHD IRB no. 1709-4). Informed consents were obtained from all patients.

3. Clinical Evaluation

Clinical evaluation procedures for the patients included an oral examination, and psychological evaluation using the SCL-90R,[19] and blood tests. An overall questionnaire was used to evaluate subjective discomforts, duration and areas of symptoms, and the characteristics of discomfort (burning, itching, numbness, taste disturbance, or dry mouth). To rule out other possible systemic factors that may cause oral burning pain and/or abnormal oral sensations, a questionnaire about recent systemic disease and medication was administered. In addition, the presence of stressful conditions and insomnia was evaluated using a dichotomous question.

The severity of oral pain was scored on a visual analogue scale (VAS) (0-100 cm, with 100 cm indicating the worst pain). The SCL-90R was used to examine the psychological status of the patients. The SCL-90R is a tool for evaluating psychological symptoms by analyzing the answers to 90 questions, and it provides results regarding nine symptom dimensions, namely, somatization (SOM), obsessive-compulsive disorder (O-C), interpersonal sensitivity (I-S), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), and psychosis (PSY).

4. Blood Tests

Blood sampling was performed between 9:00 a.m. and 11:00 a.m. to minimize variability due to the circadian rhythm. The tests included complete blood counts with leukocyte differential and various hematologic variables. The levels of gonadal hormones, including estradiol, progesterone, testosterone, LH, and FSH; stress markers, including ACTH and cortisol; ADH; and ESR were measured. The reference normal range of each variable is as follows: estradiol, 15-60 pg/mL; progesterone, 0.6-2.11 pg/mL; testosterone, 2.67-10.12 pg/mL; ACTH, 10-60 pg/mL; cortisol, morning 5-27 g/dL; FSH, 1.3-8.1 mIU/mL; LH, 1.0-5.3 mIU/mL; ESR, 0-15 mm/h; and ADH, <6.7 pg/mL.

5. Statistical Methods

We investigated the absolute and percentage distributions of all nominal and categorical variables. We also obtained their means and standard deviations, and performed descriptive data analysis. We used various statistical methods for data analysis. Results obtained for the men with BMS and men with chronic oral mucositis were compared using the t-test and Mann-Whitney U test. Fisher's exact test was used to determine the equality of the proportions. Spearman's correlation analysis was used to determine correlations between variables. Statistical significance was established at p-values <0.05. Data were analyzed using IBM SPSS Statistics ver. 20.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

1. Clinical Characteristics (Table 1)

The severity of pain scored on the VAS was not significantly different between the groups. Duration of symptom was longer in patients with BMS (9.25±1.58 years) than in the controls (2.08±2.27 years) (p=0.068). The most prevalent symptom was burning sensation, which was observed in all patients (n=5, 100.0%), and two of the five patients with BMS had the burning sensation only. One patient (20.0%) had burning sensation, itching, taste dysfunction, and dysesthesia. The prevalence of stress (80.0%) was higher in patients with BMS than in the controls. All patients reported the tongue as the main and only symptom area, especially the lateral border (n=5, 100.0%). The tongue tip (60%) and dorsum (60%) were the other main symptom areas (Fig. 1). All patients had symptoms in more than two of these three sites. Moreover, pain was not reported in the lip, cheek, alveolar mucosa, and floor of the mouth. One of the five patients had hypertension, and no other systemic or psychologic disorders were reported by the patients with BMS.

2. Symptom Checklist-90-Revised (Table 2)

The results of the analysis using the SCL-90R showed that the mean T-scores of all nine symptom dimensions were in the range of 30-60, and the scores were higher in patients with BMS than in the controls. More specifically, the dimensions for which the T-scores were significantly higher in patients with BMS were O-C, I-S, and ANX (p<0.05); the scores for SOM (p=0.069), DEP (p=0.085), and PAR (p=0.089)

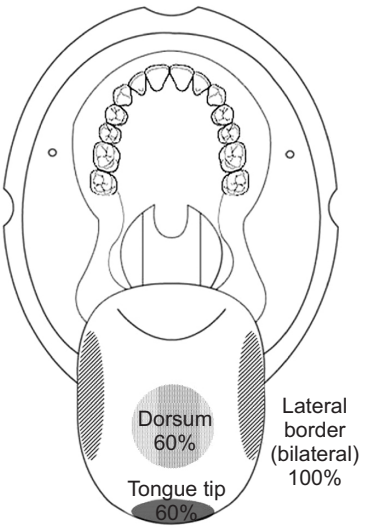

Fig. 1. Distribution of burning mouth syndrome (BMS) symptoms on the tongue. All patients had BMS symptoms on the bilateral sides of the tongue, and 60% of the patients had symptoms on the dorsum and tip of the tongue.

Table 1. Comparisons of clinical characteristics of non-BMS group and BMS group

Characteristic	Oral mucositis (n=5)	BMS (n=5)	p-value
Age (y)	49.80±15.26	48.60±6.19	0.875
Duration of symptoms (d)	759.00±828.09	3,376.00±578.93	0.068
VAS (0-100)	56.00±16.73	62.00±16.42	0.583
Accompanying status			
Oral dryness	1 (20.0)	4 (80.0)	0.103
Stress	2 (40.0)	4 (80.0)	0.262
Sleep problem	0 (0.0)	1 (50.0)	0.500
Hypertension	4 (80.0)	1 (20.0)	0.103
Symptom of BMS patients			
Burning		2 (40.0)	
Burning+itching		2 (40.0)	
Burning+itching+taste dysfunction+dysesthesia		1 (20.0)	
Area of symptoms			
Tongue tip+lateral border		2 (40.0)	
Dorsum+lateral border		2 (40.0)	
Tongue tip+lateral border+dorsum		1 (20.0)	

BMS, burning mouth syndrome; VAS, visual analogue scale.
Values are presented as mean±standard deviation or number (%).
Results were obtained via Mann-Whiteney U test and Fisher's exact test.
p-value was considered as significant when p-value<0.05.

were relatively but significantly higher in patients with BMS. The mean scores of HOS, PHOB, and PSY were also higher in patients with BMS, but the differences were not statistically significant.

3. Blood Test Results (Table 3)

Among the hormones tested, only ADH showed a statistically significant difference, with ADH levels being significantly lower in patients with BMS (5.71±1.65 pg/mL) than in the controls (8.78±1.05 pg/mL). None of the other hematologic factors were significantly different. More specifically, the mean level of estradiol, progesterone, testosterone, cortisol, FSH, LH, platelet count, and ESR was lower in patients with BMS than in the controls. The mean ACTH level was higher in patients with BMS. However, these results were not statistically significant.

The mean values of estradiol and FSH were outside the normal ranges. The normal serum estradiol level is 15-60 pg/mL in men. In our study, serum estradiol level was lower than the normal reference range in both patients with BMS and in the controls. The mean FSH level (13.10 mIU/mL) was higher in the controls than in patients with BMS, and was higher than the reference FSH level (1.3-8.1 mIU/mL).

4. Correlations with VAS and Hematologic Variables (Table 4)

In patients with BMS, the VAS scores were positively and strongly correlated with estradiol levels (r=0.971, p<0.01), whereas the VAS scores were not correlated with any other hematologic variables in the controls. Progesterone level was positively correlated with FSH and LH levels. Interestingly, ESR was positively correlated with ACTH level (r=0.999, p<0.01), and was negatively correlated with the platelet count (r=−0.998, p<0.01). Notably, ADH level was strongly and positively correlated with testosterone level (r=0.971, p<0.01). These correlations between the VAS scores and hematologic variables, and among the hematologic variables, were not observed in the controls. In addition, no correlations were observed among the nine psychologic dimensions and hematologic factors in both patients with BMS and the controls.

Table 2. Comparisons of mean values of psychological 9 dimensions

	Oral mucositis (n=5)	BMS (n=5)	p-value
SOM	41.80±2.49	50.60±9.02	0.069
O-C	39.40±2.97	49.60±7.47[a]	0.022[a,]*
I-S	40.00±2.24	52.60±8.62[a]	0.013[a,]*
DEP	39.40±2.97	43.00±2.83	0.085
ANX	41.60±1.67	52.20±8.50[a]	0.026[a,]*
HOS	44.60±9.21	51.00±4.80	0.205
PHOB	48.00±9.00	53.60±9.21	0.359
PAR	43.80±8.73	51.40±0.89	0.089
PSY	45.20±7.79	46.80±4.87	0.707

BMS, burning mouth syndrome; SOM, somatization; O-C, obsessive-compulsive disorder; I-S, interpersonal sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PHOB, phobic anxiety; PAR, paranoid ideation; PSY, psychosis.
Values are presented as mean±standard deviation.
Results were obtained via t-test.
[a]p-value was at the significant level.
*p-value was considered as significant when p-value <0.05.

Table 3. Comparisons of mean values of hematologic variables between groups

Variable	Oral mucositis (n=5)	BMS (n=5)	p-value
Estradiol(S) (pg/mL)	8.34±3.74	6.12±2.84	0.321
Progesterone(S) (pg/mL)	1.54±0.37	1.34±0.34	0.394
Testosterone(S) (ng/mL)	5.10±2.61	3.58±0.87	0.250
ACTH(P) (pg/mL)	29.65±13.14	37.90±10.57	0.330
Cortisol(S) (μg/dL)	11.08±2.90	10.94±4.25	0.959
FSH(S) (mIU/mL)	13.10±9.55	5.32±1.17	0.109
LH(S) (mIU/mL)	4.98±1.47	3.30±1.78	0.174
WBC (10^3/μL)	6.21±1.80	7.14±2.00	0.548
RBC (10^6/μL)	4.72±0.43	4.54±0.21	0.532
Hemoglobin (g/dL)	15.20±1.21	14.87±0.72	0.695
Hematocrit (%)	44.23±2.41	42.37±0.76	0.263
MCV (fL)	94.03±4.80	93.47±2.63	0.865
MCH (pg)	32.23±1.20	32.73±0.83	0.562
MCHC (g/dL)	34.30±1.15	35.03±1.04	0.425
Platelet count (10^3/μL)	231.00±44.16	184.00±25.16	0.164
MPV (fL)	7.55±0.51	7.40±0.62	0.739
ESR (mm/h)	9.25±7.54	4.67±0.58	0.352
ADH (pg/mL)*	8.78±1.05	5.71±1.65[a]	0.015[a,]*

BMS, burning mouth syndrome; S, serum; ACTH, adrenocorticotropic hormone; P, plasma; FSH, follicle-stimulating hormone; LH, luteinizing hormone; WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; ADH, anti-diuretic hormone.
Values are presented as mean±standard deviation.
[a]p-value was at the significant level.
*p-value was considered as significant when p-value <0.05.

Table 4. The correlations among the hematologic variables

	Estradiol (S)	Progesterone (S)	Testosterone (S)	ACTH (P)	Cortisol (S)	FSH (S)	LH (S)	Platelet count	ESR	ADH
Oral mucositis (r)										
VAS	−0.645	0.401	−0.532	−0.396	−0.149	−0.721	−0.565	−0.978[a,*]	0.641	0.175
Estradiol(S)		0.145	0.767	−0.196	−0.265	0.119	0.932	0.873	−0.747	−0.688
Progesterone(S)			0.538	−0.670	−0.410	−0.776	0.263	−0.699	−0.224	−0.692
Testosterone(S)				−0.188	−0.345	0.184	0.804	0.473	−0.851	−0.898
ACTH(P)					0.947	0.921	0.024	0.737	−0.999[a,**]	0.758
Cortisol(S)						0.773	0.037	0.326	−0.854	0.802
FSH(S)							0.243	0.918	−0.960	0.473
LH(S)								0.585	−0.968	−0.558
Platelet count									−0.489	0.797
ESR										0.250
BMS (r)										
VAS	0.971[a,**]	0.391	−0.649	−0.351	0.498	0.427	0.353	0.551	−0.500	−0.563
Estradiol(S)		0.219	−0.633	−0.488	0.394	0.209	0.208	0.607	−0.559	−0.515
Progesterone(S)			0.020	−0.035	0.511	0.894[a,*]	0.907[a,*]	0.060	0.000	0.055
Testosterone(S)				−0.289	0.212	−0.084	−0.223	0.134	−0.193	0.971[a,**]
ACTH(P)					−0.371	0.202	0.120	−0.996	0.999[a,**]	−0.459
Cortisol(S)						0.666	0.128	0.978	−0.963	0.165
FSH(S)							0.727	0.334	−0.277	−0.145
LH(S)								−0.381	0.435	−0.149
Platelet count									−0.998[a,**]	0.124
ESR										−0.183

S, serum; ACTH, adrenocorticotropic hormone; P, plasma; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ESR, erythrocyte sedimentation rate; ADH, anti-diuretic hormone; r, correlation coefficient; VAS, visual analogue scale; BMS, burning mouth syndrome.
Results were obtained by the Spearman's correlation test.
[a]p-value was at the significant level.
p-value was considered as significant when p-value <0.05 (*p<0.05, **p<0.01).

DISCUSSION

The results of the present study indicated that the clinical characteristics and hematologic features of men with BMS were different from those of men with chronic oral mucositis, as well as those of typical peri- and post-menopausal women with BMS. The majority of patients with chronic pain including BMS are women, and the reason is not purely biological, but mixed with sociocultural factors.[20] In the present study, ADH level was significantly lower in men with BMS than in men with oral mucositis, and ADH level was positively correlated with testosterone level. Testosterone has an analgesic role of protecting against the development of painful conditions.[21] The specific effects of testosterone on neuropathic or chronic orofacial pain are complicated because much of testosterone is metabolized to estradiol in vivo; this feature needs to be investigated in future studies. Unfortunately, few studies have compared the symptoms between the sexes or have explored the symptoms in men with BMS. To our knowledge, this is the first study to investigate the effects of changes in ADH levels on BMS symptoms in men, and to compare the psychological factors with those of controls.

Decrease in ADH levels can be a causative factor of BMS in men. In a previous animal study, ADH release was related to salivary secretion from the parotid gland in the oral cavity, as well as urine secretion.[22] Furthermore, ADH has an important role in maintaining sleep, and the total measured secretion of ADH is significantly higher during the day than during the night.[17] In contrast, if the ADH level is low, nocturia can occur. Nocturia is generally associated with increased nocturnal urine production, and conservative treatment with an ADH analogue can help reduce nocturia symptoms.[23] In addition, among men, the association between nocturia and poor sleep quality becomes stronger with increasing age.[24] Poorer sleep quality is associated with higher SCL-90R psychological distress scores.[25] Sleep disturbance and low sleep quality are well known to

aggravate the severity of pain and symptoms in BMS. In fact, one patient with BMS in our study reported sleep disturbance. Although the patients do not consciously recognize the occurrence of sleep problems, changes in sleep structure may have a causal relationship with changes in ADH levels. Further study is needed on ADH levels and sleep structure.

It is noteworthy that only estradiol level was positively correlated with pain intensity represented using the VAS score in our patients with BMS. Under the experimental pain condition, pain perception was correlated with supraphysiological estradiol levels, whereas no correlation with progesterone and LH levels was observed.[26] A previous study reported that the interaction of estrogen and progesterone plays a crucial role in the regulation of nociception and analgesia.[27] In particular, an increase or fluctuation in estrogen levels can be related to an increase in pain perception with a decrease in pain thresholds.[28] However, the extent of their role in the pain intensity of patients with BMS has not yet been fully understood. Moreover, the hematologic features, including changes in gonadal hormones, have not been fully researched in men with BMS. After the age of menopause, when estrogen and progesterone levels are very low in women, the sex differences in pain become much less prominent.[29] Both men and young women with hormonal imbalance are at risk of developing BMS.[30] Given the complexity of the hypothalamic-pituitary-ovarian regulatory system, estradiol and progesterone can be regulated independently at the pituitary level.[31] Therefore, the altered level of estradiol in men with BMS might be associated with the subjective severity of oral symptoms, which may be one of the features different from patients with oral mucositis.

BMS is conceptualized as a psychogenic physical continuum, and approximately 50% of the patients have associated psychological factors.[32] Bergdahl et al.[33] demonstrated a significantly higher score on the somatic anxiety and psychoasthenia scales, and lower socialization scores, in patients with BMS than in controls. Psychologic indices such as SOM, ANX, or DEP tend to be higher in patients with BMS.[5,34] In our study, men with BMS had higher O-C, I-S, and ANX scores than did men with oral mucositis. Unfortunately, we could not perform a comparison with healthy controls in this study. As BMS is a type of chronic pain condition, patients may experience high levels of pain and anxiety.[5] The high O-C and I-S scores may be a unique psychological feature of men with BMS.

In our patients with BMS, an oral burning sensation appeared to be the most prevalent symptom, and itching, taste disturbance, and dysesthesia were also observed. Oral mucosal pain, taste disturbance, and xerostomia are generally accepted as the symptomatic triad of patients with BMS.[35] The burning pain has moderate to severe intensity, is commonly bilateral, and most often involves the tongue followed by the palate and lower lip. In contrast, the floor of the mouth and buccal mucosa are rarely affected.[36] In our study, the symptoms were reported only on the tongue, and not in any other parts of the oral mucosa and/or throat. Regarding symptom location, the tongue, especially the tongue tip, has been reported as the most common symptom site.[4,37] However, the mean age and duration of symptoms in our patients were different from those of patients in previous studies. Danhauer et al.[38] investigated 69 patients with BMS (17% male) with an average age of 62 years. When they analyzed their results without distinction of sex, the mean pain duration was 2.45 years, and the VAS pain score was rated as 49 (range, 0-100). Schiavone et al.[5] reported that the mean illness duration was 2.90 years and the mean VAS score was 5.53. In our study, the mean duration of symptoms of patients with BMS was 9.25 years, which was significantly longer than that of patients with oral chronic mucositis and of patients included in previous studies. In addition, pain intensity on the VAS was 63, which was higher than the score reported in previous studies. The sociocultural impact of sex differences on pain have been suggested, and gender role expectations may lead to pain stoicism in men,[20] thereby causing the symptoms in men to be more chronic.

Because of the rigorous criteria used in BMS diagnosis, the small number of patients included in this study poses a limitation. However, this study was the first to analyze the hematologic factors including sex hormones, stress hormones, and ADH in men with BMS. In particular, the decrease in ADH level was suggested as a causative factor of BMS. Although no correlation was found between psychological and hematologic factors, our results suggested that interpersonal sensitivity, obsessive-compulsive disorder, and

anxiety should be considered in the diagnosis and treatment of men with BMS.

In conclusion, multiple factors are related to BMS development. In this study, we concluded that a decrease in ADH level can be a causative or aggravating factor of BMS symptoms in men with BMS, and an increase in estradiol level can increase the pain intensity. Furthermore, the incidence of obsessive-compulsive disorder, interpersonal sensitivity, and anxiety was higher in men with BMS than in men with oral mucositis. These findings suggest that both the physiological and endocrinological aspects of BMS need to be actively investigated by clinicians to successfully diagnose and manage men with BMS. Moreover, the physiological, psychological, and endocrinological aspects may not be mutually exclusive. The clinicians should therefore be cautious when diagnosing and managing men with BMS.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

The authors extend their special thanks to Jung-Pyo Hong at the Department of Orofacial Pain and Oral Medicine, Kyung Hee University Dental Hospital.

REFERENCES

1. Klasser GD, Fischer DJ, Epstein JB. Burning mouth syndrome: recognition, understanding, and management. Oral Maxillofac Surg Clin North Am 2008;20:255-271, vii.
2. Grinspan D, Fernández Blanco G, Allevato MA, Stengel FM. Burning mouth syndrome. Int J Dermatol 1995;34:483-487.
3. van der Ploeg HM, van der Wal N, Eijkman MA, van der Waal I. Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:664-668.
4. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med 1999;28:350-354.
5. Schiavone V, Adamo D, Ventrella G, et al. Anxiety, depression, and pain in burning mouth syndrome: first chicken or egg? Headache 2012;52:1019-1025.
6. Netto FO, Diniz IM, Grossmann SM, de Abreu MH, do Carmo MA, Aguiar MC. Risk factors in burning mouth syndrome: a case-control study based on patient records. Clin Oral Investig 2011;15:571-575.
7. Wardrop RW, Hailes J, Burger H, Reade PC. Oral discomfort at menopause. Oral Surg Oral Med Oral Pathol 1989;67:535-540.
8. Cairns BE. The influence of gender and sex steroids on craniofacial nociception. Headache 2007;47:319-324.
9. Gao J, Chen L, Zhou J, Peng J. A case-control study on etiological factors involved in patients with burning mouth syndrome. J Oral Pathol Med 2009;38:24-28.
10. Burger HG. The endocrinology of the menopause. Maturitas 1996;23:129-136.
11. Martínez Jabaloyas JM, Queipo Zaragoza A, Ferrandis Cortes C, Queipo Zaragoza JA, Gil Salom M, Chuan Nuez P. Changes in sexual hormones in a male population over 50 years of age. Frequency of low testosterone levels and risk factors. Actas Urol Esp 2008;32:603-610.
12. Kim HI, Kim YY, Chang JY, Ko JY, Kho HS. Salivary cortisol, 17β-estradiol, progesterone, dehydroepiandrosterone, and α-amylase in patients with burning mouth syndrome. Oral Dis 2012;18:613-620.
13. Dias Fernandes CS, Salum FG, Bandeira D, Pawlowski J, Luz C, Cherubini K. Salivary dehydroepiandrosterone (DHEA) levels in patients with the complaint of burning mouth: a case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:537-543.
14. Suri V, Suri V. Menopause and oral health. J Midlife Health 2014;5:115-120.
15. Kenchadze R, Iverieli M, Okribelashvili N, Geladze N, Khachapuridze N. The psychological aspects of burning mouth syndrome. Georgian Med News 2011;(194):24-28.
16. Adamo D, Schiavone V, Aria M, et al. Sleep disturbance in patients with burning mouth syndrome: a case-control study. J Orofac Pain 2013;27:304-313.
17. Trudel E, Bourque CW. Central clock excites vasopressin neurons by waking osmosensory afferents during late sleep. Nat Neurosci 2010;13:467-474.
18. Spanemberg JC, Rodríguez de Rivera Campillo E, Salas EJ, López López J. Burning Mouth Syndrome: update. Oral Health Dent Manag 2014;13:418-424.
19. Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. Br J Soc Clin Psychol 1977;16:347-356.
20. Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. J Neurosci Res 2017;95:500-508.
21. Fischer L, Clemente JT, Tambeli CH. The protective role of testosterone in the development of temporomandibular joint pain. J Pain 2007;8:437-442.
22. Olsson K, Rundgren M. Inefficiency of isoprenaline to induce drinking in the goat. Acta Physiol Scand 1975;93:553-559.
23. Robinson D. Nocturia in women. Int J Clin Pract Suppl 2007;(155):23-31.
24. Vaughan CP, Fung CH, Huang AJ, Johnson TM Nd, Markland AD. Differences in the association of nocturia and functional outcomes of sleep by age and gender: a cross-sectional, population-based study. Clin Ther 2016;38:2386-2393.e1.

25. Shaver JL, Lentz M, Landis CA, Heitkemper MM, Buchwald DS, Woods NF. Sleep, psychological distress, and stress arousal in women with fibromyalgia. Res Nurs Health 1997;20:247-257.
26. Nisenblat V, Engel-Yeger B, Ohel G, Aronson D, Granot M. The association between supra-physiological levels of estradiol and response patterns to experimental pain. Eur J Pain 2010;14:840-846.
27. Gordon FT, Soliman MR. The effects of estradiol and progesterone on pain sensitivity and brain opioid receptors in ovariectomized rats. Horm Behav 1996;30:244-250.
28. Stening KD, Berg G, Hammar M, et al. Influence of estrogen levels on thermal perception, pain thresholds, and pain tolerance: studies on women undergoing in vitro fertilization. J Pain 2012;13:459-466.
29. Vincent K, Tracey I. Hormones and their Interaction with the Pain Experience. Rev Pain 2008;2:20-24.
30. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain 2009;23:202-210.
31. Paller CJ, Campbell CM, Edwards RR, Dobs AS. Sex-based differences in pain perception and treatment. Pain Med 2009;10:289-299.
32. Browning S, Hislop S, Scully C, Shirlaw P. The association between burning mouth syndrome and psychosocial disorders. Oral Surg Oral Med Oral Pathol 1987;64:171-174.
33. Bergdahl J, Anneroth G, Perris H. Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: a controlled study. J Oral Pathol Med 1995;24:213-215.
34. de Souza FT, Teixeira AL, Amaral TM, et al. Psychiatric disorders in burning mouth syndrome. J Psychosom Res 2012;72:142-146.
35. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14:275-291.
36. Grushka M. Clinical features of burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:30-36.
37. Cerchiari DP, de Moricz RD, Sanjar FA, Rapoport PB, Moretti G, Guerra MM. Burning mouth syndrome: etiology. Braz J Otorhinolaryngol 2006;72:419-423.
38. Danhauer SC, Miller CS, Rhodus NL, Carlson CR. Impact of criteria-based diagnosis of burning mouth syndrome on treatment outcome. J Orofac Pain 2002;16:305-311.