

Evaluating the Etiologies of Burning Mouth Symptom in Patients of Shiraz Dental School from 2007 to 2015

Zahra Ranjbar,¹ Mehdy Davarmanesh,² Maryam Zahed,^{1*} and Sadaf Salehi³

¹Department of Oral and Maxillofacial Medicine, Oral and Dental Disease Research Center, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, IR Iran

²Department of Oral and Maxillofacial Medicine, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, IR Iran

³Undergraduate Student, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, IR Iran

*Corresponding author: Maryam Zahed, Department of Oral and Maxillofacial Medicine, School of Dentistry, Ghasrodasht Ave., Ghomabad Dist, Shiraz University of Medical Sciences, Shiraz, IR Iran. Tel: +98-9173000887, E-mail: maryamzhd@yahoo.com

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Abstract

Background: Burning Mouth Syndrome (BMS) is a burning sensation of the oral mucosa without any sign of mucosal abnormality for which no medical or dental cause can be detected. However, this syndrome belongs to a broader category of patients whose main complaint is mouth burning and, so, their etiologies can largely vary.

Objectives: This study investigates the prevalence of burning mouth symptom for the first time in an institutional group of patients in Shiraz, Iran, among whom some were found to have BMS through excluding the recognizable physical or biochemical causes of mouth burning.

Methods: In this cross sectional study, from the existing records of 2 533 patients who referred to Shiraz Dental School since 2007 To 2015, a total number of 298 patients with the chief complaint of oral burning sensation were chosen. For each patient age, sex, etiology, and site of pain were recorded.

Results: Analysis revealed that amongst 298 individuals who suffered from burning sensation of the oral mucosa, the female/male ratio was 3 to 1; and local factors were found as the primary cause for the symptom development in a large proportion of the patients (63.5%). Followed by systemic diseases with a much less contribution to cause the symptom (22.8%). A number of 8.4% of the patients were idiopathic and 5.4% suffered from psychological disorders. Tongue was the most frequent location of burning (37.2%). Overall, only 25 patients (< 1%) who were mostly elderly ($P < 0.001$) had idiopathic BMS. The burning localization in the idiopathic cases was more likely to be reported as generalized than that in the cases with recognizable causes ($P < 0.001$).

Conclusions: The results of this study show that oral burning is mostly caused by the factors recognized during examination and that the idiopathic form or BMS known as a neuropathic pain is uncommon. Understanding the prevalence of the etiologic factors in certain populations would lead to a better diagnostic approach to BMS through the exclusion of those factors.

Keywords: Burning Mouth Syndrome, Mouth Disease, Neuropathic Pain

1. Background

Burning mouth syndrome (BMS) is defined in the literature as a burning sensation of the oral mucosa for which no medical or dental cause can be detected (1). This syndrome has been described as a burning pain in the tongue or other oral mucosal sites lasting over 4 to 6 months which is associated with normal signs and laboratory findings (2).

The discomfort in BMS is typically described as a bilateral continuous pain. The tongue is the most common location involved and in this case it is referred to as glossodynia (2-4). Other symptoms which may accompany the glossodynia and BMS include oral dryness, paresthesia, and altered taste (4). Therefore, BMS is referred to as a particular form of neuropathic pain (5) with treatments relying on medications mostly used to treat neuropathic pain; medications such as clonazepam, capsaicin, and tricyclic antide-

pressants (6). Other non-pharmacological treatments suggested are cognitive behavioral therapy, cessation of smoking, biofeedback therapy, and acupuncture (5, 7, 8).

A diagnostic challenge exists in the distinction between BMS without a known cause and conditions that are responsible for oral burning symptoms (9, 10). An approach in clarifying this issue is to classify patients into either primary (essential/idiopathic) BMS where no other abnormality is evident or secondary BMS where oral burning is explained by a clinical sign or disease (11). The factors that cause oral burning and must be excluded to reach a diagnosis of primary/essential BMS, though largely vary, can be classified into three main categories of local, systemic, and psychosocial factors. Known local factors are dental trauma, mucosal irritation from dentures, allergic contact stomatitis, viral or fungal infections, dry mouth due to salivary gland disorders, and lesions of the oral mucosa like lichen planus. Systemic factors re-

sponsible for oral burning are nutritional deficiencies, endocrinopathies, medication adverse effects, and salivary hypofunction associated with autoimmune disease. Psychosocial disorders such as depression, anxiety, somatoform disease, obsessive-compulsive disorder, and cancer phobia are factors that can induce burning pain in the oral cavity (3, 4).

Because of these etiological varieties, the mean time from the onset of symptoms to BMS diagnosis is more than 1 year. Also, it is reported that each BMS case is misdiagnosed by an average of more than 3 physicians before the correct diagnosis is made (12).

Furthermore, the epidemiologic data on BMS are limited and imprecise due to the lack of a universally accepted definition (8, 9). The prevalence ranges from 1% to 40% in the literature and postmenopausal women are mostly affected (3, 13).

As the primary goal, this study investigates the prevalence of burning mouth symptom in the whole patients who referred to Shiraz Dental School in a definite duration. Besides the goal mentioned, a proportion of the patients whose evaluation could not reveal any of the etiological factors remained under the category of primary or idiopathic BMS. Recent data state that "Despite current knowledge, BMS remains an enigmatic, misunderstood, and under-recognized painful condition" (9). To the best of our knowledge, this is the first institution-based report in southern Iran on the prevalence of this important oral symptom. Owing to the fact that the treatment of this disorder relies on the diagnosis of the underlying cause, it will be a great help for practitioners, especially general dentists and physicians who are not familiar with oral lesions but confront such patients, to better understand the causes and be able to rule out all possibilities before diagnosing a patient with idiopathic BMS. Moreover, there is no study to date that has evaluated the prevalence of these factors and idiopathic BMS individually in a certain population.

2. Methods

2.1. Patients

This cross sectional study was conducted by evaluating the existing records of 2,533 patients who referred to the oral and maxillofacial medicine department of Shiraz dental school, Iran, since September 2007 to January 2015. There were no complete and reliable documents before the year 2007 in this center. Because all the existing records were evaluated, no sampling strategy was used and no expected power was considered.

Shiraz dental school is a governmental university. This center is the only known center in Fars province that offers

services for oral mucosal disease and has referral for orofacial problems from all medical/dental governmental and non-governmental centers. Patients can seek treatment in this school for any orofacial or mucosal disease.

From the records, patients with the chief complaint of oral burning sensation that had a complete filled chart and definitive diagnosis for the cause of oral burning were chosen. Cases that lacked a meticulous explanation of the method of diagnosis were excluded.

Since this study was a retrospective evaluation of past records, for preserving the patients' rights of confidentiality, the study design was approved by the research and ethical committee of Shiraz University of Medical Sciences on 29th of November 2015. The ethical code is IR.SUMS.REC.1394.S825.

2.2. Method

The existing chart of each patient consisted of a complete review of past medical and dental history, drug history, a thorough clinical examination, and a detailed history of the burning symptom. Overall, these patients were examined by 7 observers throughout these years. All observers were oral and maxillofacial medicine specialists and professors of the Shiraz dental faculty who used same protocols for patient management. There is a strict policy in the department of oral medicine of Shiraz dental school for obtaining thorough history for every patient. Also, to reach diagnosis, where appropriate, laboratory procedures had been performed including culturing for fungi, complete blood count and fasting blood glucose determination, biopsy and saliva analysis. All cultures for fungi and bacterial infections had been performed in the laboratory of the pathology department of Shiraz dental school. Histopathology evaluations of the biopsied specimens of oral lesions listed in Table 1 had been, also, performed in the same laboratory by expert oral and maxillofacial pathologists. For detecting hyposalivation, unstimulated and stimulated whole saliva flow rates had been measured by the spitting method. Unstimulated whole saliva flow rates of < 0.1 mL/min and stimulated whole saliva flow rates of < 0.7 mL/min had been considered as a marker of salivary hypofunction. Furthermore, consultation with psychiatry, neurology, and endocrinology professors of Shiraz University of Medical Sciences had been carried out when these disorders were present. More detailed information regarding techniques of diagnosis is presented in Table 1.

For each patient age, sex, and the site of burning pain was recorded in a database. Based on Conulescu's classification, the etiological factors associated with oral burning were placed in four groups of 1: local factors; 2: systemic factors; 3: psychosocial factors; and 4: idiopathic forms (3).

Table 1. The Method of Diagnosis, Frequency, and the Percentage of Etiologic Factors of Oral Burning Sensation in the Studied Population

Etiologic Factors	No. (%)	Method of Diagnosis
	189 (63.4)	
Local factors	Oral lesions	89 (29.9)
		60 (20.1)
	Oral Infections	
		22 (7.4)
	Allergic Reactions	
	Trauma	12 (4.0)
	Dry mouth due to salivary gland disorders, drugs, radiotherapy	6 (2.0)
Systemic disease		68 (22.8)
	Endocrine disorders (DM, thyroid disease)	24 (8.0)
	Drug reactions	21 (7.0)
	Xerostomia due to systemic disease	13 (4.4)
	Nutritional deficiencies	10 (3.4)
Psychological disorders	16 (5.4)	Confirmation of disorder by a psychologist/ The use of a drug prescribed by a psychologist
Idiopathic	25 (8.4)	After Ruling out other etiologies
Total	298 (100)	

Abbreviations: DLE, discoid lupus erythematosus; DM, diabetes mellitus; EM, erythema multiform; HPV, human papilloma virus; HSV, herpes-simplex virus; OLP, oral lichen planus.

2.3. Statistical Analysis

The statistical package for social sciences (SPSS Inc., Chicago, IL, USA), version 17.0, was used for statistical analysis. To assess the etiologic factors with different locations of pain and, also, the gender distribution with the diagnosis and the location of pain, the Chi-Square test was used. The age distribution of the patients was tested for normality with the Kolmogrov-Smirnov test and a P value of more than 0.050 was considered as a normal distribution. The results of this test revealed that age was distributed normally in all the groups. Therefore, the parametric test One-Way ANOVA was used to compare the mean age with oral burning in each group of diagnosis and location of pain. After checking the homogeneity of variance for age and finding a P value greater than 0.050, the Post Hoc test was used to assess this variable in every group.

3. Results

Out of the 2 533 records evaluated between September 2007 to January 2015, 304 patients (8.33%) had the chief complaint of oral burning. And 6 of the records were incomplete or lacked definitive diagnosis. Therefore, 298

complete records (8.5%) were considered for evaluation. The mean age for this group was approximately 51.08 ± 15.47 years with the range of 16 to 90, and the gender distribution was 74.8% female and 25.2% male. The definitive diagnosis of oral burning in the records that were studied is listed in Table 1. The most common group of factors leading to oral burning sensation was local factors (63.4%). Systemic diseases with the prevalence of 22.8% were next in ranking. In 8.4% of the patients the factors were idiopathic and 5.4% suffered from psychological disorders (Table 1).

The age distribution among the groups of etiologic factors showed a significant statistical difference with the One-Way ANOVA test ($P < 0.001$) (Table 2). Also, the Post Hoc test revealed that the mean age in the group with local factors was significantly lower than the group with systemic disease ($P < 0.001$) and idiopathic factors ($P < 0.001$). The mean age in systemic disease etiology was significantly greater than the psychological etiologies ($P = 0.049$). This comparison was not significant with the Post Hoc test in other groups ($P > 0.05$).

This is similar in evaluating the mean age of patients with the location of pain which showed a significant statistical difference with the One-way ANOVA test ($P = 0.002$) (Table 3). The results of the Post-Hoc test showed that older

Table 2. Age and Gender Comparison in Different Etiologies of Oral Burning Pain

Etiologic Factor	Gender Frequency	Mean Age
Local Factors	F = 136	46.98 ± 15.52
	M = 53	
Systemic Disease	F = 57	57.85 ± 13.22
	M = 11	
Psychological Disease	F = 14	49.62 ± 13.09
	M = 2	
Idiopathic	F = 16	60.96 ± 16.46
	M = 9	
P value ^a	0.083 ^b	< 0.001 ^c

Abbreviations: F, Female; M, male.

^aThe mean difference is significant at the 0.050 level.

^bChi-Square test.

^cOne-Way ANOVA test.

patients had a significant generalized burning in comparison to the pain of the tongue and the floor of the mouth ($P = 0.004$), buccal and labial mucosa ($P = 0.001$), or ridge and alveolar mucosa ($P = 0.004$). This comparison was not significant with the Post Hoc test in other groups ($P > 0.05$).

Table 3. Age and Gender Comparison in Different Locations of Oral Burning Pain

Location of pain	Gender Frequency	Mean Age
Tongue and FOM 1	F = 83	49.17 ± 15.02
	M = 28	
Generalized burning 4	F = 23	55.32 ± 14.86
	M = 6	
Buccal and Labial Mucosa3	F = 23	45.78 ± 20.36
	M = 14	
Ridge and Alveolar Mucosa2	F = 84	45.93 ± 13.73
	M = 25	
Palate and Oropharynx5	F = 8	50.80 ± 13.87
	M = 2	
P value ^a	0.424 ^b	0.002 ^c

Abbreviations: F, Female; FOM, floor of the mouth; M, male.

^aThe mean difference is significant at the 0.050 level.

^bChi-Square test.

^cOne-Way ANOVA test.

In contrast, in evaluating the gender distribution related to etiologic factors and, also, the location of burning with the Chi-Square Test, although the number of the females was more in every group, no significant difference was found between the number of the males and the females ($P = 0.083$, $P = 0.424$) (Tables 2 and 3).

Tongue together with the floor of the mouth was the most frequent location of burning affected in 37.2% of the patients. And, 36.6% had generalized oral burning, next in ranking was the buccal and labial mucosa (12.4%), the dental ridge and alveolar mucosa (29%), and the palate was the least common site (3.4%) (Figure 1).

In patients diagnosed with local factors and, also, psychological factors as the cause of oral pain, the most common location involved was the tongue together with the floor of the mouth. But, in the idiopathic group and the systemic diseases, generalized oral burning was mostly common. These differences were significant with the Chi-square test ($P < 0.001$) (Table 4).

4. Discussion

This study revealed that the prevalence of oral burning disorder in the patients who referred to the oral medicine department of Shiraz dental school between the years 2007 and 2015 was 8.5%. And only 25 patients, from the 2 533 records evaluated, had idiopathic oral pain or primary BMS (0.98%). This finding is suggestive that BMS is an uncommon disease. This clinic has the most referrals for oral and maxillofacial medicine patients in Shiraz, so almost all patients seeking help for oral symptoms were referred to this clinic during these years.

Recent articles which use the latest theories of possible etiologic factors leading to BMS show a range of 1% to 40% prevalence for this disorder. The epidemiology of BMS is imprecise in literature because of the wide range of definitions and diagnostic criteria. Most studies investigate the cause of oral burning pain rather than idiopathic BMS (3, 4, 14, 15). The concept of a pragmatic approach in dividing BMS into primary (idiopathic) and secondary (with a known cause) was first introduced by Scala et al. (11) and supported by others in the literature (3, 4). In the secondary group with evident etiologic factors leading to this painful sensation, local, systemic, and psychological factors may be responsible (2-4).

Overall, local factors were the main reasons for which the evaluated patients of this population were seeking oral care. Systemic diseases such as diabetes mellitus were the next cause of oral burning and psychological factors were next in ranking. Idiopathic BMS or primary burning mouth syndrome was the least common form.

Among the local factors evaluated, oral lesions listed in Table 1 accounted for approximately 30% of the patients. Oral mucosal diseases such as lichen planus, benign migratory glossitis, hairy tongue, and fissured tongue have been previously proposed as causative factors of BMS (3, 4). Fortunately, oral mucosal diseases are all associated with visual clinical findings and can be easily diagnosed from BMS

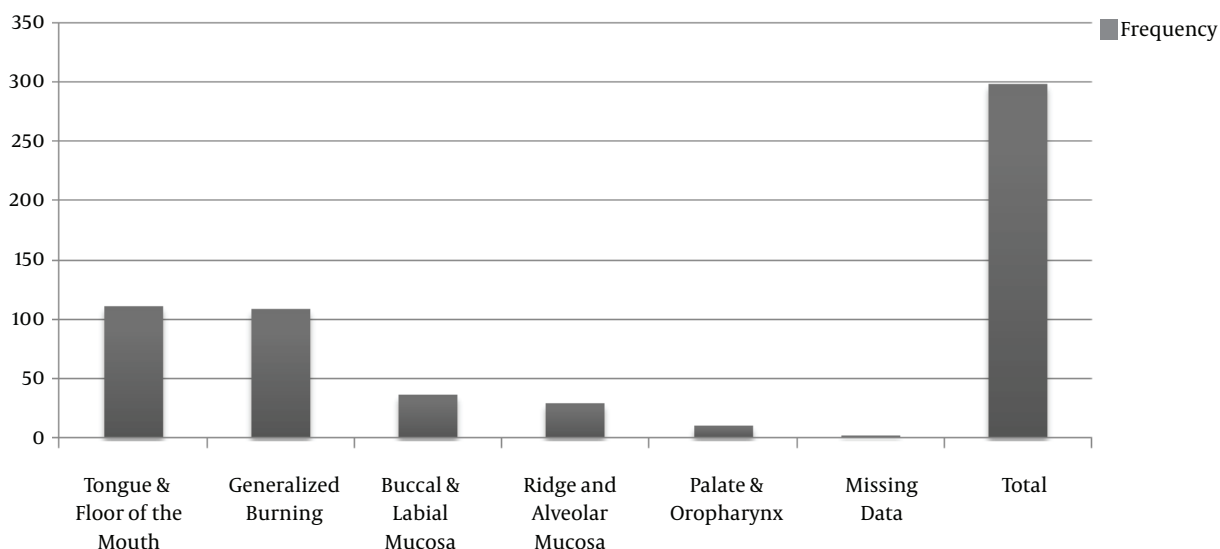


Figure 1. Common Locations of Oral Burning Sensation

Table 4. The Frequency of the Location of Pain in Different Etiologies of Oral Burning Pain

Location	Etiologic Factors			
	Local Factors	Systemic Disease	Psychological Disorders	Idiopathic
Tongue and FOM	72	19	9	11
Generalized burning	53	42	3	11
Buccal and Labial Mucosa	34	2	0	1
Ridge and Alveolar Mucosa	22	3	2	2
Palate and Oropharynx	8	1	1	0
Missing Data	0	1	1	0
Total	189	68	16	25
Chi Square Test	0.001 ^a			

Abbreviation: FOM, floor of the mouth.

^aThe mean difference is significant at the 0.050 level.

patients in whom the oral mucosa appears normal. The diagnosis of oral lesions is usually based on meticulous clinical and laboratory investigations by oral medicine experts.

Oral infections were, also, common in this population. In general, a high prevalence of candidal infection is reported in patients that complain of oral burning (3, 4). For ruling out this fungal infection, detecting signs of atrophy, erythema, and ulcer in the oral mucosa is helpful. Also, patients who have candidal infections usually experience pain upon eating, whilst BMS pain is commonly aborted in this situation. This confirms that fungal infection is not the source of pain in primary BMS patients (16). Moreover, viral and bacterial infections are, also, proposed as causes

of oral burning (17, 18). But, a “hit and run” theory is mentioned especially for viral infections, because no active infection exists in most cases, only elevation of viral IgM antibodies in the serum are detected (18).

Allergic reactions account for 7.4 % of the patients evaluated in this study. Allergic contact stomatitis is a common source of oral pain. Food allergens, dental restoration alloys, and chemical materials in dental products are all implicated in symptoms of oral burning (19, 20). Eliminating the causative factor is the best solution for separating allergic reactions from BMS pain.

Trauma due to ill-fitting dentures or parafunctional activities of the oral cavity emerged as an explanatory factor

for burning sensation of the mucosa as can be seen in the results of this study and other reports (21). Local erythema is observed in patients with ill-fitting dentures, but there is no support on the fact that mechanical trauma causes BMS (21). Oral parafunctional habits such as bruxism are chiefly associated with anxiety; but to this point of time, there are no studies that support the fact that these habits can cause BMS (22).

Only 2% of the studied population had burning pain that was due to oral dryness as a result of a local complication in the salivary glands and 4.4% due to xerostomia as a result of a systemic diseases. There is contradictory evidence on the incrimination of xerostomia in developing BMS. Reports indicate that oral burning is often concomitant with oral dryness and targeting factors associated with oral dryness may help alleviate an oral burning complaint. A high prevalence of 34% to 39% of this symptom is, also, reported for BMS patients (21, 23). It is true that a lack of lubrication in the oral mucosa results in pain often of burning quality. But, the complaint of dry mouth can be related to a change in the quality and the composition of saliva rather than its quantity (4).

Systemic factors emerged as a strong explanatory factor for oral burning and were seen in 20% of the studied population. Among these factors, endocrine disorders were the most frequent etiologic factors. Uncontrolled diabetes and hypothyroidism are known causes of oral burning (17, 21). The relationship between diabetes and BMS is explained as a peripheral neuropathy due to metabolic changes in the mouth. This state, also, generates a hypofunction of the salivary glands and subsequent saliva reduction which also promotes burning sensation of the oral mucosa (3, 24).

There are a number of drugs that are incriminated in the development of BMS among which angiotensin converting enzyme inhibitors (eg, captopril, enalapril, lisinopril), diuretic and beta blockers are mainly involved. There is a dose-dependent and duration of treatment association between the use of drug and the onset of the disease (25). In the present study, we found that 7% of the patients complaining of burning pain were consumers of these certain drugs.

Nutritional deficiencies were responsible for the burning symptom in 3.4% of the patients complaining of pain in this study. Vitamin deficiencies, iron deficiency anemia, and zinc deficiency are known systemic factors that cause burning sensation (3). There is no report on the prevalence of this symptom in patients with deficiencies aforementioned. And the exact mechanism by which these nutritional deficiencies can lead to the onset of oral burning remains hidden. Vitamin B complex replacement therapy, however, often proves ineffective for pain relief (11). Fur-

ther population studies are needed to relate this matter.

The link between BMS and psychological disorders dates back to the early 1920s. Depression, personality disorders such as hypochondria, somatization, anxiety, and cancer phobia are listed as major factors associated with BMS (3, 4, 14, 26). The prevalence of these disorders ranges from 20% to 52% in the literature (4). In the present retrospective study, the prevalence is 5.4% and known cases of psychological disorders that were under medical treatment could be solely included. But previous case-controlled studies have used different psychological screening tools to detect these disorders. Therefore, undiagnosed cases were, also, detected and included in the results (14, 26). However, many have stated that the determination between the development of BMS following psychological disorders or preceding burning symptom is not clear (26). Also, studies have revealed that there are no significant differences in personality profiles between BMS patients and control healthy subjects, concluding that BMS with no etiologic factor is different from burning mouth in psychogenic patients (27). Furthermore, many medications used in psychological conditions cause dry mouth and taste alterations that can present as burning sensation (26). So the dilemma remains whether BMS or chronic pain precipitates psychological disturbances or vice versa.

8.4% of the subjects had oral burning with no evident clinical cause or, in other words, primary BMS. A neuropathic basis is now accepted for BMS with the possibility of a dysfunction at the peripheral or central arc path and the processing of cortical excitation (5, 28). Latest studies uncover that a deficiency in the control of pain could be in part the cause of BMS and that BMS and dysgeusia conditions are not linked to similar structural changes in the brain (29). Whereas the reports of 2016 still express that there is a lack of universal definition of BMS and its characteristics and that the exact pathophysiology of primary BMS remains unknown (2, 30).

Glossodynia together with pain in the floor of the mouth was the most prevalent form of pain in the present cross sectional study. This form of pain is mostly seen in patients with local disease and psychological disorders as the cause of pain. Whereas generalized burning was the most common form of pain in older patients that had a history of certain systemic diseases. The location of pain had an interestingly equal number for the tongue and generalized involvement in patients with idiopathic primary oral burning (BMS). This is in accordance with the population-based study of the incidence of primary or idiopathic BMS by Kohorst et al. which reports tongue as the most common site of burning and after that the burning of several sites in the oral cavity (8). There are reports of a few rare cases of only lips or palate burning sparing other anatomic

locations of the oral mucosa in BMS (8, 14). It is obvious that systemic disorders cause generalized pain, but the generalized pain or the involvement of tongue whilst sparing other sites in idiopathic BMS needs more population-based studies for confirmation.

The apparent association of gender, age, and menopause with idiopathic BMS has long been confirmed (4, 8, 18). This is in accordance with our findings which reveal that primary BMS patients had a significant higher mean of age compared to the patients with evident etiologic factors. Also, female gender accounted for approximately 75% of the patients complaining of the symptom. It should be kept in mind that during perimenopause, an increase in salivary phosphate concentration, protein, Na⁺, K⁺, Ca²⁺, and Mg²⁺ is seen. Also, hormonal changes lead to chronic anxiety and stress (3). These can all be a reason for the burning sensation of the oral cavity with no evident clinical explanation in this group of patients. Although there is a probability that men are more reluctant than women to visit a physician and seek help for a symptom.

Of note, the third edition of the international classification of headache disorders in 2013 describes BMS as a recurrent daily pain for more than 2 hours per day for more than 3 months with a burning quality that is felt superficially in the oral mucosa (1). Not considering this definition is a shortcoming of this study, but whilst using data gathered before 2013, this was inevitable. Even though these criteria are not specifically used as diagnostic criteria in the present study, it is unlikely that many cases of BMS were erroneously included.

Nonetheless, it would be misleading to conclude that these percentages are completely valid for the general population. The complete records of only 7 years of the referring patients were available for this study. Possibly a wider duration of time and a greater population study can lead to more reliable conclusions. Shiraz dental school was the only center with the referral of oral mucosal disease in Fars province in the years of 2007 to 2015, and it was the only center in this province where oral and maxillofacial medicine specialists practiced in. There were probably patients that suffered from this pain but did not seek an oral and maxillofacial specialist for their problem, so this is not a general study. But it is an estimation of the prevalence of this problem in one province of Iran. Furthermore, a unique method was not used for the diagnosis of every etiology, although every case was definitively diagnosed by either an oral medicine specialist or a physician who used a reliable method of diagnosis as listed in Table 1. And also, more exact description of the symptoms such as pain intensity and duration of pain can, also, be helpful in understanding and managing BMS patients who lacked the

records that were evaluated for this population.

In conclusion, according to the description of primary BMS which is defined as a pathologic condition that causes burning sensation in an otherwise healthy individual, the diagnosis of BMS can be considered one of exclusion. For the treatment of this disorder which is a major challenge for the practitioners, identifying possible causative factors is the first step. Based on the available evidence, it is difficult to differentiate between primary and secondary BMS. Even so, it is judicious for clinicians treating BMS to recognize possible local, systemic, and psychological etiologies that may be responsible for oral burning pain and, in turn, reach a diagnosis that helps manage the patient's symptoms appropriately. Hence, substantial delay is avoided and appropriate treatment strategies are initiated.

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Footnote

Conflict of Interest: None declared.

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