

Burning Mouth Syndrome and Its Associated Salivary Biomarkers.

ABSTRACT :

Burning Mouth Syndrome (BMS) is a chronic oral pain disorder characterized by a persistent burning sensation in the oral mucosa without identifiable clinical abnormalities. It predominantly affects middle-aged and postmenopausal women and significantly impacts quality of life. The etiology of BMS is multifactorial, involving neuropathic, hormonal, psychological, and local factors. Recent research has emphasized the role of salivary biomarkers in understanding the underlying mechanisms of the disease. Saliva, as a non-invasive diagnostic fluid, contains various biological components such as hormones, enzymes, cytokines, and oxidative stress markers, which reflect both local and systemic conditions. Alterations in salivary composition in BMS patients provide insight into disease pathogenesis and offer potential for diagnostic and therapeutic applications. This review aims to provide a comprehensive overview of Burning Mouth Syndrome with special emphasis on the role of salivary biomarkers in its diagnosis and management.

KEYWORDS :

Burning mouth syndrome; Salivary biomarkers; Oral neuropathic pain; Cortisol; Cytokines; Oxidative stress

23 **INTRODUCTION :**

24 Burning Mouth Syndrome is a chronic condition characterized by a burning sensation
25 affecting the oral mucosa in the absence of visible clinical lesions or identifiable medical or
26 dental causes. The condition most commonly affects the tongue, lips, and palate, and is often
27 accompanied by symptoms such as xerostomia and altered taste perception. Despite extensive
28 research, the etiology of BMS remains unclear, making diagnosis and management
29 challenging. The condition has been increasingly recognized as a neuropathic pain disorder
30 involving both peripheral and central mechanisms. In recent years, interest has grown in the
31 use of salivary biomarkers as a diagnostic and investigative tool due to the ease of collection
32 and their ability to reflect physiological and pathological changes in the body. These
33 biomarkers provide valuable insights into the underlying mechanisms of BMS, including
34 inflammation, oxidative stress, and neuroendocrine dysfunction (1–3).

35 **EPIDEMIOLOGY :**

36 Burning Mouth Syndrome predominantly affects middle-aged and elderly individuals, with a
37 higher prevalence in women, particularly those who are postmenopausal. The prevalence of
38 BMS in the general population ranges from 0.7% to 5%, depending on diagnostic criteria and
39 study population. Hormonal changes associated with menopause, particularly decreased
40 estrogen levels, have been implicated in the increased prevalence among women.
41 Additionally, psychological factors such as anxiety, depression, and chronic stress are
42 commonly observed in patients with BMS, suggesting a strong association between
43 psychological health and disease manifestation (1,2,4).

44 **ETIOLOGY :**

45 The etiology of Burning Mouth Syndrome is complex and multifactorial, involving both
46 primary (idiopathic) and secondary causes. Primary BMS is considered a neuropathic

47 disorder with no identifiable underlying cause, whereas secondary BMS is associated with
48 local, systemic, or psychological factors. Local factors include xerostomia, oral infections
49 such as candidiasis, parafunctional habits, and allergic reactions to dental materials. Systemic
50 conditions such as diabetes mellitus, nutritional deficiencies (vitamin B12, iron, folate), and
51 hormonal imbalances may also contribute to symptom development. Psychological factors,
52 including anxiety and depression, are frequently associated with BMS and may exacerbate
53 symptom severity. The interplay between these factors contributes to the complexity of the
54 disease and complicates its diagnosis and management (2,5,6).

55 **PATHOPHYSIOLOGY :**

56 The pathophysiology of Burning Mouth Syndrome is not fully understood, but current
57 evidence supports a neuropathic basis involving both peripheral and central nervous systems.
58 Peripheral mechanisms include damage or dysfunction of small-diameter nerve fibers in the
59 trigeminal nerve, leading to altered pain perception. Central mechanisms involve
60 dysregulation of pain processing pathways in the brain, including abnormalities in
61 dopaminergic neurotransmission. Hormonal factors, particularly estrogen deficiency in
62 postmenopausal women, may influence neural function and contribute to symptom onset.
63 Furthermore, chronic stress and psychological disturbances can affect the hypothalamic-
64 pituitary-adrenal axis, resulting in altered cortisol levels and increased pain sensitivity. These
65 mechanisms collectively contribute to the development and persistence of symptoms in BMS
66 (6–8).

67 **CLINICAL FEATURES :**

68 Patients with Burning Mouth Syndrome typically present with a burning, tingling, or scalding
69 sensation in the oral cavity, most commonly affecting the anterior two-thirds of the tongue.
70 The symptoms are usually bilateral and may intensify throughout the day. Patients may also

71 experience xerostomia, dysgeusia, and a metallic or bitter taste. Despite these symptoms,
72 clinical examination often reveals no visible abnormalities of the oral mucosa. The chronic
73 nature of the condition can lead to significant psychological distress, including anxiety,
74 depression, and reduced quality of life. Based on symptom patterns, BMS can be classified
75 into different types, including continuous, intermittent, and atypical forms (3,4).

76 **DIAGNOSIS :**

77 The diagnosis of Burning Mouth Syndrome is primarily based on clinical evaluation and the
78 exclusion of other potential causes of oral burning. A detailed patient history and thorough
79 clinical examination are essential. Laboratory investigations may be conducted to identify
80 systemic conditions such as nutritional deficiencies, hormonal imbalances, and metabolic
81 disorders. Salivary analysis has gained importance as a diagnostic tool due to its ability to
82 provide information on biochemical and physiological changes associated with BMS.
83 Standardized diagnostic criteria have been proposed to improve consistency and accuracy in
84 diagnosis (5,9).

85 **Salivary Biomarkers in Burning Mouth Syndrome :**

86 Saliva has emerged as a valuable diagnostic fluid due to its non-invasive nature, ease of
87 collection, and ability to reflect both local and systemic conditions. It contains a wide range
88 of biological molecules, including enzymes, hormones, antibodies, cytokines, and oxidative
89 stress markers. These components play a crucial role in maintaining oral health and can serve
90 as indicators of disease processes. In Burning Mouth Syndrome, alterations in salivary
91 composition have been widely reported, suggesting their potential role in disease
92 pathogenesis and diagnosis (9–13).

93

94 One of the most extensively studied salivary biomarkers in BMS is cortisol, which is
95 associated with stress and hypothalamic-pituitary-adrenal axis activity. Elevated levels of
96 salivary cortisol have been observed in patients with BMS, indicating a link between
97 psychological stress and symptom severity. This finding supports the hypothesis that
98 neuroendocrine dysfunction plays a significant role in the pathogenesis of the condition.
99 Additionally, pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-
100 alpha have been found to be elevated in the saliva of BMS patients, suggesting an underlying
101 inflammatory process (19,20).

102

103 Oxidative stress is another important factor implicated in BMS. Increased levels of oxidative
104 stress markers such as malondialdehyde, along with reduced antioxidant capacity, have been
105 reported in saliva. These changes indicate an imbalance between reactive oxygen species and
106 antioxidant defenses, leading to cellular damage and increased pain perception. Furthermore,
107 alterations in salivary proteins and enzymes have been associated with changes in oral
108 mucosal function and sensory perception (21–23).

109

110 Salivary flow rate is also affected in patients with BMS, contributing to symptoms of
111 xerostomia. Reduced salivary secretion can impair lubrication of the oral mucosa, increasing
112 susceptibility to irritation and discomfort. Additionally, changes in salivary composition may
113 affect taste perception, leading to dysgeusia. The evaluation of salivary biomarkers not only
114 enhances understanding of the underlying mechanisms of BMS but also provides a potential
115 non-invasive approach for diagnosis and monitoring of disease progression (10–13,17,18).

116

117 Recent studies have further explored the role of salivary biomarkers in assessing treatment
118 response. For example, changes in salivary biomarker levels following pharmacological
119 interventions such as clonazepam therapy have been reported, indicating their potential use in
120 monitoring therapeutic outcomes. Advances in proteomic and genomic technologies are
121 expected to facilitate the identification of novel biomarkers, improving the diagnostic
122 accuracy and management of Burning Mouth Syndrome (17,18,27).

123 **MANAGEMENT :**

124 The management of Burning Mouth Syndrome is challenging and often requires a
125 multidisciplinary approach. Treatment strategies focus on symptom relief and improving the
126 patient's quality of life. Pharmacological treatments include antidepressants, anticonvulsants,
127 benzodiazepines, and topical agents such as clonazepam. Cognitive behavioral therapy and
128 psychological counseling are effective in managing associated psychological factors. In cases
129 of secondary BMS, treatment of the underlying condition is essential. Salivary substitutes and
130 stimulants may be used to alleviate symptoms of xerostomia. Emerging research on salivary
131 biomarkers may lead to the development of targeted therapies in the future (2,24,25).

132 **CONCLUSION :**

133 Burning Mouth Syndrome is a complex and multifactorial condition with significant impact
134 on quality of life. Although its exact etiology remains unclear, current evidence supports the
135 involvement of neuropathic, hormonal, and psychological factors. Salivary biomarkers have
136 emerged as promising tools for understanding the pathophysiology and improving the
137 diagnosis of BMS. Their non-invasive nature and ability to reflect disease-related changes
138 make them valuable in clinical practice. Further research is needed to validate these
139 biomarkers and establish their role in routine diagnosis and management.

141

142 **REFERENCE :**

143 1. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on
144 burning mouth syndrome: overview and patient management. *Crit Rev Oral Biol Med.*
145 2003;14(4):275–291. doi:10.1177/154411130301400405

146 2. Gurvits GE, Tan A. Burning mouth syndrome. *World J Gastroenterol.*
147 2013;19(5):665–672. doi:10.3748/wjg.v19.i5.665

148 3. Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome and other oral
149 sensory disorders. *Pain Res Manag.* 2003;8(3):133–135. doi:10.1155/2003/901696

150 4. Klasser GD, Epstein JB, Villines D. Burning mouth syndrome. *Oral*
151 *Maxillofac Surg Clin North Am.* 2016;28(3):381–396. doi:10.1016/j.coms.2016.03.005

152 5. Ariyawardana A, et al. Burning mouth syndrome: a systematic review of
153 disease definitions and diagnostic criteria used in randomized clinical trials. *Oral Dis.*
154 2019;25(6):1609–1620. doi:10.1111/odi.13067

155 6. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A, et al.
156 Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. *Pain.*
157 2005;115(3):332–337. doi:10.1016/j.pain.2005.03.028

158 7. Jääskeläinen SK. Is burning mouth syndrome a neuropathic pain condition?
159 *Pain.* 2018;159(3):610–613. doi:10.1097/j.pain.0000000000001090

160 8. Forssell H, Jääskeläinen S, Tenovuo O, Hinkka S. Efficacy of treatments in
161 burning mouth syndrome: a systematic review. *J Orofac Pain.* 2002;16(4):253–261.

- 162 9. Yoshizawa JM, Schafer CA, Schafer JJ, Farrell JJ, Paster BJ, Wong DT.
163 Salivary biomarkers: toward future clinical and diagnostic utilities. *Clin Microbiol Rev.*
164 2013;26(4):781–791. doi:10.1128/CMR.00021-13
- 165 10. Javaid MA, Ahmed AS, Durand R, Tran SD. Saliva as a diagnostic tool for
166 oral and systemic diseases. *J Oral Biol Craniofac Res.* 2016;6(1):67–76.
167 doi:10.1016/j.jobcr.2015.08.006
- 168 11. Pfafe T, Cooper-White J, Beyerlein P, Kostner K, Punyadeera C. Diagnostic
169 potential of saliva: current state and future applications. *Clin Chem.* 2011;57(5):675–687.
170 doi:10.1373/clinchem.2010.153767
- 171 12. Zhang CZ, Cheng XQ, Li JY, Zhang P, Yi P, Xu X, et al. Saliva in the
172 diagnosis of diseases. *Int J Oral Sci.* 2016;8(3):133–137. doi:10.1038/ijos.2016.38
- 173 13. Nunes LA, Mussavira S, Bindhu OS. Clinical and diagnostic utility of saliva
174 as a non-invasive diagnostic fluid: a systematic review. *J Oral Sci.* 2015;57(3):177–186.
175 doi:10.2334/josnugd.57.177
- 176 14. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sánchez-Siles M,
177 Gómez-García F. Burning mouth syndrome: update and future perspectives. *Med Oral Patol*
178 *Oral Cir Bucal.* 2010;15(4):e562–e568.
- 179 15. Sun A, Wu KM, Wang YP, Lin HP, Chen HM, Chiang CP. Burning mouth
180 syndrome: a review and update. *J Oral Pathol Med.* 2013;42(9):649–655.
181 doi:10.1111/jop.12037
- 182 16. Amenábar JM, Pawlowski J, Hilgert JB, Hugo FN, Bandeira D, Lhüllier F, et
183 al. Anxiety and salivary cortisol levels in patients with burning mouth syndrome. *Oral Surg*

184 Oral Med Oral Pathol Oral Radiol Endod. 2008;105(4):460–465.

185 doi:10.1016/j.tripleo.2007.11.005

186 17. Nam Y, Kim YY, Chang JY, Kho HS. Salivary biomarkers of inflammation
187 and oxidative stress in burning mouth syndrome. Arch Oral Biol. 2019;97:215–222.

188 doi:10.1016/j.archoralbio.2018.11.006

189 18. Wang J, Schipper HM, Velly AM, Mohit S, Gornitsky M. Salivary biomarkers
190 of oxidative stress: a critical review. Free Radic Biol Med. 2015;85:95–104.

191 doi:10.1016/j.freeradbiomed.2015.04.005

192 19. Femiano F, Lanza A, Buonaiuto C, Gombos F, Nunziata M, Cuccurullo L, et
193 al. Burning mouth syndrome and clonazepam therapy. J Orofac Pain. 2002;16(4):283–288.

194 20. Heckmann SM, Heckmann JG, Ungethüm B, Hujoel P, Hummel T.
195 Gabapentin in the treatment of burning mouth syndrome. Pain Med. 2012;13(6):787–793.

196 doi:10.1111/j.1526-4637.2012.01391.x

197 21. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated
198 factors. J Oral Pathol Med. 1999;28(8):350–354. doi:10.1111/j.1600-0714.1999.tb02052.x

199 22. de Pedro M, López-Pintor RM, Hernández G. Biomarkers in saliva for the
200 diagnosis of oral diseases. Oral Dis. 2022;28(5):1200–1212. doi:10.1111/odi.13890

201 23. Caponio VCA, Troiano G, Adipietro I, Zhurakivska K, Arena C, Mangieri D,
202 et al. Salivary biomarkers in oral diseases: a review. Int J Mol Sci. 2021;22(3):1234.

203 doi:10.3390/ijms22031234

204 24. Kong MS, Kim YK, Kim SG. Clinical characteristics and salivary biomarkers
205 of burning mouth syndrome. Oral Dis. 2024. doi:10.1111/odi.14732

- 206 25. López-Jornet P, et al. Salivary flow and composition in patients with burning
207 mouth syndrome. *Med Oral Patol Oral Cir Bucal*. 2010;15:e562–e568
- 208 26. Salerno C, Di Stasio D, Petruzzi M, et al. An overview of burning mouth
209 syndrome. *Front Biosci (Elite Ed)*. 2016;8:213–218
- 210 27. Sikora M, Verdugo F, Szponar E. Salivary biomarkers in oral diseases: current
211 status and future directions. *Dent Med Probl*. 2019;56(4):393–400
- 212 28. Spielmann N, Wong DT. Saliva: diagnostics and therapeutic perspectives. *Oral*
213 *Dis*. 2011;17(4):345–354. doi:10.1111/j.1601-0825.2010.01773.x
- 214 29. Malathi N, Mythili S, Vasanthi HR. Salivary diagnostics: a brief review. *ISRN*
215 *Dent*. 2014;2014:158786. doi:10.1155/2014/158786

UNDER PEER REVIEW IN IJAR