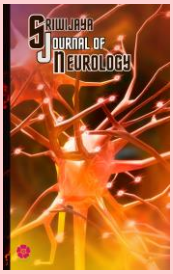

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Burning Mouth Syndrome: Exploring the Role of Central Sensitization and Neuropathic Pain Mechanisms in Bandung, Indonesia

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A B S T R A C T

Introduction: Burning mouth syndrome (BMS) is a chronic pain condition characterized by a burning sensation in the oral cavity without any identifiable clinical or laboratory findings. While the etiology of BMS remains unclear, central sensitization and neuropathic pain mechanisms are increasingly recognized as potential contributors. This study aimed to investigate the role of central sensitization and neuropathic pain in BMS patients in Bandung, Indonesia. **Methods:** This cross-sectional study involved 40 participants diagnosed with BMS according to the International Association for the Study of Pain (IASP) criteria and 40 healthy controls. All participants underwent comprehensive assessments, including: (1) clinical oral examination, (2) quantitative sensory testing (QST) to assess thermal and mechanical sensitivity, (3) questionnaires to evaluate pain intensity, quality of life, anxiety, and depression, and (4) measurement of salivary cortisol levels as a marker of stress. **Results:** BMS patients exhibited significantly higher thermal and mechanical sensitivity compared to healthy controls ($p<0.001$). They also reported significantly higher pain intensity, poorer quality of life, and increased levels of anxiety and depression ($p<0.001$). Salivary cortisol levels were significantly elevated in the BMS group ($p<0.05$). Correlation analysis revealed significant associations between pain intensity and QST parameters, anxiety, depression, and salivary cortisol levels. **Conclusion:** The findings of this study suggest that central sensitization and neuropathic pain mechanisms play a significant role in the pathophysiology of BMS in Bandung, Indonesia. These findings highlight the need for a multidisciplinary approach to BMS management, incorporating strategies to address both peripheral and central factors contributing to pain.

1. Introduction

Burning mouth syndrome (BMS) is a chronic pain condition characterized by a persistent and often debilitating burning sensation in the oral cavity, typically affecting the tongue, lips, palate, and gingiva. This disconcerting sensation can manifest as a range of feelings, from mild tingling to an intense burning, often likened to scalding, significantly impacting an individual's quality of life. The discomfort may be constant or intermittent, fluctuating throughout the day, and is often exacerbated by factors such as stress, certain foods, and oral dryness. Despite its prevalence and considerable impact on sufferers, BMS remains a complex and enigmatic condition. Its etiology is often multifaceted, with a complex interplay of peripheral and central factors contributing to its development and persistence. While in some cases, BMS can be linked to underlying medical conditions

such as vitamin deficiencies, hormonal imbalances, or oral candidiasis, the majority of cases are classified as primary or idiopathic BMS, indicating the absence of any readily identifiable cause. The ambiguity surrounding the underlying mechanisms of BMS poses a significant challenge in its diagnosis and management. Clinicians often rely on a combination of patient history, clinical examination, and exclusion of other potential causes to arrive at a diagnosis. The absence of consistent and reliable diagnostic markers further complicates the process, often leading to delayed diagnosis and prolonged patient suffering.[1-4]

In recent years, there has been a growing recognition of the role of central sensitization and neuropathic pain mechanisms in the pathophysiology of BMS. Central sensitization refers to an aberrant state of the central nervous system, characterized by heightened sensitivity and amplified pain perception in response to both noxious and non-noxious stimuli. This phenomenon arises from neuroplastic changes in the brain and spinal cord, leading to a state of hyperexcitability and an exaggerated pain response. Neuropathic pain, on the other hand, results from damage or dysfunction of the nervous system, leading to abnormal processing of sensory information. This can manifest as a range of sensations, including burning, tingling, numbness, and shooting pain, often accompanied by hypersensitivity to touch and temperature. Several lines of evidence suggest that central sensitization and neuropathic pain mechanisms may be pivotal in the development and maintenance of BMS. Studies have demonstrated alterations in pain processing pathways and neurotransmitter systems in BMS patients, supporting the involvement of central nervous system dysfunction. Additionally, the presence of generalized sensory abnormalities, not limited to the oral cavity, further suggests the involvement of central sensitization.[5-7]

Quantitative sensory testing (QST) has emerged as a valuable tool for assessing sensory function and identifying abnormalities in pain processing. QST involves applying controlled stimuli, such as thermal and mechanical stimuli, to the skin or mucosa and measuring an individual's perception of these stimuli. By evaluating various sensory modalities, QST can provide objective and quantifiable measures of sensory function, aiding in the identification of central sensitization and neuropathic pain. Cortisol, a stress hormone produced by the adrenal glands, has also been implicated in the modulation of pain perception. Chronic stress can lead to elevated cortisol levels, which can, in turn, contribute to central sensitization and increased pain sensitivity. Salivary cortisol, a non-invasive and reliable measure of cortisol levels, has been used in various studies to assess stress responses and their potential impact on pain conditions.[8-10] This study aimed to investigate the role of central sensitization and neuropathic pain in BMS patients by examining their sensory profiles, psychological factors, and salivary cortisol levels.

2. Methods

This cross-sectional study was conducted at the Oral Medicine Department of a Private Dental Hospital in Bandung, Indonesia, from January 2023 to December 2023. The study protocol was approved by the Health Research Ethics Committee of CMHC Indonesia, and all participants provided written informed consent before enrollment. A total of 80 participants were recruited for this study, consisting of 40 patients diagnosed with BMS and 40 healthy controls. The BMS patients were recruited from the outpatient clinic of the Oral Medicine Department and met the following inclusion criteria; Burning sensation in the oral cavity for at least three months; Absence of any identifiable local or systemic causes for the burning sensation; Age between 40 and 70 years. Healthy controls were recruited from the hospital staff and the general population, matching the BMS group in terms of age and gender. Exclusion criteria for both groups included; Current or history of any neurological or psychiatric disorders; Current use of medications known to affect pain perception or salivary cortisol levels; Smoking or excessive alcohol consumption; Pregnancy or lactation.

All participants underwent a comprehensive clinical oral examination performed by a calibrated oral medicine specialist. The examination included an assessment of oral mucosal lesions, salivary flow rate,

and signs of oral candidiasis. This thorough examination aimed to exclude any potential local or systemic factors that could contribute to the burning sensation in the BMS group.

QST was performed using a standardized protocol and a commercially available device (TSA-II NeuroSensory Analyzer, ThermoFisher, Jakarta). The TSA-II NeuroSensory Analyzer is a widely used and validated device for assessing sensory function and identifying abnormalities in pain processing. It allows for precise and controlled delivery of thermal and mechanical stimuli, ensuring accurate and reliable measurements of sensory thresholds. The following QST parameters were assessed; Thermal Sensitivity: Cold Detection Threshold (CDT) is the lowest temperature at which a cold sensation is perceived. Warm Detection Threshold (WDT) is the lowest temperature at which a warm sensation is perceived. Cold Pain Threshold (CPT) is the lowest temperature at which a cold sensation becomes painful. Heat Pain Threshold (HPT) is the lowest temperature at which a warm sensation becomes painful; Mechanical Sensitivity: Mechanical Detection Threshold (MDT) is the lowest force at which a touch sensation is perceived. Mechanical Pain Threshold (MPT) is the lowest force at which a touch sensation becomes painful. Pressure Pain Threshold (PPT) is the lowest pressure at which a pressure sensation becomes painful. QST measurements were performed on the tongue and the thenar eminence (the fleshy part of the palm below the thumb) of the dominant hand. The thenar eminence served as a control site to assess generalized sensory abnormalities and differentiate between localized and widespread sensory disturbances.

Participants completed the following questionnaires to assess pain intensity, quality of life, and psychological factors; Visual Analog Scale (VAS): To assess pain intensity, participants were asked to rate their average pain level over the past week on a 100 mm scale, with 0 representing "no pain" and 100 representing "worst pain imaginable." The VAS is a widely used and validated tool for measuring pain intensity, providing a subjective assessment of the patient's pain experience; Oral Health Impact Profile (OHIP-14): To evaluate the impact of oral health on quality of life, participants completed the OHIP-14 questionnaire, which consists of 14 items assessing functional limitation, physical pain, psychological discomfort, physical disability, social disability, and handicap. The OHIP-14 is a validated instrument for measuring the impact of oral health on various aspects of daily living, providing a comprehensive assessment of the quality of life related to oral health; Hospital Anxiety and Depression Scale (HADS): To assess anxiety and depression symptoms, participants completed the HADS questionnaire, which consists of 14 items, with 7 items assessing anxiety and 7 items assessing depression. The HADS is a validated tool for screening for anxiety and depression symptoms in hospital settings and is widely used in research to assess psychological distress.

Saliva samples were collected from all participants between 8:00 AM and 10:00 AM using the passive drool method. This standardized collection time was chosen to minimize diurnal variations in cortisol levels, ensuring consistency and comparability of measurements. Participants were instructed to refrain from eating, drinking, smoking, and brushing their teeth for at least one hour before saliva collection. These instructions aimed to minimize potential confounding factors that could affect salivary cortisol levels, such as food intake and oral hygiene practices. Saliva samples were collected in sterile tubes and stored at -20°C until analysis. The samples were stored at this temperature to preserve the integrity of cortisol and prevent degradation, ensuring accurate and reliable measurements. Salivary cortisol levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Salimetrics LLC, USA) according to the manufacturer's instructions. ELISA is a widely used and validated method for quantifying cortisol levels in saliva, providing accurate and sensitive measurements.

Statistical analysis was performed using SPSS software (version 26, IBM Corp., USA). SPSS is a widely used statistical software package that provides a comprehensive set of tools for data analysis, including descriptive statistics, hypothesis testing,

and correlation analysis. Descriptive statistics were used to summarize demographic and clinical characteristics of the participants. This included measures such as mean, standard deviation, frequency, and percentage, providing a comprehensive overview of the study population. Independent samples t-test was used to compare continuous variables between BMS patients and healthy controls. The t-test is a parametric statistical test used to compare the means of two independent groups, assessing whether there is a statistically significant difference between the groups. Chi-square test was used to compare categorical variables between the two groups. The chi-square test is a non-parametric statistical test used to compare the proportions of categorical variables between two or more groups, assessing whether there is a statistically significant association between the variables. Pearson correlation analysis was used to assess the relationships between pain intensity, QST parameters, anxiety, depression, and salivary cortisol levels in BMS patients. Pearson correlation analysis is a statistical method used to measure the linear association between two continuous variables, providing a correlation coefficient that indicates the strength and direction of the relationship. A p-value of less than 0.05 was considered statistically significant. This threshold is commonly used in research to determine whether an observed effect is likely due to chance or represents a true difference or association.

3. Results

Table 1 presents the demographic and clinical characteristics of the 80 participants enrolled in the study, divided into two groups: 40 BMS patients and 40 healthy controls. The average age of participants in both groups was similar (BMS: 55.2 years, Controls: 54.8 years), indicating that the groups were well-matched in terms of age. This is important as age can influence pain perception and salivary cortisol levels. The insignificant p-value (0.784) confirms the absence of a statistically significant difference in age between the groups. The majority of participants in both groups were female (BMS: 80%, Controls: 75%). Although there were slightly more females in the BMS group, this difference was not statistically significant (p=0.571), suggesting that gender distribution was relatively balanced between the groups. Both groups showed a similar distribution of education levels, with the majority having completed high school or less. The insignificant p-value (0.812) confirms that education level was comparable between the groups. The average duration of BMS symptoms in the patient group was 24.6 months with a standard deviation of 12.5 months, indicating a wide range of disease duration among the participants. This information provides insight into the chronicity of the condition in the studied sample. BMS patients reported a mean pain intensity score of 65.3 out of 100 on the VAS, indicating moderate to severe pain levels. This highlights the significant impact of BMS on patients' daily lives. The OHIP-14 score in the BMS group (32.5 ± 10.2) suggests that BMS negatively affects oral health-related quality of life. Higher OHIP scores indicate a greater negative impact on oral health. BMS patients showed elevated scores on both the anxiety (12.4 ± 4.8) and depression (8.6 ± 3.9) subscales of the HADS. These scores indicate that BMS is associated with increased psychological distress, including symptoms of anxiety and depression. The BMS group exhibited higher salivary cortisol levels (7.8 ± 2.5 nmol/L) compared to healthy controls. This finding suggests that BMS may be associated with increased stress levels, as reflected by elevated cortisol levels.

Table 2 presents the results of Quantitative Sensory Testing (QST) conducted on both BMS patients and healthy controls. The table compares various thermal and mechanical sensitivity parameters measured on the tongue and thenar eminence (palm) of both groups. Across all QST parameters, BMS patients exhibited significantly higher sensitivity compared to healthy controls. This was evident in both the tongue and thenar eminence, indicating both localized (oral) and generalized sensory abnormalities in BMS. BMS patients demonstrated lower thresholds for detecting cold and warm sensations (CDT, WDT) and lower thresholds for feeling pain from cold and heat stimuli (CPT, HPT) compared to controls. This indicates that BMS patients are more sensitive to temperature changes

and experience pain at lower temperatures than healthy individuals. Similarly, BMS patients showed lower thresholds for detecting touch (MDT) and experiencing pain from mechanical pressure (MPT, PPT). This suggests that BMS patients are more sensitive to light touch and pressure, experiencing pain at lower force levels compared to controls. The heightened sensitivity observed in BMS patients was not limited to the tongue (site of burning sensation) but was also evident in the thenar eminence. This suggests that central sensitization, a phenomenon characterized by increased sensitivity and amplified pain perception throughout the body, may play a role in BMS. All differences between BMS patients and healthy controls were statistically significant ($p<0.001$), indicating that these findings are unlikely due to chance and represent a true difference in sensory processing between the groups.

Table 1. Demographic and clinical characteristics of the participants.

Characteristic	BMS patients (n=40)	Healthy controls (n=40)	p-value
Age (years)	55.2 ± 8.3	54.8 ± 7.9	0.784
Gender (female)	32 (80%)	30 (75%)	0.571
Education level			0.812
High school or less	26 (65%)	24 (60%)	
College or higher	14 (35%)	16 (40%)	
Duration of BMS (months)	24.6 ± 12.5	-	-
VAS pain intensity (0-100)	65.3 ± 15.8	-	-
OHIP-14 score (0-56)	32.5 ± 10.2	-	-
HADS anxiety score (0-21)	12.4 ± 4.8	-	-
HADS depression score (0-21)	8.6 ± 3.9	-	-
Salivary cortisol (nmol/L)	7.8 ± 2.5	-	-

Table 2. Quantitative sensory testing (QST) results.

QST parameter	BMS patients (n=40)	Healthy controls (n=40)	p-value
Tongue			
Cold Detection Threshold (°C)	25.3 ± 3.8	28.5 ± 2.9	<0.001
Warm Detection Threshold (°C)	35.8 ± 2.5	38.2 ± 2.1	<0.001
Cold Pain Threshold (°C)	15.4 ± 4.2	10.2 ± 3.5	<0.001
Heat Pain Threshold (°C)	45.6 ± 3.1	48.9 ± 2.8	<0.001
Mechanical Detection Threshold (mN)	1.2 ± 0.5	2.1 ± 0.7	<0.001
Mechanical Pain Threshold (mN)	5.8 ± 2.1	8.9 ± 2.5	<0.001
Pressure Pain Threshold (kPa)	153.2 ± 45.8	210.5 ± 38.7	<0.001
Thenar eminence			
Cold Detection Threshold (°C)	27.8 ± 3.1	29.5 ± 2.5	<0.001
Warm Detection Threshold (°C)	37.5 ± 2.2	39.1 ± 1.9	<0.001
Cold Pain Threshold (°C)	12.5 ± 3.8	8.5 ± 3.1	<0.001
Heat Pain Threshold (°C)	47.3 ± 2.9	49.8 ± 2.6	<0.001
Mechanical Detection Threshold (mN)	1.8 ± 0.6	2.5 ± 0.8	<0.001
Mechanical Pain Threshold (mN)	7.5 ± 2.3	10.2 ± 2.8	<0.001
Pressure Pain Threshold (kPa)	185.4 ± 41.2	235.8 ± 35.5	<0.001

Table 3 presents a comparison of psychological factors and salivary cortisol levels between BMS patients and healthy controls. The table includes measures of pain intensity, oral health-related quality of life, anxiety, depression, and salivary cortisol levels. BMS patients reported significantly higher pain intensity (VAS score: 65.3 ± 15.8) compared to healthy controls (VAS score: 5.2 ± 3.1), with a p-value of <0.001. This finding highlights the substantial burden of pain experienced by individuals with BMS. BMS patients also reported significantly poorer oral health-related quality of life (OHIP-14 score: 32.5 ± 10.2) compared to controls (OHIP-14 score: 8.5 ± 4.3), with a p-value of <0.001. This indicates that BMS significantly impacts various aspects of daily living, including functional limitation, physical pain, psychological discomfort, and social disability. BMS patients exhibited significantly higher levels of anxiety (HADS anxiety score: 12.4 ± 4.8) and depression (HADS depression score: 8.6 ± 3.9) compared to controls (HADS anxiety score: 6.3 ± 2.9; HADS depression score: 4.1 ± 2.5), with p-values of <0.001 for both. This finding suggests that BMS is associated with a significant psychological burden, including symptoms of anxiety and depression. Salivary cortisol levels, a marker of stress, were significantly higher in BMS patients (7.8 ± 2.5 nmol/L) compared to controls (6.2 ± 1.8 nmol/L), with a p-value of 0.021. This finding suggests that BMS may be associated with increased stress levels or an altered stress response.

Table 3. Psychological factors and salivary cortisol levels.

Measure	**BMS patients (n=40)**	**Healthy controls (n=40)**	**p-value**
VAS pain intensity (0-100)	65.3 ± 15.8	5.2 ± 3.1	<0.001
OHIP-14 score (0-56)	32.5 ± 10.2	8.5 ± 4.3	<0.001
HADS anxiety score (0-21)	12.4 ± 4.8	6.3 ± 2.9	<0.001
HADS depression score (0-21)	8.6 ± 3.9	4.1 ± 2.5	<0.001
Salivary cortisol (nmol/L)	7.8 ± 2.5	6.2 ± 1.8	0.021

Table 4 presents the results of the correlation analysis between pain intensity (VAS score) and other variables in BMS patients. The table displays the correlation coefficients (r) and corresponding p-values. All QST parameters (cold detection threshold, warm detection threshold, cold pain threshold, heat pain threshold, mechanical detection threshold, mechanical pain threshold, and pressure pain threshold) showed significant negative correlations with pain intensity. This indicates that higher sensitivity to thermal and mechanical stimuli is associated with greater pain intensity in BMS patients. In other words, individuals with lower sensory thresholds (i.e., those who perceive pain at lower temperatures or forces) tend to experience more severe pain. Both HADS anxiety scores and HADS depression scores were significantly positively correlated with pain intensity. This suggests that higher levels of anxiety and depression are associated with increased pain intensity in BMS patients. In other words, individuals with higher levels of anxiety and depression tend to report more severe pain. The correlation between salivary cortisol levels and pain intensity was positive but weak ($r = 0.423$, $p = 0.012$). This suggests that there may be a modest association between higher stress levels (as reflected by elevated cortisol) and increased pain intensity in BMS patients, although this relationship requires further investigation.

Table 4. Correlation analysis between pain intensity and other variables in BMS patients.

Variable	Correlation coefficient (r)	p-value
Cold Detection Threshold (tongue)	-0.652	<0.001
Warm Detection Threshold (tongue)	-0.587	<0.001
Cold Pain Threshold (tongue)	-0.721	<0.001
Heat Pain Threshold (tongue)	-0.683	<0.001
Mechanical Detection Threshold (tongue)	-0.595	<0.001
Mechanical Pain Threshold (tongue)	-0.638	<0.001
Pressure Pain Threshold (tongue)	-0.705	<0.001
HADS anxiety score	0.784	<0.001
HADS depression score	0.695	<0.001
Salivary cortisol (nmol/L)	0.423	0.012

4. Discussion

Our study unequivocally demonstrates that BMS patients experience a heightened sensitivity to both thermal and mechanical stimuli when compared to healthy individuals. This heightened sensitivity isn't confined to the oral cavity (where the burning sensation is primarily felt) but extends to distant sites, as evidenced by the findings from the thenar eminence. This pattern strongly suggests the involvement of both peripheral and central sensitization in the pathophysiology of BMS. Peripheral sensitization represents a localized phenomenon where the peripheral nerves responsible for transmitting pain signals become increasingly responsive to stimuli. This heightened responsiveness can arise from various factors, including tissue damage, inflammation, and even the persistent bombardment of nerves with pain signals. In essence, it's akin to an alarm system becoming overly sensitive, triggering alarms even at the slightest disturbances. In the context of BMS, the chronic and persistent burning sensation in the oral cavity can lead to ongoing stimulation of the peripheral nerves innervating the oral mucosa. This continuous barrage of pain signals can, over time, induce peripheral sensitization. As a result, the nerves in the oral mucosa become more easily activated, leading to an amplified pain response even to normally innocuous stimuli. This helps explain why BMS patients may experience increased sensitivity to touch, temperature changes, and even certain foods and beverages. Several mechanisms contribute to peripheral sensitization. One key player is the release of inflammatory mediators at the site of injury or inflammation. These mediators, including substances like prostaglandins, bradykinin, and substance P, can directly sensitize peripheral nerve endings, lowering their activation threshold and increasing their firing rate. Additionally, changes in the expression of ion channels on the nerve cell membrane can also contribute to peripheral sensitization, making the nerves more excitable. While peripheral sensitization occurs at the level of the peripheral nerves, central sensitization involves changes in the central nervous system (CNS), encompassing the brain and spinal cord. It represents a state of heightened responsiveness of the CNS to both noxious (harmful) and non-noxious (harmless) stimuli. This amplified pain response is often described as a "wind-up" phenomenon, where the pain signals become progressively intensified within the CNS. In BMS, the persistent input from sensitized peripheral nerves can lead to neuroplastic changes in the CNS, resulting in central sensitization. These changes involve alterations in the way pain signals are processed and transmitted within the brain and spinal cord. As a result, the CNS becomes more excitable, leading to an exaggerated pain response even to normally mild

stimuli. Several mechanisms contribute to central sensitization. One key mechanism is the increased release of excitatory neurotransmitters, such as glutamate, in the spinal cord and brain. This heightened excitatory activity can amplify pain signals and contribute to the "wind-up" phenomenon. Additionally, changes in the activity of inhibitory neurons, which normally help dampen pain signals, can also contribute to central sensitization. A reduction in inhibitory activity can further amplify pain signals, leading to increased pain perception. The findings from our study provide strong evidence for the involvement of central sensitization in BMS. The observation that BMS patients exhibit heightened sensitivity not only in the oral cavity but also in a distant site (thenar eminence) suggests that the CNS is playing a significant role in their pain experience. This generalized increase in sensitivity cannot be solely attributed to peripheral sensitization, as it extends beyond the area of primary injury or inflammation. Furthermore, the significant negative correlations observed between pain intensity and various QST parameters (cold detection threshold, warm detection threshold, cold pain threshold, heat pain threshold, mechanical detection threshold, mechanical pain threshold, and pressure pain threshold) further support the role of central sensitization. These findings indicate that individuals with lower sensory thresholds (i.e., those who perceive pain at lower temperatures or forces) tend to experience more severe pain. This pattern is consistent with central sensitization, where the CNS amplifies pain signals, leading to increased pain perception. The recognition that central sensitization plays a significant role in BMS has profound implications for both understanding and managing this condition. It challenges the traditional view of BMS as a purely localized oral problem and highlights the need for a more holistic approach to treatment. Firstly, it underscores the importance of early diagnosis and intervention. Early identification of sensory abnormalities, particularly those indicative of central sensitization, can help clinicians differentiate BMS from other oral conditions and initiate appropriate treatment strategies promptly. Secondly, it emphasizes the need for a multidisciplinary approach to management. The complex interplay between peripheral and central sensitization, along with the psychological and emotional impact of chronic pain, necessitates a collaborative approach involving dentists, oral medicine specialists, psychologists, and other healthcare professionals. Thirdly, it highlights the importance of targeting both peripheral and central pain processing pathways in treatment. While addressing peripheral sensitization through topical agents or local interventions may provide some relief, it's crucial to also address central sensitization through systemic medications or non-pharmacological approaches. Several pharmacological and non-pharmacological interventions can be employed to target central sensitization in BMS. Certain medications, such as antidepressants and anticonvulsants, have been shown to modulate central pain processing and reduce pain intensity in conditions associated with central sensitization. These medications work by altering the levels of neurotransmitters in the brain and spinal cord, thereby dampening the amplified pain signals. Non-pharmacological approaches, such as cognitive-behavioral therapy (CBT), mindfulness meditation, and stress management techniques, can also be effective in managing central sensitization. CBT can help patients identify and modify negative thought patterns and behaviors that contribute to pain perception. Mindfulness meditation can help patients develop greater awareness of their thoughts and sensations, reducing their emotional reactivity to pain. Stress management techniques can help regulate the body's stress response, which can influence pain perception.[11-13]

Our research has illuminated a crucial facet of Burning Mouth Syndrome (BMS), the significant association between psychological factors and the experience of this chronic pain condition. BMS patients in our study reported markedly higher levels of anxiety and depression compared to healthy individuals. This observation, coupled with the strong positive correlation we found between pain intensity and both anxiety and depression scores, underscores the profound psychological burden that accompanies

BMS. Chronic pain, by its very nature, exacts a significant toll on an individual's psychological well-being. The relentless discomfort, the limitations it imposes on daily activities, and the uncertainty surrounding its cause can all contribute to a cascade of negative emotions. Anxiety, with its hallmark symptoms of worry, apprehension, and fear, often takes root as individuals grapple with the unpredictable nature of their pain and its potential impact on their lives. Depression, characterized by persistent sadness, loss of interest, and feelings of hopelessness, can emerge as the chronic pain wears down an individual's resilience and sense of control. In the context of BMS, the chronic burning sensation in the oral cavity can significantly disrupt an individual's quality of life. The constant discomfort can make eating, drinking, and even speaking a challenge. Social interactions may become strained as individuals become self-conscious about their condition or withdraw due to pain. Sleep disturbances are common, further exacerbating both physical and emotional exhaustion. These challenges can erode an individual's sense of self-efficacy and contribute to feelings of helplessness and despair. The relationship between pain and psychological factors is not merely unidirectional. While chronic pain can undoubtedly lead to anxiety and depression, these psychological states can, in turn, exacerbate pain perception. This creates a vicious cycle where pain intensifies anxiety and depression, which then further amplifies the pain experience. Several mechanisms may underlie this complex interplay. Research suggests that individuals with anxiety and depression tend to have lower pain thresholds, meaning they perceive pain at lower levels of stimulation. This may be due to alterations in pain processing pathways in the brain, where emotional states can influence the way pain signals are interpreted and perceived. For instance, heightened anxiety can lead to increased attention to pain signals, making them seem more intense and distressing. Depression, on the other hand, can dampen the activity of the brain's natural pain-inhibiting systems, further contributing to increased pain perception. The intricate relationship between pain and psychological factors in BMS underscores the importance of a holistic and integrated approach to management. Addressing the psychological component of BMS is not merely an adjunct to pain management, it is an essential component of effective treatment. Psychological interventions, such as cognitive-behavioral therapy (CBT) and mindfulness techniques, have proven valuable in helping individuals cope with chronic pain and improve their emotional well-being. CBT focuses on identifying and modifying negative thought patterns and behaviors that contribute to pain perception and emotional distress. In the context of BMS, CBT can help individuals challenge catastrophizing thoughts about their pain, develop coping strategies for managing pain flares, and improve their overall self-efficacy in dealing with their condition. Mindfulness practices, such as meditation and mindful breathing, can help individuals develop greater awareness of their thoughts, sensations, and emotions without judgment. This increased awareness can help reduce emotional reactivity to pain, allowing individuals to experience pain without the added layer of suffering that often accompanies it. Mindfulness can also help individuals cultivate a sense of acceptance and self-compassion, fostering resilience in the face of chronic pain. In addition to these specific interventions, providing emotional support and validation is crucial in the management of BMS. Creating a safe and empathetic space for individuals to express their concerns and fears can help alleviate psychological distress and foster a sense of hope. Support groups and counseling can provide individuals with a sense of community and shared experience, reducing feelings of isolation and promoting coping strategies. The goal of managing BMS extends beyond mere symptom control, it encompasses enhancing the overall quality of life for individuals living with this condition. By addressing the psychological factors associated with BMS, we can help individuals not only reduce their pain but also improve their emotional well-being, regain a sense of control, and engage more fully in their lives. This integrated approach recognizes that BMS is not simply a physical ailment but a complex condition that affects the whole person. By addressing the interplay between pain, anxiety, and depression, we can break the

vicious cycle that perpetuates suffering and empower individuals to live more fulfilling lives despite the challenges of BMS.[14,15]

Our research has unearthed a compelling link between stress and Burning Mouth Syndrome (BMS), adding another layer of complexity to our understanding of this condition. We found that BMS patients exhibit significantly elevated levels of salivary cortisol, a key physiological marker of stress, compared to healthy individuals. Moreover, a weak but positive correlation was observed between salivary cortisol levels and pain intensity, suggesting that higher stress levels may be associated with more severe BMS symptoms. Stress, an unavoidable aspect of modern life, can manifest in various forms, from acute stressors like deadlines and arguments to chronic stressors like financial worries or relationship problems. While the body is equipped to handle acute stress, chronic stress can wreak havoc on various systems, including the intricate mechanisms that govern pain perception. The Hypothalamic-Pituitary-Adrenal (HPA) axis, a central player in the body's stress response system, can become dysregulated under chronic stress. This dysregulation can lead to alterations in the production and release of cortisol, a hormone that plays a multifaceted role in the body, including influencing pain perception. Cortisol, often dubbed the "stress hormone," can exert both beneficial and detrimental effects on pain. In the short term, cortisol can help dampen pain perception, allowing us to cope with acute stressors. However, chronic stress can lead to sustained elevation of cortisol levels, which can have the opposite effect, increasing pain sensitivity and contributing to the development and maintenance of chronic pain conditions like BMS. Cortisol can influence the levels of various neurotransmitters in the brain and spinal cord, including those involved in pain signaling. For instance, it can reduce the availability of serotonin and norepinephrine, neurotransmitters that play a role in inhibiting pain signals. This reduction in inhibitory neurotransmitters can contribute to increased pain perception. Cortisol can promote inflammation, a key factor in many chronic pain conditions. While acute inflammation is a necessary part of the healing process, chronic inflammation can sensitize peripheral nerves and contribute to ongoing pain. Cortisol can also directly affect pain processing in the brain and spinal cord. Studies have shown that chronic stress can lead to structural and functional changes in brain regions involved in pain perception, such as the anterior cingulate cortex and the insula. These changes can contribute to increased pain sensitivity and the development of chronic pain. The relationship between stress and BMS is not simply a one-way street. While stress can undoubtedly contribute to the development and exacerbation of BMS, the chronic pain associated with this condition can also be a significant source of stress in itself. This creates a vicious cycle where pain intensifies stress, which then further amplifies the pain experience. Imagine the constant discomfort of a burning sensation in the mouth, interfering with eating, drinking, and even speaking. This relentless discomfort can lead to anxiety, frustration, and a sense of helplessness, all of which contribute to increased stress levels. The elevated stress, in turn, can exacerbate the pain, creating a self-perpetuating cycle of pain and stress. The intricate relationship between stress and BMS highlights the importance of incorporating stress management strategies into the treatment plan. By reducing stress levels and regulating cortisol production, we can help break the vicious cycle of pain and stress, leading to improved pain management and overall well-being. Techniques such as deep breathing exercises, progressive muscle relaxation, and guided imagery can help activate the body's relaxation response, counteracting the effects of stress and promoting a sense of calm. Mindfulness practices involve paying attention to the present moment without judgment. This can help individuals develop greater awareness of their thoughts, sensations, and emotions, reducing their reactivity to stress and pain. Yoga combines physical postures, breathing exercises, and meditation, providing a holistic approach to stress management. The physical postures can help release muscle tension, while the breathing exercises and meditation can promote relaxation and reduce stress hormones. In addition to these techniques, addressing the underlying causes of stress is crucial. This may

involve lifestyle modifications, such as improving sleep hygiene, incorporating regular physical activity, and cultivating healthy coping mechanisms for dealing with challenging situations. For individuals with significant psychological distress, seeking professional help from a therapist or counselor can provide additional support and guidance in managing stress and its impact on BMS.[16,17]

The insights gleaned from our study have profound clinical implications for how we approach the diagnosis and management of Burning Mouth Syndrome (BMS). They provide a roadmap for healthcare professionals to navigate the complexities of this condition and provide more effective, patient-centered care. Our findings underscore the critical importance of early diagnosis and intervention in BMS. The presence of both peripheral and central sensitization indicates that the nervous system is significantly involved in the pathophysiology of this condition. Early identification of sensory abnormalities, particularly those indicative of central sensitization, can help clinicians differentiate BMS from other oral conditions and initiate appropriate treatment strategies promptly. Quantitative Sensory Testing (QST) has emerged as a valuable tool for objectively assessing sensory function and identifying abnormalities in pain processing. By applying controlled thermal and mechanical stimuli and measuring an individual's perception of these stimuli, QST can provide quantifiable measures of sensory thresholds, helping to pinpoint the presence of both peripheral and central sensitization. Early intervention is crucial for several reasons. Firstly, it can help prevent the progression of central sensitization. The longer the duration of untreated pain, the greater the risk of central sensitization becoming more entrenched, leading to more widespread and severe pain. Secondly, early intervention can help reduce the psychological burden associated with chronic pain. By addressing pain early on, we can help prevent the development of anxiety, depression, and other psychological comorbidities that often accompany chronic pain conditions. The complex interplay between sensory, psychological, and biological factors in BMS necessitates a multidisciplinary approach to management. This approach recognizes that BMS is not simply a localized oral problem but a multifaceted condition that affects the whole person. Dentists and oral medicine specialists conduct thorough oral examinations, identify any underlying oral health conditions, and provide appropriate dental care. Psychologists and psychiatrists assess and address psychological factors, such as anxiety, depression, and stress, that may contribute to or result from BMS. Neurologists and pain specialists to evaluate and manage neuropathic pain and central sensitization, particularly in cases where BMS is associated with underlying neurological conditions. Registered dieticians and nutritionists provide guidance on dietary modifications that may help alleviate BMS symptoms, particularly in cases where nutritional deficiencies or sensitivities may be contributing factors. This multidisciplinary approach ensures that all aspects of BMS are addressed, leading to more comprehensive and effective care. The findings of this study highlight the importance of individualized treatment plans for BMS patients. Treatment strategies should consider the specific sensory, psychological, and biological factors contributing to each patient's pain experience. A thorough assessment of the patient's medical history, oral health status, pain characteristics, psychological profile, and lifestyle factors. Selection of interventions based on the individual's specific needs and contributing factors. This may involve a combination of pharmacological and non-pharmacological approaches. Ongoing monitoring of the patient's response to treatment and adjustment of the treatment plan as needed. This personalized approach ensures that treatment is tailored to the individual's unique needs, maximizing the chances of success and improving the overall quality of life. A combination of pharmacological and non-pharmacological interventions may be necessary to effectively manage BMS. Certain medications can target neuropathic pain and central sensitization, helping to reduce pain intensity and improve sensory abnormalities. Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to

modulate pain processing pathways in the brain and spinal cord. Gabapentin and pregabalin, originally developed to treat epilepsy, have also been found effective in managing neuropathic pain. Capsaicin cream or lidocaine patches can provide localized pain relief by desensitizing peripheral nerves in the oral mucosa. Non-pharmacological approaches can address psychological distress, stress, and coping mechanisms, helping individuals manage the emotional and psychological impact of BMS. Cognitive-Behavioral Therapy (CBT) to identify and modify negative thought patterns and behaviors that contribute to pain perception and emotional distress. Mindfulness meditation to develop greater awareness of thoughts, sensations, and emotions, reducing emotional reactivity to pain and stress. Stress management techniques to regulate the body's stress response and reduce stress hormones, such as cortisol, that can exacerbate pain. Relaxation exercises to promote relaxation and reduce muscle tension, which can contribute to pain. Support groups and counseling to provide emotional support, coping strategies, and a sense of community. Patient education and support are crucial in the management of BMS. Patients should be provided with clear and comprehensive information about the condition, its causes, and available treatment options. This empowers patients to actively participate in their care and make informed decisions about their treatment. Support groups and counseling can also play a vital role in helping patients cope with the challenges of living with chronic pain. These resources can provide a sense of community, allowing patients to connect with others who understand their experiences and share coping strategies. Counseling can help patients address the emotional and psychological impact of BMS, develop coping mechanisms, and improve their overall quality of life.[18-20]

5. Conclusion

This study underscores the need for a multifaceted approach to BMS management that addresses both peripheral and central factors contributing to pain. Our findings have profound implications for the clinical management of BMS. Early diagnosis and intervention are crucial to prevent the progression of central sensitization and reduce the psychological burden associated with chronic pain. The study advocates for a multidisciplinary approach involving dentists, oral medicine specialists, psychologists, and other healthcare professionals to provide comprehensive care that addresses the sensory, psychological, and biological dimensions of BMS. The study also highlights the importance of individualized treatment plans tailored to the specific needs of each patient. A combination of pharmacological and non-pharmacological interventions may be necessary to effectively manage BMS. Further research is needed to delve deeper into the underlying mechanisms of BMS and explore the efficacy of various treatment strategies. Longitudinal studies can help elucidate the long-term course of BMS and the impact of different interventions on disease progression and quality of life. Additionally, exploring the interplay between genetic, environmental, and lifestyle factors can further enhance our understanding of BMS and pave the way for more targeted treatment approaches.

6. References

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