Oxidative stress–mediated proapoptosis signaling

A novel theory on the mechanism underlying the pathogenesis of burning mouth syndrome

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ABSTRACT

Background. Burning mouth syndrome (BMS) is a chronic oral pain disorder characterized by a generalized burning sensation in the oral mucosa without apparent medical or dental causes. Despite various hypotheses proposed to explain BMS pathogenesis, a clear understanding of the cellular-level events and associated histologic and molecular findings is lacking. Advancing our understanding of BMS pathogenesis could facilitate the development of more targeted therapeutic interventions.

Types of Studies Reviewed. The authors conducted an extensive literature search and review of cellular mechanisms, focusing on evidence-based data that support a comprehensive hypothesis for BMS pathogenesis. The authors explored novel and detailed mechanisms that may account for the characteristic features of BMS.

Results. The authors proposed that BMS symptoms arise from the uncontrolled activation of proapoptotic transmembrane calcium permeable channels expressed in intraoral mucosal nerve fibers. Elevated levels of reactive oxygen species or dysfunctional antiapoptosis pathways may lead to uncontrolled oxidative stress–mediated apoptosis signaling, resulting in upregulation of transmembrane transient receptor potential vanilloid type 1 and P2X 3 calcium channels in nociceptive fibers. Activation of these channels can cause nerve terminal depolarization, leading to generation of action potentials that are centrally interpreted as pain.

Conclusions and Practical Implications. The authors present a novel hypothesis for BMS pathogenesis, highlighting the role of proapoptotic transmembrane calcium permeable channels and oxidative stress–mediated apoptosis signaling in the development of BMS symptoms. Understanding these underlying mechanisms could provide new insights into the development of targeted therapeutic interventions for BMS. Additional research is warranted to validate this hypothesis and explore potential avenues for effective management of BMS.

Key Words. Burning mouth syndrome; pathogenesis; molecular mechanisms; proapoptosis signaling; calcium signaling; oxidative stress; reactive oxygen species.

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Burning mouth syndrome (BMS) is a chronic and debilitating oral pain disorder characterized by the presence of a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.[1] The International Headache Society, in the *International Classification of Headache Disorders*, Third Edition[2] and the *International Classification of Orofacial Pain*,[3] defined BMS as an intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, without clinically evident causative lesions on examination and investigation. It occurs more commonly in middle-aged and older adult women and most often involves the tongue, with or without extension to other oral mucosa sites.[4,5] The burning pain is often accompanied by altered taste (dysgeusia), a sensation of mouth dryness (xerostomia), and oral paresthesia.[4,6] Despite these symptoms, the oral mucosa is intact and the salivary flow rate remains

normal.[6] The burning sensation is moderate to severe in intensity, present every day for most of the day, and continues for several years.[6] The onset may be spontaneous or associated with drug intake, dental treatment, or viral infections.[7] The effects of BMS can be devastating, and patients are often faced with a substantial impairment in quality of life, which is aggravated by a lack of available definitive treatment options.[4]

Despite a plethora of research and a number of postulated psychogenic and organic mechanisms, the etiopathogenesis of BMS remains unclear.[4,7,8]

In a growing body of evidence, investigators suggest that BMS is a neuropathic disorder with pathophysiological alterations at different levels of the neuraxis affecting the peripheral and central nervous systems.[8,9] Results of repeated studies in which researchers used thermal quantitative sensory testing of the tongue mucosa, with adequately small probes and reliable reference values in BMS diagnosed according to accepted criteria, have convincingly indicated loss of function in the somatosensory small-fiber system in most (two-thirds) patients with BMS.[10,11] This is also supported by the results of multiple tongue mucosal biopsy studies that showed a considerable decrease in intraepithelial nerve fiber density compared with healthy control participants.[7,8] In addition, investigators who conducted immunohistochemical studies have reported substantially increased expression of nerve growth factor (*NGF*), transient receptor potential vanilloid type 1 (*TRPV1*), and purinergic receptor *P2X 3* via the surviving nerve fibers.[7,8,12] *TRPV1*, a nonselective cation channel and polymodal receptor, is found mainly in nociceptive terminals of peripheral Aδ and C-fibers, but also centrally in the dorsal root and trigeminal ganglia. It is related to the conduction of heat or hot taste (capsaicin) and nociceptive signals, and its overexpression is associated with hypersensitivity and neuropathic pain.[6,8,13] *P2X 3* is a nonselective cationic ion channel receptor. This receptor is expressed via small-diameter primary trigeminal nociceptors and is responsible for eliciting a burning pain sensation when activated via an adenosine triphosphate (ATP) molecule.[6,14] *NGF*, a neurotrophic factor, can sensitize peripheral nociceptors and is responsible for *TRPV1* and *P2X 3* regulation.[8,15] Therefore, researchers have suggested that upregulation of these factors may play a pivotal role in BMS symptomatology.[7,8,12]

In addition, psychological factors such as anxiety and depression are thought to play a role in BMS pathogenesis.[8] Researchers have reported that 80% of patients with BMS had depression, anxiety disorder, and other chronic pain conditions before the onset of BMS.[8] Moreover, downregulation of the central dopaminergic pain inhibitory pathways has also been proposed as playing a role in BMS pathogenesis, particularly in patients with anxiety or depression, which are associated with dysregulated dopaminergic pathways.[6] In this context, central sensitization may also contribute to BMS pain due to continuous afferent input, a decrease in the functional activity of the endogenous descending inhibitory pain modulation pathway, or both.[6,8]

A coherent theory of the cellular mechanisms underlying BMS pathogenesis that aims to tie together all of its characteristics and findings is still lacking.

HYPOTHESIS

In light of the molecular, histopathologic, and clinical findings of BMS as well as an extensive review of evidence-based data on relevant cellular mechanisms, we suggest that BMS is, in essence, a symptomatic manifestation of the upregulation of apoptotic mediators of nerve fibers due to uncontrolled cellular proapoptosis signaling. We suggest this proapoptosis signaling is the consequence of the activation of oxidative stress–mediated proapoptotic pathways, the attenuation of cellular antiapoptotic pathways, or a combination of both.

HYPOTHESIS EVALUATION

Reactive oxygen species, antioxidants, and oxidative stress

Oxidative stress is manifested as an increase in the cellular and tissue concentration of reactive oxygen species (ROS), leading to extensive intracellular damage due to peroxidation and, ultimately, cell death.[16] At low to modest doses, ROS is considered essential for normal cell physiological function regulation, and its cellular generation exists in equilibrium with various antioxidant defenses.[17] However, when the ROS supply exceeds the antioxidant capacity, ROS buildup damages the cells, which can lead to activation of cell death processes, such as apoptosis. These

mechanisms are considered the driving force behind a wide range of pathologies, including neurodegenerative diseases.[16,17]

Oxidative stress is a result of the imbalance of enhanced production of ROS or impaired function of the antioxidant system.[18] Free radicals are generated from both endogenous and exogenous sources, such as inflammation, infection, mental stress, aging, surgical procedures, and certain drugs.[19,20]

Oxidative stress–mediated proapoptosis signaling pathways

Cellular oxidative stress causes damage to proteins, nucleic acids, lipids, membranes, and organelles. This stress can lead to activation of cell death processes, such as apoptosis, which is a highly regulated cell self-destructive death process.[17] ROS mediates cell apoptosis largely through calcium ion (Ca^{2+}) signaling.[21] Oxidative stress causes Ca^{2+} influx into the cytoplasm from the extracellular environment and the endoplasmic reticulum (ER) or sarcoplasmic reticulum through the cell membrane and the ER or sarcoplasmic reticulum channels, respectively. Rising Ca^{2+} concentration in the cytoplasm causes Ca^{2+} influx into mitochondria and nuclei. Ca^{2+} accumulation accelerates and disrupts normal mitochondrial metabolism and modulates nuclei gene transcription and nucleases, leading to cell apoptosis.[21] Indeed, intracellular Ca^{2+} plays a crucial role in apoptosis modulation.[22]

ROS-mediated cytosolic Ca^{2+} elevation signaling

Several Ca^{2+} transporters, such as voltage-dependent Ca^{2+} channels and store-operated Ca^{2+} entry, are localized in the plasma membrane and can be regulated via ROS.[23] In addition, *TRP* channel family members are thought to be involved in Ca^{2+} entry signals. The *TRP* superfamily members are nonselective cation channels that predominantly carry Ca^{2+} ions.[23] Oxidative stress has been found to activate *TRPV1* and *TRP* melastatin 2 channels, leading to the overload of Ca^{2+} ion entry through both channels and ultimately to neuronal death.[24] Another cation channel receptor found to be regulated via ROS is the purinergic receptor *P2X 3*.[24] *P2X* receptors are nonselective cationic channels gated via extracellular ATP. Subtype *P2X 3* receptors are selectively expressed in primary afferent sensory neurons. Extracellular Ca^{2+} influx via *P2X 3* channels was found to contribute substantially to membrane current changes and variations in intracellular concentrations and, therefore, to neuron apoptosis induction.[14,24] Moreover, increased expression of transmembrane *P2X 3* receptors and trafficking of *TRP* isomers (eg, *TRP* melastatin 2) into the plasma membrane were also found to correlate with oxidative stress.[24-26]

Antiapoptotic pathways: B-cell lymphoma 2

Ca^{2+} signaling and apoptosis induction can be counteracted via antiapoptotic pathways. B-cell lymphoma 2 (Bcl-2) is a key protein in apoptosis inhibition.[27] It is the prototype antiapoptotic member of the Bcl-2 family, which comprises proteins with contrasting effects on cell fate.[28] Antiapoptotic Bcl-2 has antioxidant effects and was found to decrease cellular ROS levels. Moreover, Bcl-2 exerts its antiapoptotic functions via regulation of Ca^{2+} transport systems at the ER, mitochondria, and plasma membrane.[29] Bcl-2 inhibits proapoptotic Ca^{2+} release from the ER, which prevents ER Ca^{2+} depletion. This prevents mitochondrial Ca^{2+} overload and, thus, Ca^{2+}-triggered apoptosis signaling.[29,30]

Antiapoptotic pathways: estrogen

Estrogens are steroid hormones with well-documented neuroprotective actions, which are exerted due to their antioxidant, antiapoptotic, and anti-inflammatory activities.[31] One important mechanism for estrogen's neuroprotection is the induction of antiapoptotic Bcl-2 expression in response to deleterious effects.[32,33] For instance, Alkayed and colleagues[32] reported that estrogen rescued neurons after focal cerebral ischemia by means of increasing the level of Bcl-2 in peri-infarct regions.

Estrogen's antiapoptotic effect can be further explained by its Ca^{2+} signaling modulation. Estrogenic agonists and estrogenic receptors were found to inhibit several Ca^{2+} entry ion channels, including store-operated Ca^{2+} channels.[34] Estrogen was also found to downregulate *TRPV1* cation channel expression in dorsal root ganglion neurons.[35] In addition, Lu and colleagues[36] reported that estrogen rapidly attenuated *P2X 3* receptor–mediated currents. Estrogens are also known as powerful antioxidants.[37] Physiologic levels of estrogen were found to profoundly suppress mitochondrial oxidative stress in the brains of both female and male rats.[38]

In line with the well-established antiapoptotic and antioxidative effects of estrogen, in an accumulating body of evidence, researchers associate estrogen deficiency with cell death and apoptosis.[39,40] Accordingly, ovariectomy was found to decrease antiapoptotic Bcl-2 expression and to increase proapoptotic Bcl-2 family protein (ie, Bax) expression, elevating the number of apoptotic cells in the rat hippocampus.[41] Estrogen deficiency results naturally from menopause; however, ovariectomy, excessive physical activity, low body weight, and psychological stress may also deplete estrogen stores.[42-44]

Psychological stress and proapoptosis signaling

Psychological stress has been found to play a role in cell damage and apoptosis mechanisms. In a growing body of research, investigators implicate an association between psychological stress and oxidative stress.[45] Elevated blood biomarkers of oxidative stress have been found in chronically stressed caregivers, with higher levels of perceived stress associated with greater oxidative damage to RNA and lipid cells.[46] Furthermore, there is evidence that psychological stress can also suppress antiapoptotic Bcl-2 protein expression.[47,48] The opposite effect occurred with antidepressant agent administration, which dramatically increased Bcl-2 messenger RNA levels.[47] Taken together, the correlation of psychological stress with estrogen deficiency, oxidative stress, and Bcl-2 levels indicates its potentially substantial role in cellular proapoptosis signaling.

Intraoral neurogenic proapoptosis signaling in BMS

We suggest that BMS symptoms are, in essence, the manifestation of uncontrolled activation of proapoptotic transmembrane Ca^{2+} permeable channels expressed in intraoral mucosal nociceptors. High ROS levels, dysfunctional antiapoptosis pathways, or a combination of both may cause uncontrolled oxidative stress–mediated apoptosis signaling, which upregulates transmembrane *TRPV1* and *P2X 3* Ca^{2+} channels in nociceptive fibers. The activation of these channels can cause nerve terminal depolarization, leading to action potential generation, which is interpreted centrally as pain.[49,50] Previously, researchers found that Ca^{2+} influx through upregulated *TRP* channels led to both apoptosis-mediated nerve terminal destruction and neuropathic pain induction. Oxidative stress was found to play a pivotal role in this process.[51]

Furthermore, this Ca^{2+} influx–mediated apoptosis and pain signaling in nociceptors may exhibit self-perpetuating amplification. Activation of *TRPV1* channels can cause calcitonin gene–related peptide (CGRP) and substance P (SP) release from nociceptor fibers.[50] CGRP has been found to increase *TRPV1* levels and activities and therefore pain sensation in the trigeminovascular nociceptive system.[52] In addition, in trigeminal neurons, CGRP was found to stimulate *P2X 3* receptors trafficking to the cell surface, which caused intense and prolonged enhancement of this receptor's function.[53,54] It was also reported that SP can induce tumor necrosis factor–α (TNF-α) and interleukin-6 production.[55] TNF-α was found to be one of the pro-inflammatory cytokines that stimulate *NGF* expression in different cell types.[56] *NGF* is known as a key factor in the generation of acute and chronic pain and peripheral sensitization.[56] Both *NGF* and TNF-α were found to increase plasma membrane expression of *TRPV1* channels,[57,58] causing Ca^{2+} influx amplification. Taken together, this self-perpetuating amplification of *TRPV1* and *P2X 3*–mediated Ca^{2+} influx causes a vicious cycle of pain induction and apoptosis that will ultimately occur when Ca^{2+} levels in the mitochondria exceed the mitochondrial Ca^{2+} uptake threshold (Figure).[59,60]

Histopathologic and molecular findings supporting Ca^{2+} and proapoptosis signaling in BMS

TRPV1, *P2X 3*, *NGF*, and TNF-α were all found to be elevated in patients with BMS.[6,61] In addition, in a 2022 study investigators found elevated salivary anandamide (AEA) levels in patients with BMS compared with healthy control participants.[62] Elevation of these endocannabinoid levels can be induced via inflammation and neural injury.[63] Moreover, van der Stelt and colleagues[64] reported that AEA is stimulated via intracellular Ca^{2+} store–emptying stimuli and acts as an intracellular messenger, participating in Ca^{2+} signaling amplification via plasma membrane *TRPV1* channels activation. Hence, AEA elevation in BMS may reflect its role as a Ca^{2+} entry mediator in apoptosis and pain signaling in this syndrome.

Despite the elevation of these markers in BMS, no elevation in SP and CGRP levels was found in this syndrome.[65,66] This was suggested to indicate the trigeminal nerve degeneration found in these patients.[66] In multiple tongue mucosa biopsy studies, researchers reported a significant decrease in

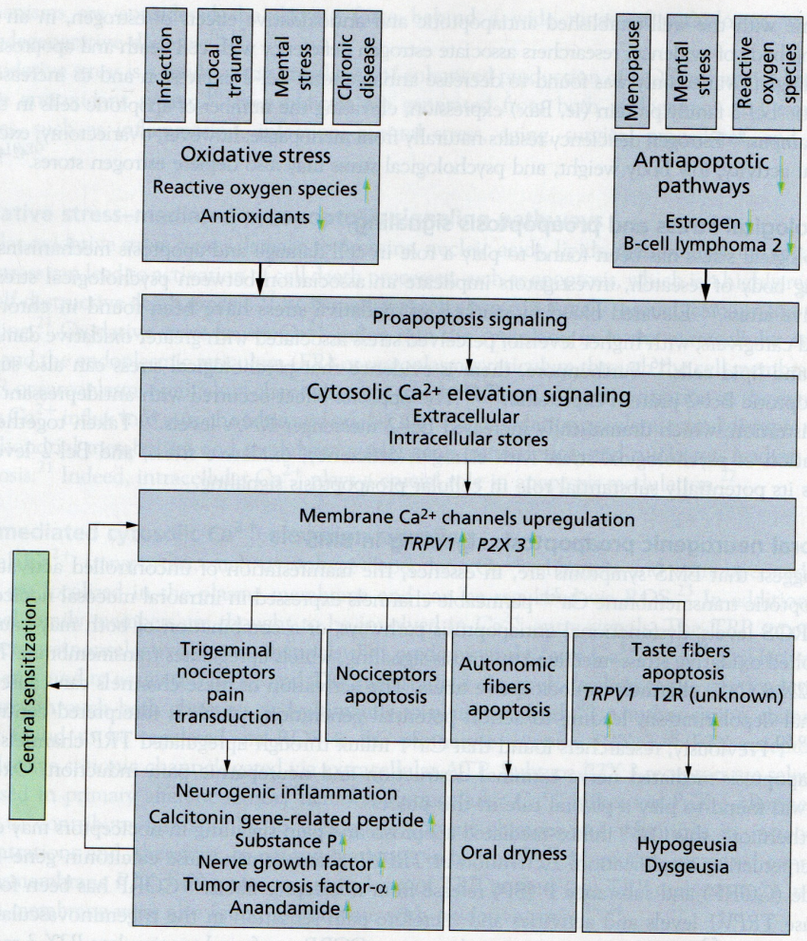

Figure. Flow chart of the proposed pathogenesis theory of burning mouth syndrome. ↓: Downregulation. ↑: Upregulation. Ca^{2+}: Calcium ion. *TRPV1*: Transient receptor potential vanilloid 1.

the intraepithelial nerve fiber density in patients with BMS compared with control participants.[7,8,67,68] This may indicate a prominent apoptosis-mediated cell death that is generated by these fibers. Nonetheless, the lack of SP and CGRP elevation despite *TRPV1* overexpression is puzzling, and further investigation is needed to understand the role of these neurotransmitters in BMS.

ILLUMINING THE UNDERLYING MECHANISMS OF BMS CHARACTERISTIC FEATURES

Persistent burning pain quality

Results of quantitative sensory testing studies highlighted intraepithelial small nerve fiber dysfunction by means of expressing more pronounced damage and degeneration of Aδ fibers than C-fibers.[8,10,67,69] The relative survival of C-fibers in BMS may explain the burning pain quality in this syndrome because C-fiber–mediated pain is typically perceived as a burning sensation.[70]

BMS pain is chronic and persistent. It is present every day for most of the day.[6,8] We suggest that the persistent pain sensation is perceived as a result of the continuous activation of intraoral mucosal nociceptors' *P2X 3* and *TRPV1* channels via the elevated intracellular ROS levels, as mentioned previously. This activation is self-amplified via the upregulated SP, CGRP, TNF-α, *NGF*, and AEA, which constantly modulate these channels.

The persistent quality of BMS pain may cause development of central sensitization in these patients due to the continuous afferent input, and the suppressed descending pain modulation pathway found in BMS.[6,8]

Circadian cycle of BMS pain

BMS pain is usually at its lowest in the morning on awakening. Once aggravated, it rises continuously, reaching maximum intensity in the late evening. However, the pain seldom interferes with sleep.[6,8] These BMS pain characteristics can be explained as follows. It is now well established that ROS can be eliminated during sleep, which is thought to provide an essential defense against oxidative stress.[71,72] Trivedi and colleagues[72] reported that sleep deprivation has induced oxidative stress. Moreover, melatonin, a hormone principally secreted at night, is a powerful ROS eliminator.[73,74] ROS is produced during wakefulness because ATP synthesis produces ROS. Therefore, during prolonged wakefulness, ROS levels are increased.[72,74] Taken together, we suggest that the pain relief during night sleep that patients with BMS typically experience is due, at least in part, to the antioxidant effects of sleep and melatonin upregulation. This leads to ROS reduction, which decreases *TRPV1* and *P2X 3* channel activation, thereby attenuating nociceptive fiber's Ca^{2+} and pain signaling. During the day, however, ROS levels accumulate again, leading to channel activation and corresponding pain.

Accompanying factors: oral dryness

Oral dryness may be attributed to an objective decrease in saliva secretion volume from the salivary glands; nevertheless, it can also be manifested as a subjective feeling (xerostomia) with no evidence of decreased secretion.[75,76] Xerostomia has been reported in up to 67% of patients with BMS,[8] and although there is a long-standing debate whether there is a reduction in salivary secretion in BMS,[77,78] contemporary researchers have found a marked decrease in BMS salivary flow rates and higher viscosity of the unstimulated whole saliva compared with control participants.[8] In line with our theory, we propose that this salivary flow reduction is due, at least in part, to nerve loss of the autonomic fibers innervating the small salivary glands, similar to the trigeminal nociceptor fiber loss discussed above. In essence, results of biopsies of the anterolateral tongues of patients with BMS showed a significantly lower density of unspecified epithelial and subpapillary nerve fibers than control patients.[68] This suggested autonomic small-fiber degeneration may reflect more diffused expression of the aforementioned oxidative stress–mediated apoptosis cell death signaling.

Accompanying factors: taste alterations

Approximately 70% of patients with BMS reported taste alteration, such as dysgeusia and phantom taste, which was thought to be related to the onset of the burning sensation.[8] Commonly, patients report intraoral metallic and bitter taste sensations. Hypogeusia is also common, with reduced taste sensitivity for salty and sweet.[8] In addition, results of an electrogustometric test on the dorsal surface of the tongue showed substantially elevated taste thresholds in patients with BMS compared with control participants, suggesting degeneration of the chorda tympani nerve.[79] In line with our theory, these subjective and objective indicators of reduced taste sensation in BMS may reflect, at least in part, a taste fiber loss due to the diffuse multicellular oxidative stress–mediated proapoptosis signaling we discussed. Furthermore, Huang and Wu[80] reported that CGRP secretion by sensory nerve terminals, forming synaptic contacts with presynaptic taste cells, decreased ATP secretion from taste buds during taste stimulation. Because ATP is thought to be an essential excitatory transmitter between taste buds and gustatory sensory afferent fibers, its reduction decreases taste signaling.[80] These findings may reflect a possible connection between the proposed trigeminal nociceptors–mediated CGRP upregulation and hypogeusia in BMS.

Several mechanisms may be associated with BMS dysgeusia and phantom taste. T2R bitter receptor activation was found to elevate nuclear and mitochondrial Ca^{2+} levels, hence, inducing apoptosis in nonciliated airway epithelial cells.[81] Therefore, it is possible that the bitter sensation symptom in BMS is associated with this proapoptotic mediator, which may be overexpressed on the cell membrane of taste fibers, as part of the aforementioned Ca^{2+}-mediated proapoptosis signaling. Additional research is required to evaluate the role of T2R receptors in BMS. Furthermore, Riera and colleagues[82] found that salts that produce a metallic taste are effective agonists for *TRPV1* receptors, which may mediate their metallic taste. Hence, the *TRPV1* overexpression found in BMS[7] may account, at least in part, for the metallic taste sensation in patients with BMS.

Epithelial degeneration in BMS

Another finding that points to the cellular deterioration process suggested in BMS is the substantial cytomorphometric changes found in oral epithelial cells of patients with BMS, exhibiting a higher

nucleus to cytoplasm area ratio for BMS than control participants.[83] These changes were thought to be associated with epithelial atrophy and a deregulated maturation process.[83] In another study, researchers found that the keratinocyte cytoplasm of patients with BMS was more intensely stained with a keratin 16 marker than that of control participants.[84] Keratin 16 expression in keratinocytes represents a highly activated and proliferative stage under pathologic conditions, enabling them to resist physical trauma and protecting them from apoptosis mechanisms.[85] Accordingly, keratin 16 overexpression in BMS could be an indication of the existence of an epithelial defense mechanism designed to protect against cellular damage. In line with our hypothesis, exposure to the multicellular oxidative stress–mediated proapoptosis signaling discussed above can be considered a possible trigger for this self-defense epithelial mechanism. Indeed, this proapoptosis signaling may affect not only the oral mucosal neuronal fibers but the epithelial cells as well. Nonetheless, further inquiry is needed to comprehend the underlying mechanisms of the epithelial cellular changes identified in BMS.

Multifactorial etiology of BMS

BMS has a clear predisposition to peri- and postmenopausal women.[5] It was reported that up to 90% of female patients with BMS are perimenopausal, with typical onset from 3 years before through 12 years after the beginning of menopause.[5] Gao and colleagues[86] reported that peri- and postmenopausal patients with BMS had significantly lower estradiol levels compared with control participants, therefore, decreased estrogen levels during menopausal stages were suggested to be an etiologic factor in BMS.[87,88] Despite its predisposition to affect women, BMS also affects men.[8] This implies that other factors beyond estrogen deficiency likely contribute to the development of BMS. Psychological or psychopathologic factors were also believed to trigger or exacerbate BMS symptoms[8] and accounted for BMS symptoms in more than 50% of patients.[89] Moreover, anxiety and depression were found to play critical roles in BMS.[90] Other local and systemic factors were suggested to precipitate BMS. These include trauma to the oral mucosa (eg, dental procedures or a burn from hot food),[91] previous illness (eg, upper respiratory tract infection), and medication use.[92] This plurality of proposed etiologic factors strengthened our hypothesis that BMS etiology is multifactorial. Estrogen deficiency and psychological stress are probably the main etiologic factors; however, any factor or combination of factors leading to uncontrolled oxidative stress–mediated proapoptosis signaling may cause BMS symptoms. Indeed, Tatullo and colleagues[93] found significantly different reactive oxygen metabolites and biological antioxidant potential levels in the plasma of women with BMS compared with control participants, indicating high oxidative stress levels in female patients with BMS.

PROPOSED MULTIDIRECTIONAL MANAGEMENT APPROACH

Given the above, we believe that a multidirectional treatment approach may be the most beneficial in BMS management. We suggest the following:

- Reduction of cellular oxidative stress generation by means of a potent antioxidant therapy.
- Targeting the source of the uncontrolled oxidative stress–mediated proapoptosis signaling; that is, addressing the oxidative stress inducers, enhancing the cellular antiapoptotic mechanisms, or a combination of both. Mainly, this points to estrogen deficiency and psychological pathology therapies. In our opinion, direct targeting of the antiapoptotic Bcl-2 proteins is not recommended as a BMS management strategy because their oncogenic potential is well recognized.[94]
- Desensitization and downregulation of both *P2X 3* and *TRPV1* ion channel receptors. For this purpose, the desensitizing actions of *TRPV1* receptor agonist capsaicin may be used. Indeed, topical capsaicin was found as one of the few effective BMS treatments.[95] In addition, the use of *P2X 3* receptor antagonists, such as eliapixant and gefapixant, may be taken under future consideration. These potent and relatively safe medications are under advanced clinical development.[96-99]
- Because the persistent afferent input in BMS may cause central sensitization, a centrally mediated pain treatment should be considered, in addition to the peripheral management strategies.

Nonetheless, clear and definitive evidence of the proposed BMS underlying mechanisms theory should be established before any management recommendations can be clinically tested.

FUTURE RESEARCH DIRECTIONS

This proposed detailed and complex BMS pathogenesis hypothesis should be evaluated in a stepwise manner. Cellular uncontrolled oxidative stress and apoptosis signaling are suggested as

leading the trajectory of this syndrome's sequence of cellular events, hence they ought to be explored first. Direct detection of ROS is often impractical since they are reactive and have short half-lives. Hence, detection of oxidative DNA, proteins, and lipid by-products may be used as oxidative stress biomarkers.[100] Such oxidative markers can be measured noninvasively in the saliva of patients with BMS. In addition, glutathione, which is the most abundant nonenzymatic low molecular weight antioxidant defense in cells, can be measured.[100] Furthermore, an investigation of the efficacy of antioxidant compounds in the treatment of patients with BMS may serve as a useful and safe clinical research tool. Such studies may evaluate compounds such as epigallocatechin-3-gallate or quercetin, which are natural flavonoids with potent ROS scavenging properties, as potential therapeutic agents for BMS.[101] α-Lipoic acid, a natural antioxidant compound, appears to have benefits in BMS management, yet the evidence supporting its efficacy is inconclusive.[95] Apoptosis signaling may be evaluated by measuring the expression of the caspase family proteases in BMS cells. For this purpose, several methods may be used, such as reverse transcriptase-polymerase chain reaction, in situ hybridization, and immunohistochemistry.[102,103]

By using the aforementioned research methods and exploring other available in vivo and in vitro relevant methodologies, we hope that enough evidence regarding the mechanisms underlying BMS will be accumulated. This would enable the development of a reliable BMS animal model. Such a model would provide researchers with a controlled and structured system to delve deeper into BMS pathogenesis and explore potential therapeutic approaches.

CONCLUSIONS

We have presented a novel comprehensive theory regarding the molecular mechanisms underlying the enigmatic pathogenesis of BMS. Despite the introduction of a plethora of relevant cellular mechanisms from evidence-based data, many of the findings supporting this theory are based on animal studies, and human studies are scarce. Hence, this hypothesis mandates careful and systematic investigation and possesses the potential to serve as the foundation for future in vivo and in vitro studies. A complete understanding of BMS pathogenesis could lead to the development of more effective therapeutic interventions that target specific aberrant pathways involved in the pathogenesis of this debilitating disorder. ■

DISCLOSURE

None of the authors reported any disclosures.

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