Original Article

Potential differences in somatosensory function during premenopause and early and late postmenopause in patients with burning mouth syndrome: An observational case—control study

Kana Ozasa [a], Noboru Noma [a*], Andrew Young [b],
Olga A. Korczeniewska [c], Eli Eliav [d], Yoshiki Imamura [a]

[a] *Department of Oral Diagnostic Sciences, Nihon University School of Dentistry, Nihon University, Tokyo, Japan*
[b] *Department of Diagnostic Sciences, Arthur Dugoni School of Dentistry, University of the Pacific, San Francisco, United States*
[c] *Center for Orofacial Pain and Temporomandibular Disorders, Department of Diagnostic Sciences, Rutgers School of Dental Medicine, Rutgers, The State University of New Jersey, Newark, NJ, USA*
[d] *Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA*

Abstract *Background/purpose:* Burning mouth syndrome (BMS) is a chronic condition presenting as intraoral burning or dysesthesia, with a high preponderance in menopausal women. This study aimed to examine the association between somatosensory dysfunction and BMS in premenopausal, early postmenopausal, and late postmenopausal patients, using a standardized Quantitative Sensory Testing (QST) protocol, and to determine the predictive value of thermal or mechanical perception by QST for detecting BMS.

Materials and methods: An observational case—control study was performed with 36 female participants with BMS (12 premenopausal, 10 early postmenopausal, and 14 late postmenopausal) and 42 age- and sex-matched healthy volunteers (21 premenopausal, 10 early postmenopausal, and 11 late postmenopausal). Neurophysiological tests were used to evaluate somatosensory dysfunction at the tongue.

Results: Z-score in the late postmenopausal BMS group revealed a gain of function for the cold pain threshold and heat pain threshold (Z = 2.08 and 3.38, respectively). In the multiple regression analysis with the Visual Analog Scale as the dependent variable, the vibration detection threshold predicted the severity of burning mouth sensation in the premenopausal group.

Conclusion: Late postmenopausal patients with BMS showed an increased response of the tongue to noxious thermal stimuli. This supports the theory that changes in sex hormones may affect trigeminal somatosensory function, particularly during the late postmenopausal stage in patients with BMS.

Introduction

Burning mouth syndrome (BMS) is characterized by intraoral numbness, stinging, and burning pain.[1,2] Women are affected 3 to 20 times more frequently than men, usually at menopausal or postmenopausal ages. The World Health Organization (WHO) defines menopause, also known as climacteric, as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Amenorrhea must occur for 12 consecutive months before natural menopause is recognized.[3,4] During menopause, women experience various predictable symptoms and conditions related to changes in sex hormone levels and aging. Menopause typically occurs between 49 and 52 years of age.[5]

Serum hormonal imbalance during menstruation, pregnancy, and the perimenopausal period may result in numerous systemic and local symptoms, including a burning sensation in the oral mucosa.[6,7] Woda et al.[8] surmised that reduced synthesis of ovarian steroids after menopause induces deficiency or dysfunction in adrenal steroids, reducing the neuroprotective effects of steroids on neural tissues. The predilection of BMS in menopausal and postmenopausal women also suggests reduced levels of sex hormones,[6,7,9] which can influence somatosensory function, may be a factor, and that nociception in the mouth is particularly sensitive to modulation by ovarian hormone levels.[10] A study in ovariectomized female rats showed an increased sensitivity to nociceptive stimulation in the orofacial region.[11] However, clinical behavioral studies have not verified this in premenopausal or early and late postmenopausal patients with BMS.

Patients with BMS often complain of pain when eating hot or spicy foods.[2,12] Quantitative sensory testing (QST) studies of the pain threshold of patients with BMS have had similar findings. Yilmaz et al. found that patients with BMS were more sensitive to cold hyperalgesia than patients with lingual nerve impairment.[13] Grushka et al. reported that heat pain tolerance was significantly decreased in patients with BMS.[14] QST alterations are not exclusive to BMS. De Kruijf et al. reported a significant association between years after menopause and cold and warmth sensitivity thresholds in patients with chronic pain.[15] In a previous study, we found an association between somatosensory dysfunction and disease duration in patients with BMS.[12,16]

We aimed to assess the somatosensory function in premenopausal and early and late postmenopausal patients with BMS, compared with healthy volunteers, and investigate the association between QST data and stage of menopause. In addition, we investigated the predictive value of thermal and mechanical parameters for detecting the severity of burning sensation.

Materials and methods

This study was approved by the Ethical Committee of Nihon University School of Dentistry (EP16 D020-1) and was conducted in accordance with the Helsinki Declaration. Informed consent of all patients and volunteers was mandatory. Fifty-four individuals gave their consent to participate in this study. A total of 49 patients accepted the invitation, and the other five declined to participate. Out of the 49 patients, 13 were excluded, including five patients who complained of intraoral burning sensation for only 1 month (n = 5), three due to a swab test that showed candida albicans growth (n = 3), two due to non-burning dysesthetic sensation (n = 2), and three due to unknow menopause status (n = 3). In the present study, a total of 36 primary BMS patients were enrolled. The study period was between April 2019 and March 2021.

The following definitions were used to determine postmenopausal and BMS status in this study. Women who had menstruated normally in each of the last three months, and whose ages were between 30 and 50 years, were categorized as premenopausal. Women whose last menstrual period occurred >12 months prior were categorized as postmenopausal. Postmenopausal women who reached menopause ≤5 years prior were classified as the early postmenopausal group, while those who had reached menopause >5 years prior were classified as the late postmenopausal group.[17,18]

This study included 36 women with BMS and 42 age-matched healthy female volunteers. The BMS patients were recruited from a tertiary outpatient pain clinic of Nihon University Dental Hospital in Tokyo. All patients were recruited by the same trained examiner (NN). Patients with BMS were divided into three groups: premenopausal BMS (n = 12; 40.1 ± 6.0 years), early postmenopausal BMS (n = 10; 53.2 ± 2.7 years), and late postmenopausal BMS (n = 14; 70.1 ± 5.0 years). Likewise, the healthy volunteers were divided into three groups: premenopausal control (n = 21; 45.2 ± 2.4 years), early postmenopausal control (n = 10; 55.6 ± 2.8 years), and late postmenopausal control (n = 11; 64.9 ± 10.8 years). The presence of intraoral spontaneous pain was assessed in patients with BMS using the Visual Analog Scale (VAS: marked at one end with 0 and at the other end with 100).

The QST protocol

The QST protocol used in this study was based on that of the German Research Network on Neuropathic Pain,[19] and consisted of the thermal and mechanical tests at the tip of the tongue. The examiner was blind to the BMS and the volunteer's status of the participants and was not involved in the recruitment. One healthy volunteer took non-steroidal anti-inflammatory drugs (NSAIDs) for tension-type headache 2—3 times per week. She was advised and was comfortable stopping the medication use 48 h prior to QST. Likewise, seven of the BMS patients took acetaminophen, antianxiety, and anticonvulsant medications regularly. Following a consultation with their primary care provider, they stopped the medications 48 h before the QST session. They resumed the medication use immediately after the sensory testing.

Thermal tests

Cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen, cold pain threshold, and heat pain threshold were determined with a computer-controlled Peltier − type thermode (Somedic®, Sales AB, Hörby, Sweden; stimulation area 16 *16 cm^2) and the Classic Method of Limits.

Mechanical tests

The mechanical QST protocol used in this study consisted of tests for the mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold, and pressure pain threshold, as described previously.

Statistical analysis

Normal distribution was tested with the goodness of fit test. For normally distributed data, we used the unpaired t-test (parametric methods) for two sample analysis. When samples that did not meet the assumption of normal distribution we used non-parametric the Mann—Whitney test. This included the QST results of premenopausal, early postmenopausal, and late postmenopausal patients with BMS and healthy controls. All data are presented as means ± standard deviations (SD). To examine the differences between patients with BMS and healthy controls in the QST variables, a Z-score transformation was performed for all QST variables to provide a somatosensory profile. The detailed method of Z-score calculation has been described elsewhere.[20] A positive Z-score indicated sensory gain, and a negative Z-score indicated sensory loss. Z-scores are presented as means ± standard errors.

In addition, multiple regression analysis was performed to define the contribution of the independent variables, such as thermal parameters (CDT, WDT, thermal sensory limen, cold pain threshold, and heat pain threshold) and mechanical parameters (MDT, MPT, vibration detection threshold, pressure pain threshold, WUR, and MPS) to the dependent variable (VAS: spontaneous pain) in the premenopausal, early postmenopausal, and late post-menopausal patients with BMS. The Durbin—Watson statistic was used to test for the occurrence of serial correlation in the residuals from the multiple regression analysis when the data did not show a normal distribution. All statistical analyses were performed using SPSS v.27 (IBM, Tokyo, Japan). Significance level was set at p < 0.05 for all statistical tests.

Sample size estimation

JMP Pro statistical software v. 15.0 (SAS Institute Inc, Cary, NC, USA) was used to calculate the required number of subjects per group to be able to detect differences between groups. Two sample means test was used to estimate the per group sample size. The parameters required to run the test (SD and the difference to detect) were selected based on the previously published data.[21] The SD of 2.0 and difference to detect of 2.9 were used. The alpha level was set to 0.05, and power was set to 0.8. Based on the selected parameters, the required per group sample size was estimated to be 9 to be able to detect significant differences between the groups.

Results

Table 1 shows the raw data at the tongue for all QST in the premenopausal, early postmenopausal, and late post-menopausal BMS groups. Pressure pain threshold was significantly decreased in the premenopausal BMS group compared to premenopausal controls (p < 0.01: Mann—Whitney test). Among the early postmenopausal groups, vibration detection threshold was significantly decreased in the BMS group compared with controls (p < 0.01: Mann—Whitney test). In the late postmenopausal groups, significant differences were observed in the comparison of cold pain threshold and heat pain threshold between controls and patients with BMS, indicating cold and heat hyperalgesia at the tongue (p < 0.01 and p < 0.05, respectively: Mann—Whitney test) (Tables 1 and 2).

Z-score

In the premenopausal and early postmenopausal BMS groups, the means of all the parameters on the tongue remained within the 95% CI of the baseline reference database (Z-scores within ±1.96; Figs. 1—2). On the other hand, in the late postmenopausal BMS group (Fig. 3a), a mean gain of function by cold pain threshold and heat pain threshold at the tongue (Z = 2.08 and 3.38, respectively) was observed (Fig. 3b).

Table 1 Quantitative sensory testing results in premenopause and early and late postmenopause in patients with BMS.

	BMS		
	Premenopause	Early postmenopause	Late postmenopause
	Tongue	Tongue	Tongue
CDT	−2.63 ± 1.29	−1.84 ± 0.86	−3.91 ± 3.04
WDT	3.52 ± 2.25	2.52 ± 0.94	3.75 ± 3.16
TSL	2.28 ± 2.91	1.37 ± 1.12	2.10 ± 1.46
CPT	12.41 ± 7.38	13.38 ± 6.54	16.10 ± 0.51**
HPT	46.86 ± 2.12	45.06 ± 4.48	43.68 ± 3.46*
MDT (mN)	0.18 ± 0.15	0.16 ± 0.09	0.16 ± 0.06
MPT (mN)	37.84 ± 44.09	60.36 ± 54.0	37.88 ± 20.07
MPS (ratio)	9.05 ± 10.38	13.32 ± 14.35	14.06 ± 16.47
WUR (ratio)	3.46 ± 2.97	2.65 ± 1.51	2.72 ± 1.25
VDT (x/8)	5.89 ± 0.84	4.92 ± 0.64*	5.54 ± 1.07
PPT (kPa)	0.56 ± 0.40**	0.90 ± 0.56	0.55 ± 0.26

BMS, burning mouth syndrome; CDT, cold detection threshold; CPT, cold pain threshold;; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warmth detection threshold; WUR, wind-up ratio.
For CDT and WDT, differences from baseline-temperature (32 °C) are shown.
There is no evidence of the occurrence of dynamic mechanical allodynia.
Mean values±SDs Premenopause control vs. premenopause BMS: **p < 0.01, early postmenopause control vs. early postmenopause BMS: *p < 0.05, late postmenopause control vs. late postmenopause BMS: **p < 0.01.

Table 2 Quantitative sensory testing results in premenopause and early and late postmenopause in healthy controls.

	Control		
	Premenopause	Early postmenopause	Late postmenopause
	Tongue	Tongue	Tongue
CDT	−2.54 ± 1.20	−2.70 ± 1.64	−3.39 ± 1.39
WDT	2.54 ± 1.22	2.50 ± 0.92	5.08 ± 1.73
TSL	2.06 ± 1.30	1.08 ± 0.84	3.18 ± 1.19
CPT	9.10 ± 5.64	10.82 ± 4.88	5.79 ± 4.94
HPT	46.6 ± 2.79	44.6 ± 3.32	48.12 ± 1.31
MDT (mN)	0.16 ± 0.09	0.16 ± 0.09	0.36 ± 0.26
MPT (mN)	55.0 ± 35.7	53.8 ± 37.4	37.12 ± 18.74
MPS (ratio)	5.41 ± 7.60	4.28 ± 8.30	16.00 ± 18.46
WUR (ratio)	3.93 ± 2.58	4.59 ± 4.52	3.06 ± 1.93
VDT (x/8)	5.47 ± 0.73	5.65 ± 0.81	5.98 ± 0.39
PPT (kPa)	1.07 ± 0.30	0.83 ± 0.29	0.41 ± 0.16

CDT, cold detection threshold; CPT, cold pain threshold; DMA, HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warmth detection threshold; WUR, wind-up ratio.
For CDT and WDT, differences from baseline-temperature (32 °C) are shown.
There is no evidence of the occurrence of dynamic mechanical allodynia.
Mean values±SDs Premenopause control vs. premenopause BMS: **p < 0.01, early postmenopause control vs. early postmenopause BMS: *p < 0.05, late postmenopause control vs. late postmenopause BMS: **p < 0.01.

Regression analysis

A stepwise multiple regression analysis was performed with spontaneous pain as the dependent variable. The model using mechanical parameters (MDT, MPT, vibration detection threshold, pressure pain threshold, WUR, MPS) explained 17.1% of variance in spontaneous pain in premenopausal patients with BMS [adj. R2 = 0.58; F = 3.56; p = 0.025, Durbin−Watson = 2.087]. Vibration detection threshold contributed significantly to the model, while the other parameters did not (Table 3). There was no evidence of the occurrence of DMA, which was not included in the parameters as an independent variable.

The model with thermal parameters (CDT, WDT, thermal sensory limen, cold pain threshold, and heat pain threshold) was not significantly predictive for spontaneous pain in premenopausal patients with BMS [adj. R2 = 0.03; F = 0.93; p = 0.30]. In the early postmenopausal BMS group, the model was not predictive when the predictor variables were mechanical [adj. R2 = 0.32; F = 0.63; p = 0.45] or thermal [adj. R2 = 0.55; F = 0.36; p = 0.79].

Similarly, in the late postmenopausal BMS group, the model was not predictive when the predictor variables were mechanical [adj. R2 = 0.17; F = 0.68; p = 0.76] or thermal [adj. R2 = 0.38; F = 2.64; p = 0.06] (Table 4). Table 5 summarizes the clinical characteristics of the BMS patients and healthy controls, such as systemic diseases and principal drugs.

Discussion

In the present study, the QST results for cold pain threshold and heat pain threshold at the tongue were significantly more sensitive in the BMS group than in the control group at the late postmenopausal stage. In a previous QST study, De Kruijf et al.[15] found a significant association between years after menopause and cold and warmth sensitivity thresholds. One possible reason for the increased cold pain threshold may be that drastic menopausal changes significantly reduce neuroprotective steroids. This reduction in neuroprotective and neuroregenerative capacities may
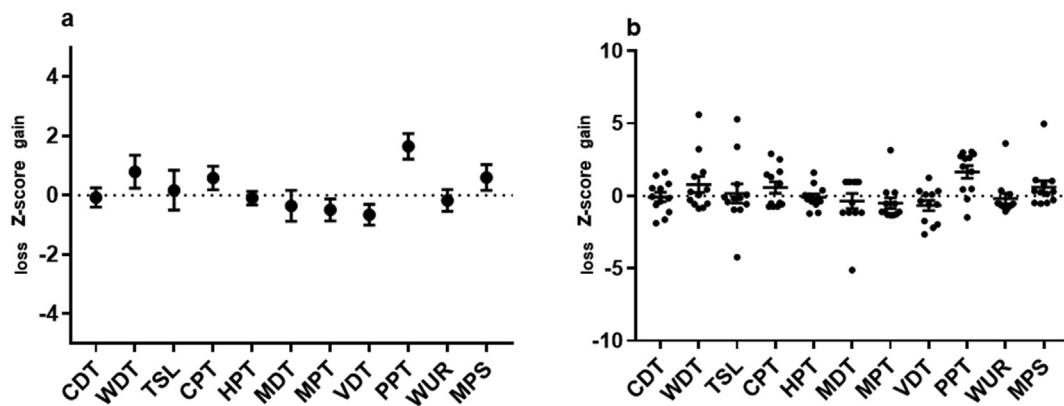
Premenopause BMS

Figure 1 Z-score QST profiles of the tongue in patients with premenopausal BMS. a. Mean overall Z-scores. b. Overall scatter plot profile. All QST variables are presented as Z-scores. A Z-score greater than 0 indicates increased sensation, and a Z-score less than 0 indicates loss of sensory function. Z-scores greater than ±1.96 indicate values outside the 95% confidence interval of the baseline values (gray zone indicates Z-scores less than ± 1.96). Abbreviations: cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), vibration detection threshold (VDT), pressure pain threshold (PPT), wind-up ratio (WUR) and mechanical pain sensitivity (MPS).
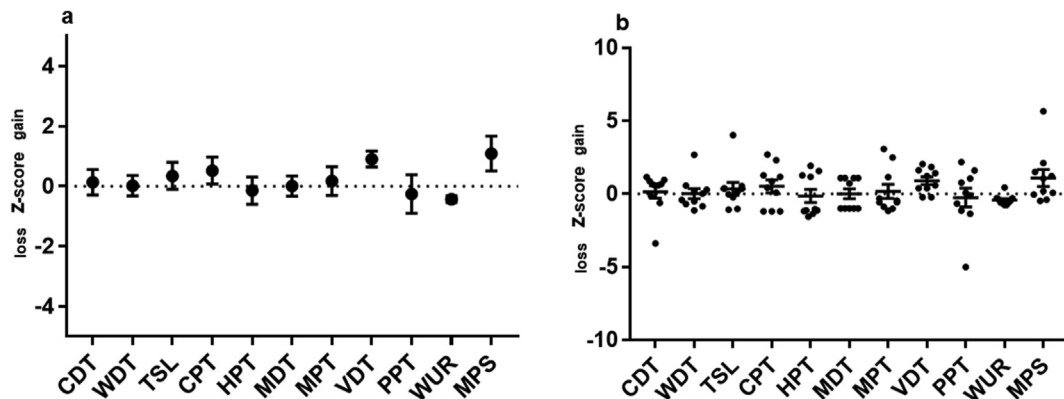
Early postmenopause BMS

Figure 2 Z-score QST profiles of the tongue in patients with early postmenopausal BMS. a. Mean overall Z-scores. b. Overall scatter plot profile. All QST variables are presented as Z-scores. A Z-score greater than 0 indicates increased sensation, and a Z-score less than 0 indicates loss of sensory function. Z-scores greater than ±1.96 indicate values outside the 95% confidence interval of the baseline values (gray zone indicates Z-scores less than ± 1.96). Abbreviations: cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), vibration detection threshold (VDT), pressure pain threshold (PPT), wind-up ratio (WUR) and mechanical pain sensitivity (MPS).

preferentially put small Aδ fibers at risk.[22] Another possible mechanism is that neuroactive steroids may directly or indirectly affect cold sensitivity in postmenopausal patients with BMS. Yilmaz et al.[13] and Hartmann et al.[23] also reported cold hyperalgesia in patients with BMS but not in patients with lingual nerve impairment.

The Z-score in the postmenopausal patients with BMS also showed an increased response of the tongue to cold pain stimulation (cold pain threshold Z-score = 2.08). Aδ

cold afferents seem to be impaired more often than C fibers in patients with BMS, indicating an imbalance in the small fiber input to the central nervous system.[13] Zagury et al.[24] reported an extended painful aftersensation following cold application in atypical odontalgia patients compared with control subjects. This suggests a neuropathic mechanism involving central factors. The cold test may be a diagnostic marker for central sensitization in patients with chronic pain, such as BMS.
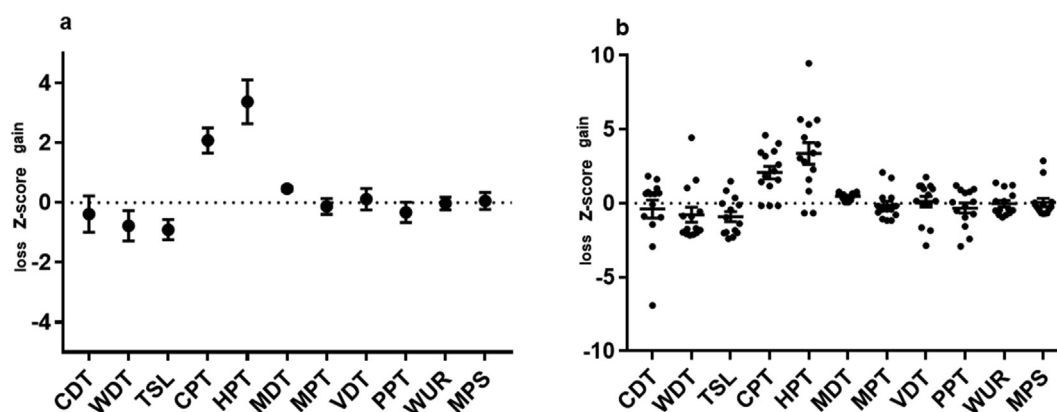
Late postmenopause BMS

Figure 3 Z-score QST profiles of the tongue in patients with late postmenopausal BMS. a. Mean overall Z-scores. b. Overall scatter plot profile. All QST variables are presented as Z-scores. A Z-score greater than 0 indicates increased sensation, and a Z-score less than 0 indicates loss of sensory function. Z-scores greater than ± 1.96 indicate values outside the 95% confidence interval of the baseline values (gray zone indicates Z-scores less than ± 1.96). Abbreviations: cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), vibration detection threshold (VDT), pressure pain threshold (PPT), wind-up ratio (WUR) and mechanical pain sensitivity (MPS).

Table 3 Results of multiple regression analyses: mechanical test.

Sependent variable	Predictor variables	β	t	p
Spontaneous pain	Constant		3.15	0.02
	Mechanical detection threshold	0.68	2.52	0.05
	Mechanical pain threshold	0.38	1.60	0.17
	Vibration detection threshold	−1.1	−2.94	0.03
	Pressure pain threshold	-0.45	−1.87	0.12
	Wind-up ratio	-0.52	−1.74	0.14
	Mechanical pain sensitivity	-0.55	−2.30	0.07

Table 4 Results of multiple regression analyses: mechanical test.

Dependent variable	Predictor variables	β	t	p
Spontaneous pain	Constant		2.19	0.06
	Cold detection threshold	−0.46	−2.00	0.08
	Warmth detection threshold	−0.30	−0.62	0.56
	Thermal sensory limen	-1.1	2.3	0.05
	Cold pain threshold	-0.31	−0.69	0.51
	Heat pain threshold	-0.88	−2.24	0.055

Late postmenopausal patients with BMS also showed an increased response of the tongue to heat pain stimulation (heat pain threshold Z-score = 3.38). Grushka et al.[14] demonstrated that patients with BMS were significantly less tolerant of heat pain on the tongue than control subjects. It is well known that the psychophysical responses to noxious thermal stimuli are dependent not only on stimulus intensity but also on the duration of the stimulus, inter-stimulus interval, and characteristics of prior conditioning stimuli. The duration of heat pain tolerance testing may cause sensitization of the C fiber polymodal nociceptors and Aδ heat nociceptors in patients with BMS.[25] This sensitization may account for the decreased heat pain tolerance of patients with BMS.

In this study, we investigated the association between QST parameters and spontaneous pain at different stages of BMS in an attempt to elucidate whether QST parameters can be used as an early sign of BMS development. Multiple regression analysis using mechanical parameters (MDT, MPT, VDT, PPT, WUR, and MPS) as predictive variables for spontaneous pain explained 17.1% of the variance in early stage of patients with BMS, although vibration detection threshold alone was found to be significant. Additionally, in the premenopausal stage, pressure pain threshold at the tongue was significantly lower in the BMS group than in the control group.

Martínez-Jauand et al.[26] demonstrated that chronic pain conditions with early age-of-onset menopause displayed greater painful and non-painful mechanical sensitivity than patients with late age-of-onset menopause. Consistent with this, the prevalence of orofacial pain with migraine or temporomandibular joint disorders seems to be much higher during peak reproductive years.[27,28] Hormonal changes associated with pre-menopause or early menopause may modulate pain hypersensitivity. Thus, ovarian

Table 5 Systemic diseases and oral medication status in patients with burning mouth syndrome and healthy controls.

Systemic diseases		
	BMS patients(n = 36)	Control(n = 42)
Age(years)	55.41 ± 13.9	48.69 ± 9.45
Insomnia	(5/36) 13.8%	
Anxiety	(4/36) 11.1%	
Bronchial asthma	(4/36) 11.1%	
High cholesterol	(3/36) 8.3%	(2/42) 4.8%
Appendicitis	(3/36) 8.3%	(1/42) 4.8%
Depression	(2/36) 5.5%	(2/42) 4.8%
Arrhythmia	(2/36) 5.5%	
Osteoporosis	(1/36) 2.7%	
Colorectal cancer	(1/36) 2.7%	
Diabetes	(1/36) 2.7%	(1/42) 2.4%
Gastritis	(1/36) 2.7%	(1/42) 2.4%
Thyroid tumor	(1/36) 2.7%	
Paget's disease	(1/36) 2.7%	
Kidney stones	(1/36) 2.7%	
Uterine fibroid	(1/36) 2.7%	
Migraine	(1/36) 2.7%	
Parotid tumor	(1/36) 2.7%	
Low back pain	(1/36) 2.7%	(1/42) 2.4%
Uterine fibroid		(1/42) 2.4%
Ovarian cyst		(1/42) 2.4%
Meningioma		(1/42) 2.4%
Medication		
	BMS patients(n = 36)	Control(n = 42)
Age(years)	55.41 ± 13.9	48.69 ± 9.45
Bronchial asthma drug	(5/36) 13.8%	
Antianxiety	(4/36) 11.1%	
Antidepressant	(4/36) 11.1%	
Antihypertensive agent	(3/36) 8.3%	(1/42) 2.4%
Anti cholesterol	(3/36) 8.3%	(1/42) 4.8%
nticonvulsant	(2/36) 5.5%	
Gastrointestinal drug	(2/36) 5.5%	
Nsaids	(1/36) 2.7%	(2/42) 4.8%
Acetaminophen	(1/36) 2.7%	
Chinese medicine	(1/36) 2.7%	
hypoglycemic agent	(1/36) 2.7%	
Vitamin	(1/36) 2.7%	
Supplement	(1/36) 2.7%	(2/42) 4.8%

referral to an orofacial pain specialist are crucial and may reduce the chronic pain and associated cost.

A standardized battery of QSTs demonstrated that an early transition to menopause may influence mechanical pain sensitivity, while late menopause may influence thermal pain sensitivity. Overall, our findings suggest that changes in sex hormones may directly or indirectly affect trigeminal somatosensory function during the post-menopausal stage in patients with BMS.

This study had limitations. In the late postmenopausal group, heat pain threshold and thermal sensory limen trended toward significance in the multiple regression analysis (p = 0.055 and p = 0.05 respectively; constant p = 0.06). It is possible that the small sample size contributed to the insufficient power to detect significant predictive values for those thermal tests.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

References

1. Jääskeläinen SK, Woda A. Burning mouth syndrome. *Cephalalgia* 2017;37:627–47.
2. Imamura Y, Shinozaki T, Okada-Ogawa A, et al. An updated review on pathophysiology and management of burning mouth syndrome with endocrinological, psychological and neuropathic perspectives. *J Oral Rehabil* 2019;46:574–87.
3. Research on the menopause in the 1990s. Report of a WHO scientific group. *World Health Organ Tech Rep Ser* 1996;866: 1–107.
4. Munro MG. Southern California permanente medical group's abnormal uterine bleeding working group. Investigation of women with postmenopausal uterine bleeding: clinical practice recommendations. *Perm J* 2014;18:55–70.
5. Takahashi TA, Johnson KM. Menopause. *Med Clin North Am* 2015;99:521–34.
6. Meurman JH, Tarkkila L, Tiitinen A. The menopause and oral health. *Maturitas* 2009;63:56–62.
7. Friedlander AH. The physiology, medical management and oral implications of menopause. *J Am Dent Assoc* 2002;133:73–81.
8. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). *J Orofac Pain* 2009; 23:202–10.
9. Aryeh HB, Gottlieb I, Ish-Shalom S, et al. Oral complaints related to menopause. *Maturitas* 1996;24:185–9.
10. International classification of orofacial pain, 1st edition (ICOP). *Cephalalgia* 2020;40:129–221.
11. Pajot J, Ressot C, Ngom I, et al. Gonadectomy induces site-specific differences in nociception in rats. *Pain* 2003; 104(1–2):367–73.

hormones may exert their effect on somatosensory brain activity by altering opiate neurotransmitters.[29]

To the best of our knowledge, this is the first study to demonstrate that QST can generate objective information (specifically the vibration detection threshold) that aids in the early detection of BMS in premenopausal patients. BMS is challenging to treat, though there is sufficient evidence suggesting that for patients with significant anxiety, topical clonazepam in combination with systemic anxiolytic drugs may be an effective approach, particularly when introduced early.[30] Therefore, early detection and timely

12. Imamura Y, Okada-Ogawa A, Noma N, et al. A perspective from experimental studies of burning mouth syndrome. *J Oral Sci* 2020;62:165—9.

13. Yilmaz Z, Egbuniwe O, Renton T. The detection of small-fiber neuropathies in burning mouth syndrome and iatrogenic lingual nerve injuries: use of quantitative sensory testing. *J Oral Facial Pain Headache* 2016;30:87—98.

14. Grushka M, Sessle BJ, Howley TP. Psychophysical assessment of tactile, pain and thermal sensory functions in burning mouth syndrome. *Pain* 1987;28:169—84.

15. de Kruijf M, Peters MJ, Jacobs LC, et al. Determinants for quantitative sensory testing and the association with chronic musculoskeletal pain in the general elderly population. *Pain Pract* 2016;16:831—41.

16. Watanabe K, Noma N, Sekine N, et al. Association of somatosensory dysfunction with symptom duration in burning mouth syndrome. *Clin Oral Invest* 2019;23:3471—7.

17. G K P, Arounassalame B. The quality of life during and after menopause among rural women. *J Clin Diagn Res* 2013;7:135—9.

18. Dalal PK, Agarwal M. Postmenopausal syndrome. *Indian J Psychiatr* 2015;57(Suppl 2):S222—32.

19. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006;123:231—43.

20. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain* 2006;10:77—88.

21. Mo X, Zhang J, Fan Y, et al. Thermal and mechanical quantitative sensory testing in Chinese patients with burning mouth syndrome-a probable neuropathic pain condition? *J Headache Pain* 2015;16:84.

22. Jääskeläinen SK. Is burning mouth syndrome a neuropathic pain condition? *Pain* 2018;159:610—3.

23. Hartmann A, Seeberger R, Bittner M, et al. Profiling intraoral neuropathic disturbances following lingual nerve injury and in burning mouth syndrome. *BMC Oral Health* 2017;17:68.

24. Zagury JG, Eliav E, Heir GM, et al. Prolonged gingival cold allodynia: a novel finding in patients with atypical odontalgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011;111:312—9.

25. LaMotte RH, Thalhammer JG, Torebjörk HE, et al. Peripheral neural mechanisms of cutaneous hyperalgesia following mild injury by heat. *J Neurosci* 1982;2:765—81.

26. Martínez-Jauand M, Sitges C, Femenia J, et al. Age-of-onset of menopause is associated with enhanced painful and non-painful sensitivity in fibromyalgia. *Clin Rheumatol* 2013;32:975—81.

27. Schmidt PJ, Cardoso GM, Ross JL, et al. Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *J Am Med Assoc* 2006;295:1374—6.

28. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. *J Psychosom Obstet Gynaecol* 2000;21:167—74.

29. Martin VT. Ovarian hormones and pain response: a review of clinical and basic science studies. *Gend Med* 2009;6:168—92.

30. Silvestre-Rangil J, Silvestre F-J, Tamarit-Santafé C, et al. Burning mouth syndrome: correlation of treatment to clinical variables of the disease. *Med Oral Pathol Oral Cir Bucal* 2011;16:e890—4.