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Differences in somatosensory function during premenopause and early and late postmenopause in patients with burning mouth syndrome

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ABSTRACT

Background: This study aimed to examine the association between somatosensory dysfunction and burning mouth syndrome (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.

Methods: The study included 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-scores 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 Analogue Scale as the dependent variable, the vibration detection threshold predicted severity of burning mouth sensation in the premenopausal group.

Conclusions: 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 in particular, during the late postmenopausal stage in patients with BMS.

KEYWORDS: Burning mouth syndrome, Quantitative sensory testing, Menopause, Visual Analogue Scale

Background

Burning mouth syndrome (BMS) (also known as glossodynia, glossopyrosis, oral dysesthesia, or stomatodynia) is chronic oral mucosal pain or discomfort, usually with a burning quality, that is not caused by any other condition or disease [1]. Women are affected 3 to 20 times more frequently than men, usually at menopausal or postmenopausal ages. The character of BMS condition is described as numbing, stinging and pain [2].

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 a variety of predictable symptoms and conditions related to changes in sex hormone levels and aging. It typically occurs between 49 and 52 years of age [5].

Oral homeostasis is affected by systemic hormonal balance, in part because receptors for sex steroidal hormones, similar to those located in the genital epithelium, are also present in the oral mucosa [6, 7]. During the female lifetime, distinct changes in

estrogen and progesterone activities occur several times. These steroids are neuroprotective and are involved in the synthesis of neurotransmitters that generate pain-related behaviors. The serum hormonal imbalance during menstruation, pregnancy, and the perimenopausal period can result in numerous systemic and local symptoms, including a burning sensation in the oral mucosa [7]. More recently, an enticing hypothesis has been proposed that BMS is associated with an alteration of gonadal, adrenal, and neuroactive steroid levels. Woda et al 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 [8]. The predilection of BMS in post-menopausal women also suggests reduced levels of sex hormones, which can influence somatosensory function, may be a factor [9-11].

Among patients with BMS, a high preponderance in menopausal women suggests that nociception in the mouth is particularly sensitive to modulation by ovarian hormone levels [12]. A study in ovariectomized female rats showed an increased sensitivity to nociceptive stimulation in the orofacial region [13]. However, clinical behavioral studies have not verified this in premenopausal or early and late postmenopausal patients with BMS.

91

92 Patients with BMS often complain of pain when eating hot or spicy foods [2, 14].
93 Quantitative sensory testing (QST) studies of the pain threshold of patients with BMS
94 have had similar findings. Yilmaz et al. found that patients with BMS were more sensitive
95 to cold hyperalgesia than patients with lingual nerve impairment [15]. Grushka et al.
96 reported that heat pain tolerance was significantly decreased in patients with BMS [16].
97 QST alterations are not exclusive to BMS. De Kruijf et al. reported a significant
98 association between years after menopause and cold and warmth sensitivity thresholds in
99 patients with chronic pain [17]. In a previous study, we found an association between
100 somatosensory dysfunction and disease duration in patients with BMS [14, 18].

101

102 We aimed to assess the somatosensory function in pre-menopausal and early and
103 late postmenopausal patients with BMS, compared with healthy volunteers, and to
104 investigate the association between QST (Quantitative Sensory Testing) data and stage of
105 menopause. In addition, we investigated the predictive value of thermal and mechanical
106 parameters for detecting the severity of burning sensation.

107

108

Methods

Participants and Methods

This study was approved by the Ethical Committee of Nihon University School of Dentistry ((EP16 D020-1; Feb.19.2020) and was conducted in accordance with the Helsinki Declaration. Informed consent of all patients and volunteers was mandatory. All patients were recruited by the same trained examiner (NN). Systemic diseases as well as participants who had used pain medication, antidepressants, or non-steroidal anti-inflammatory drugs during the previous 1 month were excluded.

The following definitions were used to determine post-menopausal status in this study: Women who had a regular period in the past three months were categorized as premenopause. 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 post-menopausal group, while those who had reached menopause >5 years prior were classified as the late postmenopausal group [19].

The study included 36 women with BMS and 42 healthy female volunteers. Patients with BMS were divided into three groups: premenopausal BMS (n=12), early

postmenopausal BMS (n=10), and late postmenopausal BMS (n=14). Likewise, the healthy volunteers were divided into three groups: premenopausal control (n=21), early postmenopausal control (n=10), and late postmenopausal control (n=11).

QST was performed at the tip of the tongue. BMS was diagnosed according to the International Classification of Headache Disorders, Third Edition [20]. All participants were examined in a quiet, temperature-controlled room (20–23°C). The presence of intraoral spontaneous pain was assessed in patients with BMS using the Visual Analogue Scale (VAS). For the VAS, each patient was shown a paper on which a 100-mm-long line was drawn, marked at one end with 0 and at the other end with 100; the patients were asked to point to the position on the line that indicated the degree of pain they were feeling at the first visit, considering 0 as the absence of pain and 100 as the highest pain.

The QST protocol

The QST protocol used in this study was based on that of the German Research Network on Neuropathic Pain [21].

Thermal tests

Cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), and heat pain threshold (HPT) were determined by using a computer-controlled Peltier – type thermode (stimulation area 16 *16 cm², Somedic® Sales AB, Hörby, Sweden) and the Classic Method of Limits. The baseline temperature was set to 32°C, and temperature modulation was performed between 5 and 50°C. CDT and WDT were represented as the temperature difference from 32°C for non-noxious warm or cold temperature changes. The first painful cold (CPT) or hot (HPT) sensation was recorded, and TSL was determined by alternating warm and cold stimuli. The investigators instructed the patients to press a button as soon as they noticed the required sensation. Subjects had to keep their eyes closed during the entire QST procedure. Three repetitive measurements were taken to reduce bias, and thresholds were represented as means.

Mechanical tests

The mechanical QST protocol used in this study was comprised 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 (VDT), and pressure pain threshold (PPT). For a full discussion of the protocol, see [21]. MDT was investigated with a standardized set of modified von Frey filaments (Optihair2®-Set, Marstock Nervtest, Germany) and using the “Method of Limits” with forces between 0.125 and 512 mN graded by a factor of 2 (1–2 s contact time). For MPT, custom-made weighted pinprick stimuli with a flat contact area of 0.25 diameter were used. Five repetitive measurements were performed for MDT and MPT and presented as the geometric mean. MPS was measured using pinprick stimuli and calculated as the geometric mean of all numerical ratings. DMA was assessed by using soft stimuli with a cotton wisp exerting a force of ~5 mN, a cotton wool tip fixed to an elastic strip (~100 mN), and a cotton wool tip fixed to a stiff strip (~200–400 mN). WUR was evaluated by applying repeated painful stimuli (single pinprick stimulus 128 mN compared with a series of 10 repetitive pinprick stimuli of the same intensity). VDT was investigated by applying a Rydel–Seiffer (Aesculap, Tuttlingen, Germany) graded tuning fork (64 Hz, 8/8 scale) over the tongue in three stimulus repetitions.

Statistical analyses

Unpaired t test was used to determine the significance of any differences between the QST results of premenopausal, early postmenopausal, and late postmenopausal patients

with BMS and healthy controls. All data in the text and table are presented as means $\pm$ standard deviations (SD). To examine differences between patients with BMS and 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 [22]. Briefly, $Z\text{-score} = (\text{single premenopausal patient with BMS } X - \text{premenopausal control means}) / \text{premenopausal control SD}$, or $(\text{single early postmenopausal patient with BMS } X - \text{early postmenopausal control means}) / \text{early postmenopausal control SD}$, or $(\text{single late postmenopausal patient with BMS } X - \text{late postmenopausal control means}) / \text{late postmenopausal control SD}$. A Z-score greater than ± 1.96 (i.e., outside the 95% confidence interval [CI]) was considered an abnormal value. A positive Z-score indicated sensory gain, and a negative Z-score indicated sensory loss. Z-scores in the figures are presented as means $\pm$ standard errors.

In addition, multiple regression analysis was performed to define the contribution of the independent variables such as thermal parameters (CDT, WDT, TSL, CPT, and HPT) and mechanical parameters (MDT, MPT, VDT, PPT, WUR, and MPS) to the dependent variable (VAS: spontaneous pain) in the premenopausal, early postmenopausal, and late postmenopausal patients with BMS. All statistical analyses

were performed using SPSS (ver. 27 for Windows; IBM, Tokyo, Japan). Significance level was set at $p<0.05$ for all statistical tests.

Results

There was no significant difference in age between premenopausal patients with BMS (40.1±6.0 years) and premenopausal controls (45.2±2. years 4), between early postmenopausal patients with BMS (53.2±2.7 years) and early postmenopausal controls (55.6±2.8 years), and between late postmenopausal patients with BMS (70.1±5.0 years) and late postmenopausal controls (64.9±10.8 years). The mean severity of oral mucosal burning pain (spontaneous pain) in premenopausal, early postmenopausal, and late postmenopausal patients with BMS (53.2±2.7 years) was 31.8±25.3, 47.0±28.7 and 52.7±32.5, respectively.

Table 1 shows the raw data at the tongue for all QST in the premenopausal, early postmenopausal, and late postmenopausal BMS groups. Likewise, QST raw data in the premenopausal, early postmenopausal, and late postmenopausal control groups are showed in Table 2.

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218

219 PPT was significantly decreased in the premenopausal BMS group compared to
220 premenopausal controls ($p<0.01$). Among the early postmenopausal groups, VDT was
221 significantly decreased in the BMS group compared with controls ($p<0.05$). In the late
222 postmenopausal groups, significant differences were observed in the comparison of CPT
223 and HPT between controls and patients with BMS, indicating cold and heat hyperalgesia
224 at the tongue ($p<0.01$) (Table 1).

225

226 **Z-score**

227 In the premenopausal and early postmenopausal BMS groups, the means of all the
228 parameters on the tongue remained within the 95% CI of the baseline reference database
229 (Z-scores within ± 1.96 ; Fig. 1a and Fig. 2a). Of 12 patients with BMS in the
230 premenopausal group, abnormal Z-scores at the tongue were detected for WDT in two
231 patients, TSL in three patients, CPT in two patients, MDT in one patient, MPT in one
232 patient, VDT in one patient, PPT in seven patients, WUR in one patient, and MPS in one
233 patient. (Fig. 1b). Of 10 patients in the early postmenopausal BMS group, abnormal Z-
234 scores at the tongue were detected for CDT in one patient, WDT in one patient, TSL in

one patient, CPT in two patients, MPT in two patients, VDT in one patient, PPT in one patient, and MPS in two patients (Fig. 2b).

On the other hand, in the late post-menopausal BMS group, Figure 3a shows a mean gain of function by CPT and HPT at the tongue ($Z=2.08$ and 3.38 , respectively). Of 14 patients, individually, abnormal Z-scores at the tongue were detected for CDT in two patients, WDT in five patients, TSL in four patients, CPT in seven patients, HPT in nine patients, MPT in one patient, VDT in one patient, PPT in one patient, and MPS in two patients. (Fig. 3b).

Regression analysis

A stepwise multiple regression analysis was performed with spontaneous pain as the dependent variable. The model using mechanical parameters (MDT, MPT, VDT, PPT, WUR, MPS) explained 17.1% of variance in spontaneous pain in premenopausal patients with BMS [adj. $R^2=0.58$; $F=3.56$; $p=0.025$]. VDT 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, TSL CPT, and HPT) was not significantly predictive for spontaneous pain in premenopausal patients with BMS [adj. $R^2=0.03$; $F=0.93$; $p=0.30$]. When analyzed for the early postmenopausal BMS group, the model was not predictive when the predictor variables were mechanical [adj. $R^2=0.32$; $F=0.63$; $p=0.45$] or thermal [adj. $R^2=0.55$; $F=0.36$; $p=0.79$]. Similarly, when analyzed for the late postmenopausal BMS group, the model was not predictive when the predictor variables were mechanical [adj. $R^2=0.17$; $F=0.68$; $p=0.76$] or thermal [adj. $R^2=0.38$; $F=2.64$; $p=0.06$] (Table 4).

Discussion

In the present study, the QST results for CPT and HPT 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. found a significant association between years after menopause and cold and warmth sensitivity thresholds [17]. One possible reason for the increased CPT may be that drastic menopausal changes induce a significant reduction in neuroprotective steroids. This reduction in neuroprotective and neuroregenerative capacities may preferentially put small A δ fibers at a risk [23]. Another

possible mechanism is that neuroactive steroids may directly or indirectly affect cold sensitivity in postmenopausal patients with BMS. Yilmaz et al. and Hartmann et al. also reported cold hyperalgesia in patients with BMS but not in patients with lingual nerve impairment [15, 24].

The Z-score in the postmenopausal B patients with MS also showed an increased response of the tongue to cold pain stimulation (CPT 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 [15]. Zagury et al. reported an extended painful aftersensation following cold application in atypical odontalgia patients compared with control subjects [25]. 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. Several histological studies related to cold hypersensitivity have also been reported [26,27]. Possible mechanisms that underlie the cold hypersensitivity in chronic pain may include increased expression and activity of the transient receptor potential ankyrin 1 (TRPA1) receptors on trigeminal sensory neurons [28]. The BMS mouse model showed overexpression of both TRPV1 and TRPA1 receptors in the trigeminal ganglion [29]. Recent animal studies also

demonstrated low incidences of transient receptor potential melastatin 8 (TRPM8) and TRPV1 co-expression in trigeminal ganglion neurons [30]. Thus, cold pain might be mediated via the activation of TRPM8-expressing polymodal nociceptor cold receptors. The modulation of the interaction of TRPV1, TRPA1 receptors, and TRPM8 in trigeminal ganglion neurons may contribute to cold hyperalgesia.

Late post-menopausal patients with BMS also showed an increased response of the tongue to heat pain stimulation (HPT Z-score=3.38). Grushka et al. demonstrated that patients with BMS were significantly less tolerant of heat pain on the tongue than control subjects [16]. It is well known that the psychophysical responses to noxious thermal stimuli are dependent not only on stimulus intensity, but also duration of stimulus, interstimulus interval, and characteristics of prior conditioning stimuli. It is possible that duration testing for heat pain tolerance may cause sensitization of the C fiber polymodal nociceptors and A δ heat nociceptors in patients with BMS [30]. This sensitization may account for the decreased heat pain tolerance of patients with BMS.

There are several animal studies on sex hormones and trigeminal somatosensory function in terms of sensitization [13, 32]. Neuroactive steroids are synthesized by

cutaneous cells and neurons, glia, and Schwann cells in the peripheral and central nervous systems [1]. Neuroactive steroids may modulate the transmission and modulation of thermal nociceptive signals from the orofacial regions.

Decreased heat pain tolerance may be dependent upon temporal summation, which may occur more readily with higher temperatures and longer durations. Shinozaki et al. proposed that the mechanism of pain habituation observed during the repetition of a noxious stimulus is explained by C - fiber function, and lack of this phenomenon may be associated with impaired function of C fibers [33]. Recently, we demonstrated in another study that BMS is associated with a deficit in inhibitory conditioned pain modulation [34]. The pain inhibitory system was impaired when the 47°C conditioning stimulus was applied to the hand in patients with BMS [34]. It is possible that this pain inhibitory impairment may have developed due to the lack of habituation of pain sensation when applying noxious thermal stimulation to the hand. This may be associated with the increased response to thermal nociceptive stimuli, which may result in heat hyperalgesia.

In this study, we also investigated the relationship 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 VDT alone was found to be significant. Additionally, in the premenopausal stage, PPT at the tongue was significantly lower in the BMS group than in the control group.

Martínez-Jauand et al. demonstrated that chronic pain conditions with early age-of-onset of menopause displayed greater painful and non-painful mechanical sensitivity than patients with late age-of-onset of menopause [34]. In fact, prevalence of orofacial pain with migraine or temporomandibular joint disorders seems to be much higher during peak reproductive years [35, 36]. Hormonal changes associated with pre-menopause or early menopause may modulate pain hypersensitivity. Thus, ovarian hormones may exert their effect on somatosensory brain activity by altering opiate neurotransmitters [38].

To the best of our knowledge, this is the first study to demonstrate that QST can generate objective information (specifically the VDT) that aids in the early detection of BMS in premenopausal patients. Treatment for BMS is more effective when introduced

early [39]. Therefore, the early detection and timely referral to an orofacial pain specialist are critical and may reduce the chronic pain and associated cost.

This study had some limitations. First, circulating sex hormone quantities, which vary according to the ovulatory phase of the menstrual cycle, may affect sensory changes in the masticatory muscle, abdomen, and lower back areas in healthy women. In this study, we did not determine the phase of the menstrual cycle in healthy volunteers. This may have affected the QST results. Further studies are needed to determine whether a relationship exists between QST data and progesterone and estrogen levels. Also, in the late postmenopausal group, HPT and TSL trended towards 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 lacked the power to detect significant predictive value for those thermal tests.

Conclusions

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

361 indirectly affect trigeminal somatosensory function during the postmenopausal stage in
362 patients with BMS.

363

364

365 **List of Abbreviations**

366 BMS – Burning mouth syndrome

367 CDT – Cold detection threshold, thermal sensory limen (TSL)

368 CPT – Cold pain threshold

369 DMA – Dynamic mechanical allodynia

370 HPT – Heat pain threshold

371 MDT – Mechanical detection threshold

372 MPS – Mechanical pain sensitivity

373 MPT – Mechanical pain threshold

374 PPT – Pressure pain threshold

375 QST – Quantitative Sensory Testing

376 TRPA1 – Transient receptor potential ankyrin 1

377 TRPM8 – Transient receptor potential melastatin 8

378 VAS – Visual Analogue Scale

379 VDT – Vibration detection threshold

380 WDT – Warmth detection threshold

381 WUR – Wind-up ratio

382

383

384 **Declarations**

- 385 • Ethics approval and consent to participate

386 Ethical approval was permitted by the Ethical Committee of Nihon University

387 School of Dentistry ((EP16 D020-1). Informed written consent was obtained

388 from all patients and volunteers.

- 389 • Consent for publication

390 Not applicable.

- 391 • Availability of data and materials

392 The datasets used and analysed during the current study are available from the

393 corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests.

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- Authors' contributions

NN is for thesis writing, clinical data collection and data arrangement. KO and KW are for clinical data collection. AY, EE and Y. I have reviewed the article. All the authors have read and approve the final manuscript.

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Figure Legends

Fig1a : Mean overall Z scores. Results of quantitative sensory testing (QST) (Z scores) with BMS in the premenopausal group. 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. 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). All data are presented

as mean $\pm$ SE.

Fig1b : scatter plot with individual data point (premenopausal BMS patients).

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). All data are presented as mean $\pm$ SE.

Fig2a : Mean overall Z scores. Results of quantitative sensory testing (QST) (Z scores) with BMS in the early postmenopausal group. 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. 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). All data are presented as mean $\pm$ SE.

Fig2b : scatter plot with individual data point (the early postmenopausal patients).

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). All data are presented as mean $\pm$ SE.

Fig3a : Mean overall Z scores. Results of quantitative sensory testing (QST) (Z scores) with BMS in the late postmenopausal group. 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. 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

571 pain threshold (MPT), vibration detection threshold (VDT), pressure pain threshold (PPT),
572 wind-up ratio (WUR), and mechanical pain sensitivity (MPS). All data are presented
573 as mean $\pm$ SE.

574

575 Fig3b : scatter plot with individual data point (the late postmenopausal patients).

576 Abbreviations: cold detection threshold (CDT), warmth detection threshold (WDT),
577 thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT),
578 mechanical detection threshold (MDT), mechanical pain threshold (MPT), vibration
579 detection threshold (VDT), pressure pain threshold (PPT), wind-up ratio (WUR), and
580 mechanical pain sensitivity (MPS). All data are presented as mean $\pm$ SE.

Figures

Figure 1

See the Manuscript Files section for the complete figure caption.

The early postmenopause BMS

Figure 2

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The late postmenopause BMS

Figure 3

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