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ORIGINAL ARTICLE

Age-of-onset of menopause is associated with enhanced painful and non-painful sensitivity in fibromyalgia

M. Martínez-Jauand · C. Sitges · J. Femenia · I. Cifre · S. González · D. Chialvo · P. Montoya

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Abstract Fibromyalgia (FM) is a chronic pain condition characterized by high prevalence in women. In particular, estrogen deficit has been considered as a potentially promoting factor of FM symptoms. This study was aimed to examine the relationship between age-of-onset of menopause and pain sensitivity in FM. For this purpose, pain sensitivity was assessed in 74 FM and 32 pain-free control women. All participants were postmenopausal and underwent a detailed semi-structured clinical interview, including data about menopause transition, previous history of hysterectomy or ovariectomy, and menses time. Participants were divided into two groups depending on age-of-onset of menopause: early menopause [≤49 years] vs. late menopause [>49 years]. Pain and non-pain thresholds were assessed by using cold, heat, mechanical, and electrical stimulation. FM women showed higher overall pain sensitivity as compared with healthy subjects. FM women with early age-of-onset of menopause displayed greater pain and non-pain sensitivity than FM women with late age-of-onset of menopause, whereas no differences were observed in healthy women due to age-of-onset of menopause. These results suggest that an early transition to menopause (shortening the time of exposure to estrogens) may influence pain hypersensitivity and could be related to aggravation of FM symptoms.

M. Martínez-Jauand · C. Sitges · J. Femenia · I. Cifre · P. Montoya (✉)
Research Institute on Health Sciences (IUNICS), University of the Balearic Islands, Cra. de Valldemossa km 7.5, 07122 Palma de Mallorca, Spain
e-mail: pedro.montoya@uib.es

S. González
Instituto de Biología y Medicina Experimental, CONICET, Buenos Aires, Argentina

D. Chialvo
Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET), Rosario, Argentina

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Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterized by generalized and enhanced pain sensitivity, as well as by sleep disturbance, fatigue, morning stiffness, affective and cognitive dysfunctions, and a generalized hypersensitivity to pain stimulation [1, 2]. In addition, several surveys have reported that approximately 80 to 90 % of FM patients are women [2, 3] and that FM women display significantly more symptoms than FM men [5]. Furthermore, it has been observed that directing attention to pain produced a significant inhibition of the wind-up phenomenon in FM women, but not in healthy women or men [4]. Although pathophysiological mechanisms underlying FM are still unknown, these gender-specific differences suggest the possibility that a less effective pain inhibitory mechanism in women as compared to men may be a predisposing factor in the development and maintenance of FM and in the hypersensitivity to pain characteristic of these patients. In this sense, it has been observed that FM symptoms are aggravated during sex hormone-related events such as premenstrual period, pregnancy, or postpartum [5, 6]. Moreover, it has been reported that FM patients displayed higher levels of premenstrual discomfort and dysmenorrhea, as well as less positive mood during the luteal phase of the menstrual cycle than healthy controls, suggesting that cyclic fluctuations of ovarian hormones during the menstrual cycle could be linked to pain perception in these patients [7].

Nevertheless, assessment of pain sensitivity in FM women during the course of the menstrual cycle has provided only limited and inconsistent results [7–11]. Thus, while some studies have reported elevated levels of testosterone [9] and luteal hormones [10] during the follicular phase in

FM patients as compared with healthy controls, other studies have found no significant group differences in sex hormones levels [8], or just a modest relationship between progesterone levels and pain sensitivity during the late follicular phase [11]. Accordingly, it has been suggested that pain hypersensitivity observed in these chronic pain patients could be related to menopausal transition rather than to fluctuating ovarian hormones during the menstrual cycle [12]. In this sense, epidemiological studies have revealed that FM patients show an early onset of menopause [13], and that FM symptoms frequently started or worsened after menopause [6, 13], suggesting that a reduced time of exposure to sex hormones may aggravate pain and other related symptoms. However, the relationship between altered pain sensitivity and age-of-onset of menopause has not been previously examined in FM patients.

The present study was aimed to investigate the relationship between FM syndrome and menopause. In particular, we evaluated the influence of age-of-onset of menopause on pain and non-painful sensitivity in FM patients and healthy women. For this purpose, participants' history of sex hormone-related events, clinical features such as depression and anxiety, as well as sensory thresholds to painful and non-painful stimuli were assessed in postmenopausal women. We hypothesized that pain sensitivity would be higher in FM patients with an early menopause onset than in those with later menopause onset.

Material and methods

Participants

Seventy-four women with FM (mean age±SD, 55.5±6.5) and 32 healthy controls (HC) (57.0±6.2) with comparable sociodemographic characteristics participated in the study. Only postmenopausal women were included in the study. Menopause was defined as having the last menstrual period more than 1 year ago. Subjects were excluded from the study if they were pregnant or had a neurologic disease. FM patients were included in the study if they fulfilled the classification criteria of the American College of Rheumatology [14] and refered pain as their dominant symptom. Participants were divided according with age-of-onset of menopause by using a cutoff age of 49 years [15] into "early" (40 FM patients and 17 HC) and "late menopause" (34 FM patients and 15 HC).

At the time of recruitment, participants were verbally informed about the study and a specifically designed information leaflet was given. All participants provided written consent. The study was in accordance with the Declaration of Helsinki (1991) and approved by the Ethics Committee of the University of the Balearic Islands (Spain).

Assessment of clinical pain characteristics and sex hormone-related events

All participants underwent an extensive medical and psychological semi-structured interview, including participants' history of sex hormone-related events, as well as questions about clinical pain characteristics and quality of life. Specifically, participants were asked about age-of-onset of menopause and menarche, previous experience of menstrual pain, regularity of menstrual cycle, infertility, use of hormonal contraceptives, time from last menstrual cycle, hormone replacement therapy, hysterectomy, ovariectomy, and other relevant sex hormone-related diagnoses (uterine or breast cancer, polycystic ovarian syndrome, etc.). The Beck Depression Inventory [16], the State-Trait Anxiety Inventory [17], the West Haven–Yale Multidimensional Pain Inventory (WHYMPI) [18], and the Edinburgh Handedness Inventory [19] were also completed.

Assessment of pain and non-pain sensitivity

Electrical detection thresholds Non-painful electrical thresholds were assessed by using a Grass stimulator (Model S88) coupled to a constant current unit (Grass Model CCU1, Grass Technologies, Astro-Med Industrial Park, Rhode Island, USA). Series of ascending stimulus intensities were applied on the ventral side of the non-dominant wrist by using a modified version of the electrode described by Inui and colleagues [20]. Electrical stimuli were single pulses of 1 s of duration. Stimulus intensity was manually controlled by increasing the voltage from 10 to 150 V at a rate of 10 V every 5 s. A maximum of 15 stimulus intensities were presented. Participants were instructed to say "yes" if they were feeling any electrical sensation. Participants were previously trained to recognize the sensation induced by the stimulator through an initial trial. Responses with delays greater than 3 s were considered as invalid, and trial was repeated. Electrical detection threshold was defined as the less intense electrical stimulus (from 1 to 15) which was perceived.

Mechanical thresholds Non-painful mechanical thresholds were assessed by using Von Frey monofilaments [21] (Somedic Sales AB, Hörby, Sweden) at three locations of the non-dominant body side: (1) elbow, (2) ventral surface of the wrist, (3) and index fingertip. The test was performed by touching the skin with a thick filament, and depending on participant's detection, thicker or thinner filaments were applied. A sleeping mask was used to keep participants' eyes closed during the test. Participants were instructed to say "yes" if they were feeling any sensation on the skin when touch. Responses with delays greater than 3 s were considered as invalid, and trial was repeated. The detection

threshold at one specific body location was defined as the lowest pressure perceived by the subject. Stimulation was applied in pseudo-randomized order at the three body areas.

Mechanical pain thresholds were assessed by using a digital dynamometer with a flat rubber tip (1 cm^2) (Force One, Wagner Instruments, Greenwich, Connecticut, USA) at three body locations (elbow, ventral surface of the wrist, and index fingertip). The mechanical pain threshold was defined as the amount of pressure (expressed in newtons) at which participants perceived the stimulation as painful.

Thermal pain thresholds Thermal pain thresholds were obtained by using a computer-controlled contact thermal stimulator (cold/warm plate AHP-301CPV, Teca, Schubert, Chicago, USA). Subjects were asked to put the index fingertip on the middle of the thermal plate, emphasizing to remain in a relaxed position to avoid differences due to the contact pressure. In the case of heat pain, temperature was increased from 37 to 52 °C at a rate of 0.2 °C/s. Participants were instructed to remove their fingertip from the thermal plate when pain began. Heat pain threshold was defined as the temperature intensity (in degree Celsius) at which participants first perceived heat pain.

Assessment of cold pain tolerance was conducted with the thermal plate at a constant temperature of 1 °C. Participants were instructed to keep their fingertip in contact with the thermal plate until the pain sensation was unbearable. They were also asked to rate pain intensity on a 0–100 numerical rating scale every 10 s, with 0 representing "no pain" and 100 "worst imaginable pain." Cold pain tolerance threshold was defined as the time until the fingertip was removed from the thermal plate (maximal testing time was 150 s).

Non-painful thresholds (mechanical and electrical) were evaluated three times at the non-dominant body side to avoid possible effects of handedness [22]. All pain thresholds (cold, heat, and mechanical) were assessed once bilaterally, following a pseudo-randomized order to avoid possible effects associated to summation effects on pain perception or pain lateralization. Values from right and left body sides were averaged. Different orders of non-painful and painful threshold tests were designed avoiding the consecutive presentation of two different thermal stimuli (heat and cold) or consecutive assessments at the same body side. Subjects were assessed by the same person in order to avoid experimenter bias. Subjects were tested in the lab alone with the experimenter in order to avoid social influences in pain perception [23].

Data analyses

Threshold data were previously transformed to *z* scores and a summary index was computed separately for pain and non-pain thresholds. A pain threshold index was computed by averaging *z* scores of the mechanical and heat pain thresholds, and measures of cold pain responsiveness (average of *z* scores of cold pain tolerance and continuous pain ratings during the contact with the thermal plate). A non-pain threshold index was computed by averaging *z* scores of mechanical and electrical detection thresholds (previously, *z* scores for the three body locations were separately averaged for mechanical and electrical modalities).

Differences on pain and non-pain threshold indexes were analyzed by using an analysis of variance with somatosensory measure (pain vs. non-pain threshold) as within subject factor and group (FM patients vs. HC women) and menopause onset ("early" vs. "late" menopause) as between-subjects factors. In order to control for potential effects due to hysterectomy and age, both variables were included as covariates in all statistical analyses. Post hoc tests were carried out with Bonferroni adjusted for multiple pairwise mean comparisons included in the SPSS package (SPSS Inc., Chicago, Illinois, USA). Univariate analyses of variance were also computed to test differences on clinical pain characteristics and sex hormone-related events due to menopause onset and group. Differences on frequency data were analyzed by means of Chi-square tests. The statistical significant level was set at $p<0.05$ for all comparisons.

Results

Differences between FM patients and healthy controls on clinical pain characteristics and sex hormone-related events

FM patients reported higher scores than healthy controls for depression ($F_{1,\ 102}=37.2$, $p<0.001$), trait anxiety ($F_{1,\ 104}=28.6$, $p<0.001$), and state anxiety ($F_{1,\ 104}=8.8$, $p=0.004$) (Table 1). Moreover, mean age-of-onset of menopause resulted significantly earlier in FM patients (mean±SE, 46.4±0.7) than in healthy women (mean±SE, 49.3±1.1) ($F_{1,\ 105}=5.3$, $p=0.023$). The percentage of women who suffered menstrual pain was significantly higher in FM patients (74 %) than in healthy volunteers (35.7 %) ($\chi^2=12.8$, $p<0.001$). In addition, the percentage of women with irregular menstrual cycle was also significantly higher in FM patients (33.8 %) than in healthy controls (7.1 %) ($\chi^2=7.4$, $p=0.006$). Nevertheless, no group differences were found in mean age-of-onset of menarche, frequency of hysterectomies, and previous use of hormonal contraceptives or previous hormonal replacement therapy (Table 1).

Table 2 displays sociodemographic and clinical data according to age-of-onset of menopause in FM patients. Univariate analyses of variance revealed that FM patients with early age-of-onset of menopause reported higher scores on WHYMPI subscale pain interference ($F_{1,\ 64}=6.0$, $p=0.017$), as well as lower scores on WHYMPI subscales

Table 1 Sociodemographic and clinical characteristics of FM patients and healthy controls

	FM patients (n=74)	Healthy controls (n=32)	p value[a]
Age (years)			
Mean±SE	55.5±0.7	57.0±1.1	–
Range	44–71	47–68	
Clinical data			
Depression (BDI) (mean±SE)	19.8±1.1	7.94±1.6	<0.001
State anxiety (mean±SE)	27.8±1.3	20.8±2.0	0.004
Trait anxiety (mean±SE)	34.4±1.3	22.2±1.9	<0.001
Medication (%)			0.023
Antidepressants	53.7	20.7	
Analgesic/relaxants/ NSAID	77.6	6.9	
Anxiolytics	53.7	37.9	
Hormone-related events			
Irregular menses (%)[b]	33.8	7.1	0.006
Menstrual pain (%)[b]	74.0	35.7	<0.001
Menarche onset (mean±SE)	12.3±0.2	12.6±0.3	–
Menopause onset (mean±SE)	46.4±0.7	49.3±1.1	0.023
Hysterectomy (%)	28.6	20.0	–
Use of hormonal contraceptives (%)[b]	59.7	51.7	–
Substitutive hormone therapy (%)[b]	24.3	10.3	–

BDI Beck Depression Inventory, *SE* standard error

[a] Calculated using Chi-square and one-way analysis of variance

[b] Items referred to the period previous to the experiment (during reproductive years or peri-menopausal period)

social activities ($F_{1,\ 62}$=9.9, p=0.003) and activities away from home ($F_{1,\ 62}$=6.8, p=0.011) than FM patients with late menopause onset (Table 2).

Differences on pain and non-pain thresholds due to age-of-onset of menopause

ANCOVA for pain and non-pain thresholds revealed significant effects of group ($F_{1,\ 95}$=20.9, p<.001), group × somatosensory measure ($F_{1,\ 95}$=30.7, p<.001), and group × menopause onset ($F_{1,\ 95}$=4.9, p=0.035). Post hoc analyses revealed that FM patients had lower pain thresholds than healthy controls (p<0.001), whereas no group differences were observed in non-pain thresholds (p=0.863). Post hoc results also showed that FM patients with early menopause onset displayed lower pain (p=0.038) and non-pain thresholds (p=0.005) than FM patients with late menopause onset, whereas no differences were yielded in healthy controls due to age-of-onset of menopause (Fig. 1).

Discussion

In the present study, FM women reported higher pain sensitivity, anxiety, and depression, as well as more frequent painful menses during the reproductive years and earlier age-of-onset of menopause than healthy women. No differences were observed in other hormone-related events such as hysterectomy, previous use of contraceptives, or hormone replacement therapy. Moreover, we found that age-of-onset of menopause modulated overall pain and non-pain sensitivity in FM women, but not in healthy women. Age-of-onset of menopause was also associated with higher pain interference and more reduced levels of social and outdoor activities in FM. These results suggest that hormonal abnormalities due to early age-of-onset of menopause might play an important role in the altered processing of somatosensory information in FM.

Our results are in line with previous retrospective studies showing that FM patients displayed earlier age-of-onset of menopause and higher rates of surgery-related menopause, suggesting that estrogen deficiency could be related to aggravation of FM symptoms such as pain, sleep, mood, and anxiety [13]. This hypothesis seems to be also supported by studies in which increased incidence of pain was linked to depletion of estrogen levels through administration of aromatase inhibitors (i.e., for breast cancer treatment) [24]. In a similar way, increased pain prevalence has been reported in postmenopausal women after interruption of hormone replacement therapy [25]. Nevertheless, the idea that estrogen deficiency in postmenopausal women may lead to development of musculoskeletal pain seems to be in disagreement with the observed higher prevalence of pain disorders among women in comparison with men. In this sense, it should be taken into account that the modulatory role of estrogens in pain is a complex and multi-faceted phenomenon [32]. Thus, considerable evidence has suggested that estrogens can produce both pro- and anti-nociceptive effects depending on the extent to which a physiological system is mainly involved in a particular type of pain [32]. Furthermore, it has been observed that fluctuations of ovarian hormones during the menstrual cycle and the reproductive status could have differential modulatory effects on chronic pain disorders [14]. Thus, prevalence of pain in patients with migraine [33] or temporomandibular joint disorder [34] seems to be much higher during peak reproductive years, whereas other chronic pain syndromes such as fibromyalgia [26], arthritis [27], and osteoarthritis [28] are more common after menopause. Moreover, it has been found that pain severity is increased during the late luteal and early follicular phases of the menstrual cycle in some chronic pain conditions (e.g., migraine, temporomandibular joint disorder, rheumatoid arthritis, irritable bowel syndrome) [14], whereas no pain fluctuations have been observed during the menstrual cycle in fibromyalgia [12].

Table 2 Sociodemographic and clinical data of FM patients according to age-of-onset of menopause

	Early menopause (n=40)	Late menopause (n=34)	p value[a]
Age (years)			
Mean±SE	55.5±1.0	55.5±1.1	–
Range	44–71	50–64	
Clinical data			
Pain intensity (0–10, mean±SE)	7.1±0.3	7.3±0.3	–
Depression (BDI) (mean±SE)	20.9±1.7	17.4±1.9	–
State Anxiety Inventory (mean±SE)	29.5±1.9	25.3±2.1	–
Trait Anxiety Inventory (mean±SE)	35.1±1.9	33.7±2.1	–
Medication (%)			
Antidepressants	48.6	60.0	–
Analgesic/relaxants/NSAID	73.0	83.3	–
Anxiolytics	48.6	60.0	–
WHYMPI (0–6, mean±SE)			
Social support	3.7±0.3	3.5±0.3	–
Affective distress	3.8±0.2	3.5±0.2	–
Pain interference	4.1±0.2	3.2±0.3	0.017
Pain intensity	4.3±1.9	3.9±2.1	–
Life control	3.5±0.2	4.0±0.5	–
Distracting responses	3.5±0.3	3.3±0.3	–
Solicitous responses	3.2±0.3	2.4±0.3	–
Punishing responses	2.0±0.3	1.3±0.3	–
Household chores	3.9±0.2	3.7±0.3	–
Outdoor work	2.4±0.2	2.6±0.2	–
Social activities	0.8±0.3	2.2±0.3	0.003
Activities away from home	1.8±0.2	2.7±0.2	0.011

BDI Beck Depression Inventory, *WHYMPI* West Haven–Yale Multidimensional Pain Inventory, *SE* standard error

[a]Calculated using Chi-square and one-way analysis of variance

Therefore, a deeper understanding of mechanisms by which estrogens attenuate or exacerbate pain should help to better understanding differences associated with gender or reproductive stage on pain sensitivity and prevalence of chronic pain.

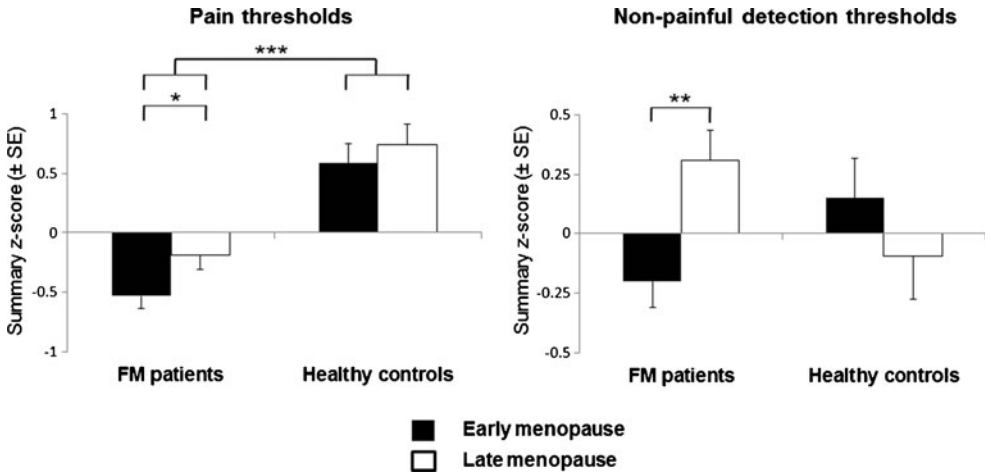

Fig. 1 Mean and error bars of painful and non-painful detection thresholds in FM patients and healthy controls categorized by age-of-onset of menopause (early or late menopause). Pain thresholds were computed by averaging z scores from pressure and cold and heat pain thresholds. Non-painful thresholds were computed by averaging z scores from mechanical and electrical thresholds. Only pain thresholds differed between FM patients and HC women. Moreover, FM patients with an early age-of-onset of menopause revealed lower pain and detection thresholds as compared with FM patients with a late age-of-onset of menopause. No significant differences were found due to age-of-onset of menopause in healthy controls. Data are expressed as means of z scores±SE. *p<0.05; **p<0.01; ***p<0.001, significant differences between groups

We also found that FM patients were more sensitive to pain than healthy controls, and that responses to painful and non-painful stimuli were significantly modulated by age-of-onset of menopause in FM. Thus, FM women with early age-of-onset of menopause displayed more pain sensitivity than FM women with early age-of-onset of menopause, whereas no differences were yielded in healthy controls. These findings are in accordance with previous studies suggesting that heightened pain sensitivity may be the result of generalized central sensitization in chronic pain conditions as FM [1, 29]. There are several mechanisms by which hormonal changes associated with early menopause could modulate pain hypersensitivity and central sensitization in chronic pain patients. Thus, for instance, ovarian hormones could exert their influence on somatosensory brain activity by altering opiate neurotransmitter systems [12]. Indeed, decreased μ-opioid receptor availability in response to tonic pain has been observed in FM patients as compared to healthy subjects over pain-related brain areas (i.e., amygdala, cingulate cortex, nucleus accumbens) [30], suggesting that sustained activation of μ-opioid receptors by endogenous agonists released to alleviate pain could ultimately lead to downregulation of receptor density or receptor function (or both). Furthermore, in vivo neuroimaging studies have revealed that women had higher μ-opioid receptor binding potential than men during the reproductive years, but lower than men after menopause [31]. According with the authors, these changes in the postmenopausal women suggest that the adult hormonal milieu is capable of modulating the opioid brain system. Thus, it could be possible that a shortening of exposure time to estrogens during reproductive years as it occurs in postmenopausal FM women with early age-of-onset of menopause may have led to an abnormal downregulation of μ-opioid receptors in the brain and, therefore, to enhanced pain hypersensitivity in comparison with postmenopausal FM women with late age-of-onset of menopause.

In the present study, we also found that FM women with early age-of-onset of menopause reported higher pain interference than FM women with late age-of-onset of menopause. In this sense, the psychosocial impact of traumatic episodes such as early or surgical menopause on chronic pain and pain hypersensitivity should be also considered. Previous studies have shown that hysterectomy and surgical menopause are associated with higher risk for depression especially in young women [32], and that persons with premature ovarian failure reported higher levels of depression and perceived stress, as well as lower levels of self-esteem and life satisfaction compared to general population [33, 34]. Moreover, it has been observed that FM patients with clinically significant post-traumatic stress disorder (PTSD) symptoms reported greater levels of avoidance, hyperarousal, anxiety, and depression than did FM patients without PTSD symptoms [35]. In line with this interpretation, animal and human studies have also demonstrated that trauma-exposed individuals are more sensitive to painful stimulation than non-trauma-exposed individuals [36, 37].

Nevertheless, these findings have to be considered with caution. First, biochemical analyses should be carried out to corroborate changes in estrogen and other sex hormones in women with early or late age-of-onset of menopause. Second, information concerning menopause transition was collected retrospectively; therefore, possible recall biases should be taken into account. Third, FM affects not only to midlife women but also to men and persons at different ages. Thus, hormonal changes associated with menopause transitions may act as aggravators of FM symptoms.

Conclusions

To our knowledge, this is the first study showing a relationship between early age-of-onset of menopause and pain sensitivity in FM patients. Our findings support the notion that an abrupt decline or a reduced time of exposure to ovarian hormones may contribute to pain hypersensitivity in musculoskeletal chronic pain syndromes such as FM.

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