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Menopause could be involved in the pathogenesis of muscle and joint aches in mid-aged women

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ABSTRACT

Background: Muscle and joint aches (MJA) are frequently observed among menopausal women. They impair quality of life and are a burden to the healthcare system.
Objective: To analyze the relation between MJA and several variables related to the menopause.
Methods: In this cross-sectional study, 8373 healthy women aged 40–59 years, accompanying patients to healthcare centers in 18 cities of 12 Latin American countries, were asked to fill out the Menopause Rating Scale (MRS) and a questionnaire containing personal data.
Results: Mean age of the whole sample was 49.1 ± 5.7 years, 48.6% were postmenopausal and 14.7% used hormone therapy (HT). A 63.0% of them presented MJA, with a 15.6% being scored as severe to very severe according to the MRS (scores 3 or 4). Logistic regression model determined that vasomotor symptoms (OR: 6.16; 95% CI, 5.25–7.24), premature menopause (OR: 1.58; 95% CI, 1.02–2.45), postmenopausal status (OR: 1.43; 95% CI, 1.20–1.69), psychiatric consultation (OR: 1.93; 95% CI, 1.60–2.32) and the use of psychotropic drugs (OR: 1.35; 95% CI, 1.08–1.69) were significantly related to the presence of severe-very severe MJA. Other significant variables included: age, tobacco consumption and lower education. Self perception of healthiness (OR: 0.49; 95% CI, 0.41–0.59), private healthcare access (OR: 0.77; 95% CI, 0.67–0.88) and HT use (OR: 0.75; 95% CI, 0.62–0.91) were significantly related to a lower risk for the presence of severe-very severe MJA.
Conclusion: In this large mid-aged sample the prevalence of MJA was high, which was significantly associated to menopausal variables, especially vasomotor symptoms. This association may suggest a potential role of mid-life female hormonal changes in the pathogenesis of MJA.

1. Introduction

Research related to muscle and joint aches (MJA) has increased in the last decade as a consequence of its high prevalence and the increased costs (personal and institutional) they generate [1–3]. An estimated 10% of the general population suffer this complaint, mainly mid-aged women and when it is generalized and accompanied by sleep and mood problems, it is known as fibromyalgia [4]. The etiology of the fibromyalgia syndrome is unknown but it involves neurophysiological disorders related to pain perception and the modulation of mood, sleep and cognition [5]. In this sense, tricyclic antidepressants, serotonin/noradrenaline reuptake inhibitors and pregabalin have shown effectiveness in decreasing pain and fatigue [6]. On the other hand, there is the climacteric syndrome which is a group of symptoms mainly originated by decreased ovarian hormone secretion, causing vasomotor symptoms (VMS), mood disorders, sleep complaints and frequently MJA [7].

As with the climacteric syndrome, fibromyalgia is related to neurotransmission failure; hence it is not of surprise that several antidepressants be useful for the treatment of both conditions [8]. As fibromyalgia and the climacteric syndrome share similar epidemiology, etiology, symptomatology and therapy this recently

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lead us to propose that in some patients with fibromyalgia etiology may rely on the hormonal changes seen during the climacteric [9]. This hypothesis is not only important from a theoretical point of view yet also a clinical one owing to the fact that fibromyalgia has no successful treatment; whereas hormone therapy (HT) is highly effective for the management of the climacteric syndrome. Independent of diagnosis, MJA are relevant in both syndromes. The aim of the present study was to relate MJA with various factors related to the climacteric and determine the correlation between the intensity of MJA and climacteric symptoms. This relationship could suggest a possible role for female mid-aged hormonal changes in the etiology of MJA.

2. Method

2.1. Study design and participants

The present document represents a data reanalysis of a cross-sectional study, of the Collaborative Group for Research of the Climacteric in Latin America (REDLINC IV) [10], originally designed to assess menopausal symptoms and related risk factors in mid-aged Hispanic women (40–59 years) accompanying patients attended at 22 health centers located in 18 Latin American cities with populations of more than 500,000 inhabitants in 12 different countries. More details of involved researchers, cities, clinical centers and used methodology in this REDLINC study and prior ones can be found elsewhere [10–13]. A minimal sample size of 380 participants per center was calculated for the original study considering that each center covered an estimated population of 50,000 women [14] and assuming that 50% would present menopausal symptoms [15] with a 5% desired precision and 95% confidence level. Healthiness status was defined by the National Center for Health Statistics as that compatible with the performance of daily routines [16]. Women who were indigenous, black or pregnant or did not consent to participate or were incapable of understanding the items included in the questionnaire were excluded.

2.2. Procedure

Women fulfilling the inclusion criteria were requested to fill out the Menopause Rating Scale (MRS) and a general data questionnaire. All participants were informed about the research and its purposes, the MRS and its content and provided written consent prior to any interview according to the principles of the Helsinki Declaration [17]. The research protocol of this study was reviewed and approved by the Bioethics Committee of the PROSAM Foundation, Santiago de Chile, Chile.

2.3. Variables included in the general questionnaire

2.3.1. General data

In order to record all data, an itemized questionnaire was previously constructed and validated among 50 women before implementation at the Latin American centers affiliated to the REDLINC.

2.3.2. Studied variables

Data included: age (years), parity, REDLINC center number (city and country), menopausal status (pre-, peri- or post), years since menopause onset, surgical menopause (yes/no), sexual status in last 4 weeks (active or inactive), educational level (expressed in years), accessed healthcare system (free-minimal cost [<25% of private consultation fee], or paid [paying more than the minimal cost]). Daily temperature (maximum average) and city location (altitude from sea level) were also registered.

2.3.3. Lifestyle and other personal factors

This section included: current smoking habit (yes/no), church attendance, history of sexual abuse and if currently having a stable partner or perception of healthiness status (yes/no). Female insufficient educational level was considered as 12 years or less of study [18].

2.3.4. Medical care and drug use

Variables included in this section were: history of psychiatric attention (yes/no) and the use of psychotropic drugs (yes/no), menopausal HT (yes/no), alternative therapies for the menopause (yes/no) or oral contraceptive pills (yes/no).

2.3.5. Menopausal status definitions

Concerning the menopausal status the following definitions were used: premenopausal (women having regular menses); perimenopausal (irregularities >7 days from their normal cycle) and postmenopausal (no menses in the last 12 months). The latter was further divided as early postmenopausal (1–4 years) and late postmenopausal (≥5 years)[19]. Those with bilateral oophorectomy were considered as postmenopausal. Premature menopause was defined as that occurring before 40 years of age [20].

2.4. The Menopause Rating Scale (MRS)

The MRS is composed of 11 items that assess menopausal symptoms divided into three subscales: (a) *somatic*: hot flushes, heart discomfort, sleeping problems and muscle and joint problems (items 1–3 and 11, respectively); (b) *psychological*: depressive mood, irritability, anxiety and physical and mental exhaustion (items 4–7, respectively); and (c) *urogenital*: sexual problems, bladder problems and dryness of the vagina (items 8–10, respectively). Each item can be graded by the subject from 0 (not present) to 4 (1 = mild; 2 = moderate; 3 = severe; 4 = very severe) [21]. For a particular individual, the total score per each subscale is the sum of each graded item contained in that subscale. The total MRS score is the sum of the scores obtained for each subscale. The present analysis focused on data obtained with items 1 and 11 which assess VMS and MJA, respectively. Severe-very severe VMS and MJA were those displaying scores 3 or 4 [22]. The MRS has been translated to more than 27 languages. For this research the Spanish language version was used [23], which has been validated in Ecuador and Chile [24,25]. More details of the scale and its scoring system can be found elsewhere [26,27].

2.5. Statistical analysis

Data analysis was performed using the EPI-INFO statistical program (Version 3.5.1, 2008, Centers for Disease Control and Prevention, Atlanta, GA, USA; WHO, Basel, Switzerland). Results are presented as mean ± standard deviations, percentages (95% confidence intervals, CI) and odds ratios. The Kolmogorov–Smirnov test was used to assess the normality of data distribution and the Bartlett test to evaluate the homogeneity of the measured variance. According to this, group comparisons were performed with the Student's *t*-test (two independent samples) or analysis of variance (several independent samples) for parametric continuous data; and the Mann–Whitney *U* test (two independent samples) or the Kruskal–Wallis test (several independent samples) for non-parametric continuous data. According to each case, percentages between groups were evaluated with the chi-square test (straight or for the linear trend). Logistic regression analysis was performed to determine factors related to the presence of severe/very severe MJA. For this, scores obtained with item 11 of

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the MRS (continuous variable) were transformed into a categorical one, now considered as cases (dependant variable) those scoring 3 or 4 (recoded as 1; severe/very severe MJA). Scores 0, 1 and 2 were recoded as 0. Bivariate analysis (Data not shown in table) was then performed to test recoded independent variables (yes = 1 and no = 0). Those achieving a $p = 0.20$ were then used to construct a final logistic regression model. These variables included: older age (≥50 years, median), severe/very severe VMS (MRS item 1 scoring 3 or 4), postmenopausal status, premature menopause, surgical menopause, nulliparity, having a partner, sexually active, history of rape, medication use (contraceptives, HT or alternatives for the menopause, psychiatric drugs), history of psychiatric care, residency at high-altitude (>2500 m) or hot-climate (average maximum temperature >30 °C), access to private health care, low schooling (12 or less years), current smoking, church attendance and self-perceived healthiness. Interactions between significant variables found during regression model construction were also considered for the final model. Adequacy of the regression model was demonstrated with the Hosmer–Lemeshow goodness of fit test.

3. Results

A total of 8394 women fulfilled inclusion criteria and were requested to participate at 22 participating health centers in 12 Latin American countries. Refusal rate for participation was 6.5% and 21 subjects provided incomplete data, leaving 8373 complete surveys for analysis. General characteristics of all studied women and in accordance to the severity of MJA are depicted in Table 1.

Overall mean age and educational level of surveyed women was 49.1 ± 5.7 and 11.6 ± 4.4 years, with 43.8% accessing a private healthcare system. Mean parity was 2.6 with 69.0% of them having a stable partner and sexual activity in 76.9%. One third of women lived at high latitude and 45.4% in cities with mean daily temperatures above 30 °C. Nearly half were postmenopausal (48.6%), 14.1% had surgical menopause and 6.0% used oral contraceptives, 14.7% HT and 7.6% alternative therapies for the treatment of their menopausal symptoms. An 11.6% had a history of psychiatric care, 4.4% history of rape and 8.0% were using psychotropic drugs. Nearly all women had the perception of being healthy (90.5%). Despite this, a 63.0% of all surveyed women presented MJA, with a 15.6% of these being scored as severe to very severe.

General characteristics significantly differed when women with severe/very severe MJA were compared to those with mild-moderate aches and those without the symptom. Indeed, women with severe-very severe MJA were older, less educated and displayed higher rates of being postmenopausal and surgically menopausal, psychotropic drug use and past psychiatric consultation and rape. Overall, perception of healthiness was lower in women with severe/very severe MJA as compared to those without MJA (82.6% vs. 92.0%, $p = 0.0001$).

Prevalence of severe/very severe MJA increases two fold in women aged 55–59 years as compared to those 40–44 (10.2% vs. 20.8%; OR: 2.31; 95% CI, 1.93–2.77) (Table 2). Impact was however more important when variables related to the menopause were analyzed. Indeed prevalence increases three fold in women five or more years postmenopausal compared to premenopausal ones aged 40–44 (7.9% vs. 21.4%; OR: 3.19; 95% CI, 2.56–3.97). Women with surgical menopause also displayed a higher prevalence of severe/very severe MJA (14.6% vs. 21.6%, OR: 1.61; 95% CI, 1.37–1.88). A much more significant relation was observed with VMS. Prevalence of severe/very severe MJA increased from 8.2% observed in women without VMS to 60.2% in those with very severe VMS (OR 16.95; 95% CI, 13.22–21.74). MJA prevalence did not differ in relation to HT use, however women on oral contraceptives displayed a lower prevalence of these symptoms (16.1% vs. 8.7%; OR: 0.50; 95% CI, 0.36–0.69).

Logistic regression model displayed in Table 3 shows that factors related to severe/very severe MJA were mainly those linked to the menopause. The top three significant factors were: the presence of severe/very severe VMS (OR: 6.16; 95% CI, 5.25–7.24), premature menopause (OR: 1.58; 95% CI, 1.02–2.45) and being postmenopausal (OR: 1.43; 95% CI, 1.20–1.69). Other significant factors included: history of psychiatric care (OR: 1.93; 95% CI, 1.60–2.32), history of rape (OR: 1.38; 95% CI 1.04–1.82), use of psychotropic drugs (OR: 1.35; 95% CI, 1.08–1.69), older age (OR: 1.39; 95% CI, 1.18–1.65), tobacco use (OR: 1.21; 95% CI, 1.03–1.42) and lower educational level (OR: 1.16; 95% CI 1.01–1.34).

Self perception of healthiness (OR: 0.49; 95% CI, 0.41–0.59), accessing private healthcare (OR: 0.77; 95% CI, 0.67–0.88), HT use (OR: 0.75; 95% CI, 0.62–0.91), living at high altitude and

Table 1
Epidemiological characteristics of all studied women and according to the severity of muscle and joint aches.

Characteristics	All ($n = 8373$)	Muscle and joint aches[a]			p-Values[*]
		Absent ($n = 3100$)	Mild-moderate ($n = 3966$)	Severe-very severe ($n = 1307$)	
Age (years)	49.1 ± 5.7	47.5 ± 5.6	49.9 ± 5.7	50.7 ± 5.6	0.0001[2]
Education (years)	11.6 ± 4.4	11.7 ± 4.4	11.9 ± 4.4	10.7 ± 4.5	0.0001[2]
Private healthcare access (%)	43.8	43.9	46.0	37.2	0.0001[4]
Has a stable partner (%)	69.0	72.0	67.8	65.6	0.0001[4]
Sexually active (%)	76.9	81.1	75.6	70.7	0.0001[4]
Parity	2.6 ± 1.6	2.5 ± 1.5	2.6 ± 1.6	2.7 ± 1.7	0.0001[3]
Living at high altitude (>2500 m, %)	31.9	31.7	33.1	29.0	0.0001[4]
Living in hot cities (>30 °C, %)	45.4	45.7	45.2	45.4	0.0200[4]
Postmenopausal (%)	48.6	37.3	52.9	62.4	0.0001[4]
Surgically menopausal (%)	14.1	11.0	14.6	19.4	0.0001[4]
HT use (%)	14.7	13.0	16.4	13.6	0.0002[4]
Oral contraceptive use (%)	6.0	8.5	5.0	3.4	0.0001[4]
Alternative menopausal therapy use (%)	7.6	5.9	8.6	9.0	0.0001[4]
Current smoker (%)	17.4	18.2	15.7	20.6	0.0001[4]
History of psychiatric care (%)	11.6	8.3	11.2	20.2	0.0001[4]
History of rape (%)	4.4	4.0	3.9	6.5	0.0001[4]
Psychotropic drug use (%)	8.0	6.6	7.6	12.9	0.0001[4]
Healthiness status (self-perception) (%)	90.5	92.0	92.1	82.6	0.0001[4]

Data are presented as mean ± standard deviations or percentages.
[a] Muscle and joint aches (item 11 of the MRS) absent: score 0; mild/moderate: scores 1 or 2; severe/very severe: scores 3 or 4.
[*] p-Values as determined with ANOVA[2], the Kruskall Wallis test[3] or the chi-square test[4].

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Table 2
Prevalence of severe-very severe muscle and joint aches according to several female variables related to the menopause.

Variables	No. of women	% Women with severe/very severe muscle and joint aches[a] % (95% CI)	OR (95% CI)[b]
Age (years)			
40–44	2208	10.2 (9.0–11.5)	1.00
45–49	2183	13.7 (12.3–15.3)	1.40 (1.16–1.70)
50–54	2066	18.6 (16.9–20.3)	2.01 (1.68–2.42)
55–59	1916	20.8 (19.0–22.7)	2.31 (1.93–2.77)
p-Value[*]		*0.0001*[3]	
Premenopause			
40–44 years	1523	7.9 (6.6–9.4)	1.00
≥45 years	1132	13.2 (11.3–5.3)	1.77 (1.36–2.31)
Perimenopause	1648	13.5 (11.9–15.2)	1.82 (1.43–2.32)
Early postmenopause	1821	18.3 (16.6–20.2)	2.63 (2.09–3.30)
Late postmenopause	2249	21.4 (19.8–23.2)	3.19 (2.56–3.97)
p-Value[*]		*0.0001*[3]	
Surgical menopause			
No	7196	14.6 (13.8–15.5)	1.0
Yes	1177	21.6 (19.3–24.1)	1.61 (1.37–1.88)
p-Value[*]		*0.0001*[4]	
Vasomotor symptoms (item 1 MRS)			
Absent (score 0)	3806	8.2 (7.4–9.1)	1.00
Mild (score 1)	1800	11.5 (10.1–13.1)	1.46 (1.20–1.76)
Moderate (score 2)	1960	20.0 (18.3–21.9)	2.80 (2.37–3.30)
Severe (score 3)	440	39.8 (35.2–44.5)	7.40 (5.87–9.32)
Very severe (score 4)	367	60.2 (55.0–65.2)	16.95 (13.22–21.74)
p-Value[*]		*0.0001*[3]	
Hormone therapy use			
No	7143	15.8 (15.0–16.7)	1.00
Yes	1230	14.5 (12.6–16.6)	0.90 (0.76–1.08)
p-Value[*]		*0.23*[4]	
Oral contraceptive use			
No	7869	16.1 (15.2–16.9)	1.00
Yes	504	8.7 (6.5–11.6)	0.50 (0.36–0.69)
p-Value[*]		*0.0001*[4]	

CI, confidence interval; OR, odds ratios.
[a] Severe/very severe muscle and joint aches (item 11 of the MRS): score 3 or 4.
[b] Calculated ORs for each category as compared to the reference OR 1.00 group.
[*] *p*-Values as determined with chi-square test for the linear trend[3] or the chi-square test[4].

being sexually active were factors related to a lower risk of presenting severe/very severe MJA. Non significant variables included: nulliparity, having a stable partner, surgical menopause, oral contraceptive use, use of alternative menopausal therapies, church assistance and living in cities with average maximum temperatures >30 °C.

Table 3
Risk factors related to severe-very severe muscle and joint aches[a]: logistic regression analysis.

Risk factors	OR	95% CI
Severe-very severe VMS[b]	6.16	5.25–7.24
History of psychiatric consulting	1.93	1.60–2.32
Premature menopause	1.58	1.02–2.45
Postmenopausal status	1.43	1.20–1.69
Age ≥ 50 years	1.39	1.18–1.65
History of rape	1.38	1.04–1.82
Use of psychotropic drugs	1.35	1.08–1.69
Current smoker	1.21	1.03–1.42
Education ≤ 12 years	1.16	1.01–1.34
Living at high altitude (≥2500 m)	0.82	0.71–0.95
Sexually active	0.79	0.68–0.91
HT use	0.75	0.62–0.91
Access to private healthcare system	0.77	0.67–0.88
Healthiness status (self-perception)	0.49	0.41–0.59

VSM, vasomotor symptoms; HT, hormone therapy; OR, odds ratios; CI, confidence intervals; Non significant variables are not displayed.
[a] Item 11 of the MRS scored as 3 or 4.
[b] Item 1 of the MRS scored as 3 or 4.

4. Discussion

The present study shows that prevalence of MJA was high among mid-aged women (63.0%) with 15.6% of them rating the problem as severe to very severe. Various studies have also reported the prevalence of MJA using the same MRS. In this sense, our data is consistent with those presented by Chuni and Sreeramareddy [28] who reported that 68.6% of women aged 40–65 have MJA. Another study using the MRS found that 58% of Nigerian women aged 40–60 presented MJA, the most prevalent menopausal symptoms [29]. Similarly, Monterrosa et al. [30] found that 43.5% of mid-aged mestizo Colombian women complained about MJA, and that this rate increased to 77.1% in those who were black.

Besides finding in our study a high prevalence of women with MJA, it was also observed that women with this complaint display epidemiological characteristics that differ to those who do not present the problem. In general those with the complaint were older, had lower socio-economical status, referred a history of psychiatric care and were mostly postmenopausal. Regarding older age as a risk factor for MJA, a German study reported that this type of discomfort is more prevalent in women after age 50 [31] and could translate, in part, an increased prevalence of osteoarthritis (OA) observed with aging [32]. Another study, carried out within a representative Austrian sample, found that 36.4% of individuals over age 15 have had MJA in the last three weeks [33]; after regression analysis, higher age was the only risk factor associated to pain. The present Latin American research found that the risk of

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presenting severe-very severe MJA increases two fold when women aged 40–44 are compared to those 55–59.

In our study, another variable related to a higher risk of presenting severe/very severe MJA was socio-economical status; those more symptomatic had lower educational level, a recognized poverty indicator for Latin America [18]. Indeed, it is reasonable to understand that these women are less likely to finance their health care. Our data is in accordance with a Swedish study that also reported low socio-economic status linked to a higher rate of MJA [34]. Even in relatively egalitarian societies such as Norway musculoskeletal pain is more severe in individuals living in a less residential area as compared to those living in a more affluent one [35].

Psychiatric morbidity is another factor that increases the risk of more intense MJA. A multicenter study found that individuals with MJA displayed a previous history of psychiatric disorders such as major depression, panic disorders and significant psychological distress [36]. Similarly, repeated traumatic experiences (during childhood and as adults) can be observed more frequently in patients with MJA, a feature seen in fibromyalgia [37]. Psychiatric evaluation in patients with this type of pain reveals a diagnosis of psychiatric illness in 87% of cases (depression 56% or other psychiatric illnesses 31%) [38]. Our study found that women with severe painful discomfort presented higher rates of past psychiatric consultations and rape, psychotropic drug use and a lower percentage of self-rated healthiness.

Our results highlight the fact that MJA were directly associated with several variables related to the menopause. The rate of postmenopausal women was observed to be two fold among women with severe/very severe MJA (62.4 vs. 37.3%) and there was a direct relationship between the stages of the menopause and intensity of MJA. Indeed, the rate of MJA was three fold higher in late postmenopausal women as compared to young premenopausal ones under 45 years. Similarly, women with surgical menopause presented a higher risk of presenting severe-very severe MJA (OR 1.61). More striking was the direct relationship observed between the intensity of VMS and MJA. It was found that in women without VMS only 8.2% present severe/very severe MJA, whereas in those with very severe VMS this rate increased to 60.2%. Bivariate analysis could not find a significant protective relationship for HT over MJA. This is not surprising, since we have previously reported [39] that HT users in fact do not have lower VMS prevalence (bivariate analysis). However, after logistic regression, HT finally appeared as a positive protective factor. The explanation for this seems to rely on the fact that HT users are mostly surgically menopausal, a group of women who are more symptomatic than those with natural menopause [39]. Similarly, in the present study, logistic regression analysis showed a protective role for HT on the risk of MJA. This observation is consistent with the largest randomized controlled trial (RCT) carried out to date regarding HT, The Women's Health Initiative, a trial involving 16,608 postmenopausal women, with a mean age of 63.3 years who were randomized to conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg or placebo. Symptom changes and treatment-related effects were analyzed in all participants after one year. It was found that women assigned to HT reported relief of joint pain or stiffness, and general aches or pains [40]. Supporting this is the observation that MJA increase after HT withdrawal [41]. Contrary to this, a small RCT ($n = 29$) found no relief in pain symptoms after using transdermal estrogen for 8 weeks [42]. Of course this outcome seems to be shadowed by the small sample and the short follow-up period which does not allow drawing definitive conclusions.

Our current results show that MJA among mid-aged women are directly and most preferably linked to VMS, an indisputably recognized menopausal symptom [43,44]. This association may suggest that the pathogenesis of both symptoms may underlie common metabolic disorders [9]. Several neurotransmitters (i.e. serotonin, noradrenalin, substance P, glutamate) are involved in the genesis of MJA. Central serotonin and noradrenalin are important in endogenous pain inhibitory pathways; substance P is a neuropeptide that is important for spinal nociception; and glutamate plays an important role in nociception, as it has excitatory and sensitizing effects [45]. Furthermore, it has been observed that the severity of MJA correlates with increased sympathetic activity of the central nervous system [46]. Coincidentally, increased sympathetic activity has been postulated as a central element in the pathogenesis of VMS. An elevated sympathetic activation, acting through the central alpha (2)-adrenergic receptors, contributes to the initiation of hot flashes, possibly by narrowing the thermoneutral zone in symptomatic women; hot flashes are then triggered by small elevations in core body temperature acting within this narrowed zone [47]. Another observation that suggests a common pathogenesis is the fact that musculoskeletal pain of fibromyalgia (a disorder seen preferably in perimenopausal women) is accompanied by symptoms such as weakness, anxiety and insomnia, all seen during the menopausal transition and which have also been linked to neurotransmitter disorders [48]. As mentioned previously [31,32], MJA increase in postmenopausal women and could be the consequence of an increase in the prevalence of OA. A key element in OA is the breakdown of matrix proteins (proteoglycans and glycosaminoglycans) via metalloproteinases (MMPs). To date, most of the basic science research has focused on whether estrogens directly influence cartilage degradation (through an antioxidative effect) or they affect modulatory proteins, such as MMP or their inhibitors. Castrated rats display increased urinary excretion of CTX-II (a marker of type II collagen destruction); this effect decreases after exogenous estrogen supplementation [49]. In addition to the strong association between MJA and VMS, our study also determined a significant relationship between musculoskeletal pain and the postmenopausal status. Indeed prevalence of severe-very severe MJA was higher in this group, whether natural or surgical.

The logistic regression model of the present research showed that severe-very severe VMS was the strongest factor related to presenting MJA (six fold). Other less striking factors included a premature menopause, age, psychotropic drug use, cigarette smoking, low educational level and a history of psychiatric consultations or rape. Perception of healthiness, higher economic status (reflected by the ability of accessing private health care), and HT use were factors related to a lower risk of presenting MJA. The latter suggesting a link between hormones and pain perception. The interaction between MJA and organic, psychological, cultural and lifestyle factors reflects the complexity of pain perception in humans [50].

Finally as for the limitations of our study one can mention its cross-sectional design which cannot allow determining causality. The presence of MJA was assessed with an instrument designed to evaluate menopausal symptoms (MRS), but not specifically musculoskeletal symptoms. This may also be seen as a weakness. Contrarily, using the MRS may also be seen as strength as this tool has psychometric properties and has been validated in five continents, including Latin America. The large number of studied women coming from various Latin American participating centers may also be seen as a potential strength. Nevertheless one must bear in mind that results cannot be extrapolated or generalized to any single or the whole Latin American population.

In conclusion, prevalence of MJA in this large mid-aged female sample was high and was significantly associated to menopausal symptoms, especially VMS. This relationship may suggest a potential role for mid-life female hormonal changes in the pathogenesis of MJA. This seems to be supported by the fact that HT was related to a lower risk of presenting severe-very severe MJA. Our results suggest that RCT are needed to assess the potential utility of HT for the management of MJA in mid-aged women.

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Contributors

Juan E. Blümel and Peter Chedraui were involved in the conception and design of the study. German Baron, Emma Belzares, Ascanio Bencosme, Andres Calle, Peter Chedraui, Luis Danckers, Maria T. Espinoza, Daniel Flores, Gustavo Gomez, Jose A. Hernandez-Bueno, Humberto Izaguirre, Patricia Leon-Leon, Selva Lima, Edward Mezones-Holguin, Alvaro Monterrosa, Desiree Mostajo, Daysi Navarro, Eliana Ojeda, William Onatra, Monique Royer, Edwin Soto, Konstantinos Tserotas and Maria S. Vallejo conducted the clinical surveys. Juan E. Blümel performed the statistical analysis. Juan E. Blümel and Peter Chedraui performed drafting of the manuscript. All authors were involved in critically revising the manuscript for its intellectual content and approving the final version of the manuscript.

Competing interest

All authors declare no conflict of interests.

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Appendix A.

Participating countries: investigators and (City)

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