ORIGINAL STUDY

Association of muscle disorders in late postmenopausal women according to the type of experienced menopause

María S. Vallejo, MD,¹ Juan E. Blümel, MD, PhD,² Peter Chedraui, MD, PhD,^{3,4} Konstantinos Tserotas, MD,⁵ Carlos Salinas, MD,⁶ Marcio A. Rodrigues, MD,⁷ Doris A. Rodríguez, MD,⁸ Claudia Rey, MD,⁹ Eliana Ojeda, MD,¹⁰ Mónica Ñañez, MD,¹¹ Álvaro Monterrosa-Castro, MD,¹² Gustavo Gómez-Tabares, MD,¹³ María T. Espinoza, MD,¹⁴ Carlos Escalante, MD,¹⁵ Alejandra Elizalde, MD,¹⁶ Maribel Dextre, MD,¹⁷ Andrés Calle, MD,¹⁸ and Sócrates Aedo, MSc¹⁹

Abstract

Objective: Musculoskeletal disorders frequently affect postmenopausal women. This study aims to compare muscle disorders between women according to the type of experienced menopause: premature (PM) or normal age of menopause (NAM).

Methods: This was a cross-sectional study conducted in nine Latin American countries in which late postmenopausal women (55 to 70 years) were surveyed with a general questionnaire, the Menopause Rating Scale (MRS: item #4 exploring musculoskeletal discomfort), and strength, assistance with walking, rising from a chair, climbing stairs, and falling questionnaire (risk of sarcopenia).

Results: A total of 644 women were included: 468 who had NAM, and 176 who had PM (116 spontaneous and 60 surgical). The overall mean age of the participants was 60.9 ± 4.2 years. Women who had PM experienced more musculoskeletal discomfort (33.5% vs 20.9%, P < 0.001) and a higher likelihood of sarcopenia (35.2% vs 19.9%, P < 0.001) than women who had a NAM. Women who had surgical PM exhibited a higher prevalence of severe musculoskeletal discomfort (46.7% vs 29.3%, P < 0.02) and a higher likelihood of sarcopenia (45.0% vs 27.6%, P < 0.02) than women who had a NAM. After adjusting for covariates (age, body mass index, menopausal hormone therapy use, physical activity, education, cigarette consumption, use of antidepressants, sexual activity, comorbidities, and having a partner), our logistic regression model determined that spontaneous PM was not associated with higher odds of musculoskeletal discomforts (odds ratio: 2.26; 95% confidence interval: 1.22-4.17) and higher odds for sarcopenia (odds ratio: 2.05; 95% confidence interval: 1.16-3.65) as compared to women who experienced a NAM.

Conclusions: Women experiencing surgical PM have a higher likelihood of developing muscle disorders. This underscores the potential significance of hormonal levels in influencing musculoskeletal health during postmenopause.

Key Words: Muscle disorders – POI – Premature menopause – Primary ovarian insufficiency – Sarcopenia – Surgical menopause.

Valle, Cali, Colombia; ¹⁴Unidad de Ginecología Obstétrica, Clínica Los Ángeles, Cochabamba, Bolivia; ¹⁵Departamento de Ginecología, Facultad de Medicina, Universidad de Costa Rica, San José, Costa Rica; ¹⁶Departamento de la Mujer, Niñez y Adolescencia, Facultad de Medicina de la Universidad Nacional del Nordeste, Corrientes, Argentina; ¹⁷Ginecología Obstetricia, Clínica Internacional - Clínica Javier Prado, Lima, Perú; ¹⁸Centro Integral de Salud Obstétrica y Femenina. Ginecología, Universidad Indoamérica, Academia Ecuatoriana de Medicina, Quito, Ecuador; and. ¹⁹Escuela Medicina, Universidad Finis Terra, Santiago de Chile, Chile.

Received December 28, 2023; revised and accepted February 21, 2024. From the ¹Servicio de Obstetricia y Ginecología, Hospital Clínico de la Universidad de Chile, Santiago de Chile, Chile; ²Departamento de Medicina Interna Sur, Facultad de Medicina, Universidad de Chile, Santiago, Chile; ³Escuela de Posgrado en Salud, Universidad Espíritu Santo, Samborondón, Ecuador; ⁴Facultad de Ciencias de la Salud, Universidad Católica "Nuestra Señora de la Asunción", Asunción, Paraguay; ⁵Clínica Tserotas, Ciudad de Panamá, Panamá; ⁶Servicio de Obstetricia y Ginecología, Hospital Ángeles, Puebla, México; ⁷Department of Gynecology and Obstetrics, Federal University of Minas Gerais, Belo Horizonte, Brazil; ⁸Hospital de Clínicas José de San Martín, Universidad de Buenos Aires, Buenos Aires, Argentina; ⁹Asociación Argentina para el Estudio del Climaterio, Buenos Aires, Argentina; ¹⁰Departamento Académico de Medicina Humana, Universidad Andina del Cusco, Cusco, Perú; ¹¹II Cátedra de Ginecología, Universidad Nacional de Córdoba, Córdoba, Argentina; ¹²Grupo de Investigación Salud de la Mujer, Universidad de Cartagena, Cartagena, Colombia; ¹³Departamento de Ginecología, Escuela de Medicina, Facultad de Salud, Universidad del

Funding/support: None reported.

Financial disclosure/conflicts of interest: K.T. is currently receiving funding from Novo Nordisk and Exeltis. M.A.R. currently receives funding from Theramex Pharmaceutical. The other authors have nothing to disclose.

Address correspondence to: Juan E. Blümel, MD, PhD, Departamento de Medicina Sur, Facultad de Medicine, Universidad de Chile, Orquídeas 1068, Departamento 302, P.O. BOX 7510258, Providencia, Santiago de Chile, Chile. E-mail: jeblumelm@gmail.com

uscle pain is a prevalent menopausal symptom. A classic German study showed that in general, women L experience more pain than men, and the prevalence of this discomfort increases in the female population around the age of 50.¹ Another study, conducted in more than 8,000 Latin American middle-aged women, found that 63% of them presented muscle pain, of which 15.6% pain was severe.² In the United States, the SWAN study also confirmed that this symptom is the most prevalent during menopause, affecting 54.3% of women aged 40 to 55.3 In Thailand, it is also the most prevalent symptom bothering 56.4% of postmenopausal women in the first year of amenorrhea.⁴ This prevalent symptom appears linked to menopause, as demonstrated by a study showing that women with natural menopause, after adjusting for covariables, have a higher odds of musculoskeletal pain (odds ratio [OR]: 1.43, 95% confidence interval [CI]: 1.20-1.69).⁵

Not only is muscle pain associated with the menopausal period; but also, muscle function, and mass. A meta-analysis that evaluated six studies showed that women who had premature ovarian insufficiency (POI) had lower handgrip strength and gait speed compared to women who had a normal age of menopause (NAM). Unfortunately, no comparisons were made regarding muscle mass assessment, due to insufficient data on POI women.⁶ Despite this, a known fact is that women during normal menopausal transition experience a decrease in skeletal muscle mass and an increase in total and central fat mass in association with a decrease in sex hormone levels.⁷

Due to the progressive deterioration of muscle function and mass in the postmenopausal period, assessment of the muscleestrogen relationship acquires special relevance. Ovarian hormone levels decrease significantly in women who have experienced premature menopause (PM), either spontaneous or surgical. One study found lower median estradiol blood levels in women <40 years who had surgical PM (7.15, interquartile range :5.0-20.5 pg/mL) as compared to premenopausal women of similar age (34.30, interquartile range: 25.3-44.9 pg/mL). Testosterone levels also fell significantly in women with surgical PM.8 Another study of Korse et al9 found that women with surgical menopause aged 46 displayed estradiol levels of 11.1 pmol/L lower than levels in natural postmenopausal women of 56 years of age. Furthermore, testosterone levels of natural postmenopausal women remained stable at a level of 0.89 nmol/L, while testosterone levels of surgical postmenopausal women declined by 0.04 nmol/L per year.

As muscle deterioration increases with female age,¹⁰ the objective of this study was to evaluate the impact of different types of menopause over muscle discomfort and function in late postmenopausal women aged 55 and over. We hypothesized that the presence of more pronounced muscle symptoms in women who had experienced PM compared to those who experienced menopause later could be attributed to a more prolonged time that PM women have been deprived of estrogen, and not age (at survey both groups will be similar).

METHODS

Study design and participants

This was a cross-sectional, observational, and multinational study, conducted between January 2023 and November 2023

in general gynecological consultations in the following nine Latin American countries: Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Panamá, and Perú. Participants were otherwise healthy women aged 55 to 70 years who attended a routine health check-up (convenience sampling) and either had menopause before the age of 40 (spontaneous or surgical) or natural menopause at the age of 45 years or older. We excluded women who had undergone chemotherapy or radiotherapy that might have impacted ovarian function or had surgical menopause after the age of 40; also, those with a diagnosis of dementia that did not allow them to understand the questionnaires or suffered from deafness or blindness or declined participation. All women were required to be literate in either Spanish or Portuguese (Brazil). The majority of the women included in the study had moderate incomes and received healthcare services from private and/or state clinical centers. Investigators from the participating centers were requested to survey 100 postmenopausal women, with at least one-third having experienced PM.

Studied variables

We collected the following data: age (years), years of education (years), body mass index (BMI; weight [kg]/squared height [m]), parity/number of children, current partner status, sexual activity (sexual intercourse at least once in the last year), housewife, smoker, inactive lifestyle (performs <75 min/wk of intense aerobic physical activities such as running, gym, tennis, etc., or <150 min/wk of moderate aerobic physical activities as fast walking, cycling, and dancing),¹¹ postmenopausal stages (defined according to the STRAW +10 criteria), hysterectomy, bilateral oophorectomy, systemic use of menopause hormone therapy (MHT), former MHT use, hypertension (either self-reported or on medication), diabetes mellitus (either self-reported or on medication), and the use of antidepressants, hypnotics, or medication for dyslipidemia.

For this study, PM was defined as women experiencing menopause before the age of 40.¹² Additionally, PM women were subclassified as spontaneous or surgical. The latter category comprised women with a history of bilateral oophorectomy. For this investigation, "NAM" was defined as menopause presentation at the age of 45 or later.

Musculoskeletal discomfort was assessed using question #4 of the Menopause Rating Scale (MRS). This scale has 11 items and allows participants to grade each symptom from 0 (not present) to 4 (very severe). For this research, we considered musculoskeletal discomfort to be severe when women scored \geq 3 points on item#4. It is worth noting that the MRS has previously been validated in both the Spanish¹³ and Portuguese (Brazil) languages, ensuring the reliability and accuracy of the collected data in these linguistic contexts.¹⁴

The risk of sarcopenia was assessed using the SARC-F tool, which has been designed as a rapid screening tool for the risk of sarcopenia. This instrument comprises the following five components: strength, assistance with walking, rising from a chair, climbing stairs, and falling (SARC-F). Participants were scored on each component from 0 to 2 points, resulting in a total score ranging from 0 to 10. A score \geq 4 on the SARC-F is

indicative of an increased risk of sarcopenia and poor outcomes.15 The SARC-F is an excellent test to exclude muscle function impairment and sarcopenia.16

Sample size calculation

Assuming that the prevalence of women with severe / very severe muscle and joint aches in a population with NAM is 15.6%⁵ and our study is interested in estimating the effect of PM, with an odds ratio of 2, at the significance level of 5% (two-sided test) and power of 80%, the sample size with ratio of case to control of 2: 1 would be 160 cases and 320 controls (Fleiss with correction for continuity).¹⁷ Thus, with 10% losses, the total number is 176 cases and 352 controls.

Statistical analysis

SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL) was used for statistical analysis. Data are presented as means, standard deviations, or frequencies/percentages. The Levene test was used to assess the homogeneity of variance, with statistical significance set at P > 0.05. The normality of data distribution was evaluated with the Kolmogorov-Smirnov test. Based on the results of these tests, differences between numeric variables were analyzed using either the Student t test for parametric data or the Mann-Whitney U test for nonparametric data. Logistic regression analysis was performed to determine the model that predicts higher musculoskeletal discomfort scores (3 or more in MRS # 4) or a higher likelihood for sarcopenia (SARC-F score ≥ 4).¹⁵ The covariates were categorized according to median values, except for age, year of education, and BMI, which were treated as continuous values. Additionally, the diagnoses of hypertension, diabetes, and hypercholesterolemia were combined into a single variable referred to as "comorbidities" in the logistic regression model. A stepwise procedure was used for the inclusion of the variables into the model, considering a significance level set at 10%. The variance inflation factor was used to evaluate multicollinearity in the regression analysis (variance inflation factor <10). Interactions between variables found to be statistically significant in the bivariate analysis were also considered. A P value of <0.05 was considered statistically significant for all calculations.

Ethical considerations

The study protocol was approved by the ethics committee of the Southern Metropolitan Health Service, Santiago de Chile, Chile (Memorandum 15/2022; June 22, 2022) and complies with the Declaration of Helsinki. All participants were informed of the study, its aims, and used tools, after which they provided written consent for participation.

RESULTS

The present study includes 644 women, 468 women with NAM, and 176 with PM (116 spontaneous and 60 surgical). The overall mean age of the participants in the entire sample was 60.9 ± 4.2 years, with a mean education level of 12.9 ± 4.8 years, and a mean BMI of 26.5 ± 5.8 kg/m². Among the participants, 43.6% were identified as housewives and had an average of 2.5 ± 1.8 children. Additionally, 65.1% reported having a partner. Lifestyle factors included 50.3% of women with an inactive lifestyle, 68.0% who had never smoked, and 55.7% who had engaged in sexual activity within the past 12 months. Regarding medication use, 15.5% of the participants used MHT, 24.4% hypnotics, 17.9% antidepressants, and 14.3% anxiolytics. The main cardiometabolic risk factors found in this population were hypertension 42.4%, hypercholesterolemia 38.6%, obesity 19.8% (BMI > 30 kg/m²), and diabetes mellitus 17.2% (data not shown in tables). Women who had PM had an average of 25.4 ± 6.2 years of postmenopause versus 10.2 ± 4.7 for those who had a NAM (data not presented in tables).

Women with PM exhibit distinct features, despite having comparable age and BMI as compared to women with NAM.

TABLE 1. Clinical characteristics of postmenopausal women who had premature menopause (POI or surgical) and those who had a normal age at menopause

Characteristics		Normal age of		
	Spontaneous $(n = 116)$	Surgical PM $(n = 60)$	All PM (n = 176)	$\begin{array}{c} \text{menopause} \\ (n = 468) \end{array}$
Age (yr)	61.1 ± 4.5	61.0 ± 4.3	61.1 ± 4.4	60.8 ± 4.2
BMI (kg/m^2)	26.4 ± 4.4	27.3 ± 4.0	26.7 ± 4.3	26.4 ± 5.0
Years of education	11.7 ± 4.4	12.5 ± 4.4	11.9 ± 4.4	13.3 ± 4.9^{c}
Housewives	62 (53.4)	27 (45.0)	89 (50.6)	$192 (41.0)^a$
No. children	2.2 ± 1.5	2.8 ± 1.9^{a}	2.4 ± 1.6	2.6 ± 1.9
With partner	67 (57.8)	36 (60.0)	103 (58.5)	$316(67.5)^a$
With sexual activity	51 (44.0)	24 (40.0)	75 (42.6)	$284(60.7)^{c}$
Never smoker	61 (52.6)	23 (38.3)	85 (55.9)	$342(69.5)^c$
Inactive lifestyle	53 (45.7)	$18(30.0)^a$	105 (59.7)	$219(46.8)^{b}$
MHT users	10 (8.6)	6 (10.0)	16 (9.1)	$84(17.9)^{b}$
Anxiolytics users	16 (13.8)	15 (25.0)	31 (17.6)	61 (13.0)
Antidepressants users	17 (14.7)	$24(40.0)^{c}$	41 (23.3)	$74(15.8)^{a}$
Hypnotics users	27 (23.3)	$28(46.7)^{b}$	55 (31.3)	$102(21.8)^{a}$
Arterial hypertension	62 (53.4)	39 (65.0)	101 (57.4)	$172(36.8)^{c}$
Diabetes mellitus	23 (19.8)	19 (31.7)	42 (23.9)	$69(14.7)^{b}$
Hypercholesterolemia treatment	46 (36.2)	$34(56.7)^b$	76 (43.2)	172 (36.8)

Data are presented as mean ± standard deviation or frequencies, n (%).

BMI, body mass index; MHT, menopause hormone therapy; NAM, normal age of menopause; POI, premature ovarian insufficiency. When spontaneous and surgical PM women are compared: ${}^{a}P < 0.05$, ${}^{b}P < 0.01$, and ${}^{c}P < 0.001$ as determined with Student *t* test or the χ^{2} test as appropriate. The same applies when all PM (POI and surgical) women are compared to those experiencing NAM.

Specifically, they are more frequently identified as housewives and tend to lead sedentary lifestyles and use antidepressants and hypnotics more frequently, in addition to presenting higher rates of diabetes and hypertension. Furthermore, women who had PM less commonly reported having a partner, engaging in sexual activity, and using MHT (Table 1).

Table 2 reveals significant differences among women who had a PM, indicating that those who underwent surgical PM displayed significantly higher scores for item 4 of the MRS and a higher rate of severe musculoskeletal discomfort (46.7% vs 29.3%, P < 0.02) as compared to spontaneous PM women. They also presented more frequently the likelihood of sarcopenia (45.0% vs 27.6%, P < 0.02). When combining both types of PM (spontaneous and surgical) and comparing them with women who experienced menopause at a normal age, a notably increased prevalence of musculoskeletal discomfort (33.5% vs 20.9%, P < 0.001) and a higher likelihood of sarcopenia (35.2% vs 19.9%, P < 0.001) was evident in the former group. After adjusting for age, BMI, MHT use, physical activity, years of education, cigarette consumption, use of antidepressants, sexual activity, comorbidities, and having a partner, our binary logistic regression model found that spontaneous PM was not associated with higher odds for musculoskeletal discomfort (odds ratio [OR]: 1.05; 95% CI: 0.64-1.72) compared to women experiencing natural age menopause. However, women with surgical PM had higher odds of presenting these discomforts (OR: 2.26; 95% CI: 1.22-4.17). Notably, MHT use was associated with reduced odds of such discomfort (OR: 0.20; 95% CI: 0.08-0.48) in these women with premature surgical menopause, while comorbidities were associated with increased odds (OR: 3.14; 95% CI: 1.87-5.28).

After adjusting for covariates, the odd for sarcopenia did not differ significantly between women with spontaneous PM and those experiencing natural age menopause (OR: 1.05; 95% CI: 0.70-1.92). However, women with surgical PM menopause had significantly higher odds of sarcopenia in the same comparison (OR: 2.05; 95% CI: 1.16-3.65). Furthermore, MHT use and

physical activity were associated with reduced odds of sarcopenia (OR: 0.40; 95% CI: 0.18-0.89; and OR: 0.41; 95% CI: 0.27-0.64, respectively) in these women with surgical PM, while comorbidities were associated with increased odds (OR: 1.90; 95% CI: 1.23-2.92).

DISCUSSION

This study shows that musculoskeletal discomfort and the risk of sarcopenia increase in postmenopausal women who underwent menopause before the age of 40, as opposed to those who experienced menopause at age 45 or later. Previous studies have shown that musculoskeletal pain is a common symptom related to menopause, and its prevalence tends to rise with age.²⁻⁵ However, discerning whether hormonal deficiency or aging is the primary factor contributing to musculoskeletal discomfort is challenging. Nevertheless, our findings seem to imply that hormonal factors may bear an important significance. Indeed, in our study, this conclusion may be supported by the fact that there were no significant age differences between groups at the moment of clinical evaluation (PM: 61.1 vs NAM: 60.8 years), despite a substantial disparity in the duration of hormonal deprivation between them (PM: 25.4 vs NAM: 10.2 years).

The modulation of pain and its perception is influenced by neurochemical changes in various pathways that impact both the central and peripheral nervous systems. Serotonin is among the extensively studied neurotransmitters related to pain disorders. Estrogen can alter serotonin synthesis and metabolism, therefore influencing pain perception.¹⁸ In addition to the decline in estrogen levels during the climacteric phase, the reduction of testosterone further plays a role by promoting pain relief through the inhibition of proinflammatory cytokine production (ie, IL- β and TNF- α). This interplay of hormonal changes may contribute to the greater antinociception observed in males compared to females.¹⁹

The significance of hormonal changes characteristic of menopause in the development of climacteric musculoskeletal pain is underscored by the findings of our study. Our results indicate

TABLE 2.	Muscle	disorders in	postmenopausal	women	according to	o tvpe of	^c experienced	menopause
			rr					r mor

	PM			
Parameters	Spontaneous $(n = 116)$	Surgical $(n = 60)$	All PM (n: 176)	Normal age of menopause (n = 468)
Musculoskeletal discomfort (MRS #4)				
Score	1.59 ± 1.40	2.18 ± 1.51^{b}	1.79 ± 1.46	1.36 ± 1.29^{c}
Women with severe discomfort	34 (29.3)	28 $(46.7)^a$	59 (33.5)	98 $(20.9)^c$
(MRS # 4 score \geq 3)	· · /	× /	~ /	
SARC-F				
1. Strength	0.61 ± 0.67	0.75 ± 0.65	0.66 ± 0.67	0.43 ± 0.63^{c}
2. Assistance in walking	0.27 ± 0.46	0.53 ± 0.68^{b}	0.36 ± 0.56	$0.27\pm0.51^{\rm NS}$
3. Rise from a chair	0.40 ± 0.57	0.63 ± 0.61^{b}	0.48 ± 0.60	0.28 ± 0.53^c
4. Climb stairs	0.59 ± 0.70	0.80 ± 0.63^{a}	0.66 ± 0.68	0.40 ± 0.59^c
5. Falls	0.36 ± 0.60	0.62 ± 0.61^{b}	0.45 ± 0.61	$0.38\pm0.58^{\rm NS}$
Total SARC-F score	2.22 ± 2.05	3.33 ± 2.39^{c}	2.60 ± 2.23	1.76 ± 2.13^{c}
Higher likelihood for sarcopenia (total SARC-F score ≥4)	32 (27.6)	27 $(45.0)^a$	62 (35.2)	93 (19.9) ^c

Data are presented as mean \pm standard deviations or frequencies, *n* (%).

MRS, Menopause Rating Scale; NAM, normal age of menopause; NS, nonsignificant; PM, premature menopause; POI, premature ovarian insufficiency; SARC-F, Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls.

When POI and surgical PM women are compared: ${}^{a}P < 0.05$, ${}^{b}P < 0.01$, and ${}^{c}P < 0.001$ as determined with Student *t* test, Mann-Whitney *U* or the χ^2 test as appropriate. The same applies when all PM (POI and surgical) women are compared to those experiencing NAM.

644 Menopause, Vol. 31, No. 7, 2024

that women who have experienced PM and, consequently enduring more prolonged hormonal deprivation, report a higher prevalence and intensity of musculoskeletal pain compared to women who had a NAM. Moreover, women who underwent early surgical menopause, marked by a more extensive hormonal deprivation than those experiencing nonsurgical PM,¹⁰ exhibited an even greater intensity of musculoskeletal pain. These observations highlight the pivotal role of hormones in the musculoskeletal pain associated with menopause.

We analyzed the risk of sarcopenia (as determined with the SARC-F) among studied women. Females demonstrate a distinct pattern of muscle aging compared to males, potentially due to menopause when the production of endogenous sex hormones declines.²⁰ In the present study, we observed that women who had PM displayed higher SARC-F total scores and thus a greater risk of sarcopenia as compared to women who had NAM. This was expected, because we know that estrogens play a pivotal role by interacting with their receptors located in muscle cells, thus influencing the expression of genes associated with muscle growth, differentiation, and regeneration. Additionally, estrogens control intracellular signaling pathways responsible for muscle contraction, relaxation, and adaptation to physical activity.²¹ This multifaceted impact of estrogens results in several advantageous outcomes for muscle health, including improvements in muscle mass, strength, and quality. During the female menopausal transition and aging, progressive muscle degeneration occurs.¹⁹ This muscle dysfunction results from diminished proliferation of muscle satellite cells, heightened levels of inflammatory markers, and fluctuations in sex hormone levels, collectively exposing women to an augmented prevalence of sarcopenia.²²

On the other hand, we must also consider the potential role of testosterone deficiency in the muscle deterioration observed in postmenopausal women. In this study, we observed that women with spontaneous PM did not experience significant muscular impact compared to women who underwent menopause at a later age. Conversely, women with surgical PM exhibited more musculoskeletal discomfort and a higher likelihood of sarcopenia. This increased muscle deterioration could be attributed, at least partially, not only to estrogen deficiency but also to testosterone deficiency. Testosterone, known for its anabolic actions, acts directly through androgen receptors and indirectly through conversion to estradiol.²³ The decline in testosterone levels is gradual during natural postmenopause but more abrupt in surgical menopause.²⁴ Some studies have demonstrated positive effects on muscle function with testosterone therapy. For instance, one study showed that low doses of testosterone in women elevated serum testosterone concentrations and induced a significant increase in total lean body mass, along with microscopic type II muscle fiber hypertrophy.²⁵ However, a meta-analysis did not yield conclusive results regarding the effect of testosterone on muscle function.²⁶ Nonetheless, because of the scarcity of studies that rigorously assess muscle mass and function in women with early menopause, drawing conclusions requires caution.

We cannot dismiss the possibility that the heightened risk of sarcopenia observed in women who had PM may stem from an underlying condition that contributes to both disorders. For example, it has been suggested that combinations of specific genes could be linked to increased longevity.²⁷ Consequently, women experiencing PM might lack these particular genes, thereby leading to the early cessation of ovarian function as an outcome rather than a causative factor of premature aging in general.²⁸ Sarcopenia, in this context, could be regarded as another manifestation of this premature aging phenomenon. Consistent with this hypothesis, it has been reported that early menopause is associated with lower longevity.²⁹

In our study, MHT use was associated with a 72% reduction in the rate of presenting musculoskeletal pain (OR: 0.28). This finding adds a compelling layer to our understanding of the relationship between hormonal dynamics and climacteric musculoskeletal pain, suggesting that MHT may play a protective role in mitigating such pain during menopause. These findings are linked to the antiallodynic, anti-inflammatory, and neuroprotective effects of estrogen.³⁰ Supporting evidence from an observational study⁵ indicates that MHT users present a decreased odds of experiencing musculoskeletal pain (OR: 0.75; 95% CI: 0.62-0.9).

Concerning sarcopenia, the impact of estrogen on muscle becomes apparent when comparing premenopausal women with postmenopausal ones. The latter group exhibits diminished muscle mass and strength, yet the effects of menopause on markers of muscle damage and the expression of genes involved in metabolic signaling pathways remain unclear. Some studies suggest a beneficial effect of estrogen therapy on muscle size and strength, but the evidence is largely conflicting and inconclusive.²⁰

We noted in our series a positive impact of physical activity on musculoskeletal discomfort and the risk of sarcopenia. This aligns with findings from a study involving middle-aged women, where moderate physical activity was associated with a reduction in muscle pain at a 2-year follow-up.³¹ Similarly, a study conducted among Chinese women demonstrated that engaging in light and moderate physical activity correlated with a decreased risk of muscle mass loss.³² These outcomes underscore the potential benefits of maintaining an active lifestyle in mitigating musculoskeletal discomfort and reducing the likelihood of developing sarcopenia.

Concerning the limitations of the current study, it is important to acknowledge its observational nature, which precludes the establishment of causal relationships. Furthermore, the inclusion of women from both private and public healthcare settings should be noted, implying that the findings may not be generalized to the broader Latin American population, which predominantly relies on the public health sector. The absence of widespread access to preventive health check-ups in Latin America introduces a potential selection bias. Another constraint lies in the utilization of screening instruments, specifically the MRS for muscle pain and the SARC-F for sarcopenia risk. To enhance the precision of future investigations, it is recommended to use diagnostic instruments with greater specificity and sensitivity for the evaluation of pain and sarcopenia.

Despite these limitations, however, our study has several strengths, such as the representation of common characteristics of Latin American women, including ethnicities, cultural and socioeconomic factors, and social female roles. Furthermore, the study included a multinational sample of women living in Latin America, and validated tools were used specifically for that population. In addition, all women were evaluated by doctors specialized in female health, and valid statistical methods were used to control for various potential confounders.

CONCLUSIONS

Our findings suggest that muscle discomfort and the likelihood of sarcopenia in women in the late postmenopausal stage may be more closely linked to hormonal deficiency than to chronological age alone. Our observations indicate that, at comparable ages, women who had a surgical PM, thus experiencing an extended period of hormonal deficit, have a heightened likelihood of developing muscle disorders compared to those who had a NAM. This underscores the potential significance of hormone levels in influencing musculoskeletal health during the postmenopausal phase, emphasizing the need for further exploration of the nuanced interplay between hormonal deficiency and the risk of muscle-related conditions in women.

REFERENCES

- Kohlmann T. Musculoskeletal pain in the population. *Schmerz* 2003;17: 405-411. doi: 10.1007/s00482-003-0250-x
- Blümel JE, Chedraui P, Baron G, et al, Collaborative Group for Research of the Climacteric in Latin America (REDLINC). Menopausal symptoms appear before the menopause and persist 5 years beyond: a detailed analysis of a multinational study. *Climacteric* 2012;15:542-551. doi: 10.3109/ 13697137.2012.658462
- Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med 2001;52:345-356. doi: 10.1016/s0277-9536(00)00147-7
- Sueblinvong T, Taechakraichana N, Phupong V. Prevalence of climacteric symptoms according to years after menopause. *J Med Assoc Thai* 2001; 84:1681-1691.
- Blümel JE, Chedraui P, Baron G, et al. Menopause could be involved in the pathogenesis of muscle and joint aches in mid-aged women. *Maturitas* 2013;75:94-100. doi: 10.1016/j.maturitas.2013.02.012
- Divaris E, Anagnostis P, Gkekas NK, Kouidi E, Goulis DG. Early menopause and premature ovarian insufficiency may increase the risk of sarcopenia: a systematic review and meta-analysis. *Maturitas* 2023;175: 107782. doi: 10.1016/j.maturitas.2023.05.006
- Karvonen-Gutierrez C, Kim C. Association of mid-life changes in body size, body composition and obesity status with the menopausal transition. *Healthcare (Basel)* 2016;4:42. doi: 10.3390/healthcare4030042
- Jiao X, Meng T, Zhai Y, et al. Ovarian reserve markers in premature ovarian insufficiency: within different clinical stages and different etiologies. *Front Endocrinol (Lausanne)* 2021;12:601752. doi: 10.3389/fendo.2021.601752
- Korse CM, Bonfrer JM, van Beurden M, Verheijen RH, Rookus MA. Estradiol and testosterone levels are lower after oophorectomy than after natural menopause. *Tumour Biol* 2009;30:37-42. doi: 10.1159/000199449
- Blümel JE, Salinas C, Danckers L, et al. Muscle health in Hispanic women. REDLINC VIII. *Climacteric* 2020;23:184-191. doi: 10.1080/13697137. 2019
- WHO. Physical activity. Available at: https://www.who.int/es/news-room/ fact-sheets/detail/physical-activity. Accessed December 21, 2023.
- "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022; 29:767-794. doi: 10.1097/GME.00000000002028

- Chedraui P, Aguirre W, Hidalgo L, Fayad L. Assessing menopausal symptoms among healthy middle-aged women with the Menopause Rating Scale. *Maturitas* 2007;57:271-278. doi: 10.1016/j.maturitas.2007. 01.009
- ZEG Berlin. Available at: https://zeg-berlin.de/expertise/diagnostics-tools/ menopause-rating-scale/languages/ Accessed November 16, 2023.
- Morley JE, Cao L. Rapid screening for sarcopenia. J Cachexia Sarcopenia Muscle 2015;6:312-214. doi: 10.1002/jcsm.12079
- Bahat G, Yilmaz O, Kılıc C, Oren MM, Karan MA. Performance of SARC-F in regard to sarcopenia definitions, muscle mass and functional measures. J Nutr Health Aging 2018;22:898-903. doi: 10.1007/s12603-018-1067-8
- Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. 3rd ed, Hoboken, New Jersey: John Wiley & Sons; 2013
- Paredes S, Cantillo S, Candido KD, Knezevic NN. An association of serotonin with pain disorders and its modulation by estrogens. *Int J Mol Sci* 2019;20:5729. doi: 10.3390/ijms20225729
- Lenert ME, Avona A, Garner KM, Barron LR, Burton MD. Sensory neurons, neuroimmunity, and pain modulation by sex hormones. *Endocrinology* 2021; 162:bqab109. doi: 10.1210/endocr/bqab109
- Critchlow AJ, Hiam D, Williams R, Scott D, Lamon S. The role of estrogen in female skeletal muscle aging: a systematic review. *Maturitas* 2023;178: 107844. doi: 10.1016/j.maturitas.2023.107844
- Yoh K, Ikeda K, Horie K, Inoue S. Roles of estrogen, estrogen receptors, and estrogen-related receptors in skeletal muscle: regulation of mitochondrial function. *Int J Mol Sci* 2023;24:1853. doi: 10.3390/ijms24031853
- Wiedmer P, Jung T, Castro JP, et al. Sarcopenia molecular mechanisms and open questions. *Ageing Res Rev* 2021;65:101200. doi: 10.1016/j.arr.2020. 101200
- Saki F, Kasaee SR, Sadeghian F, Talezadeh P, Ranjbar Omrani GH. The effect of testosterone itself and in combination with letrozole on bone mineral density in male rats. *J Bone Miner Metab* 2019;37:668-675. doi: 10.1007/s00774-018-0972-6
- Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Mühlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85: 645-651. doi: 10.1210/jcem.85.2.6405
- Horwath O, Apró W, Moberg M, et al. Fiber type-specific hypertrophy and increased capillarization in skeletal muscle following testosterone administration in young women. *J Appl Physiol* 2020;128:1240-1250. doi: 10.1152/japplphysiol.00893.2019
- Correa C, Bieger P, Perry IS, Souza GC. Testosterone supplementation on sarcopenia components in chronic patients: a systematic review and meta-analysis. *Curr Pharm Des* 2022;28:586-594. doi: 10.2174/ 1381612827666211115155541
- Sebastiani P, Bae H, Sun FX, et al. Meta-analysis of genetic variants associated with human exceptional longevity. *Aging (Albany NY)* 2013;5: 653-661. doi: 10.18632/aging.100594
- Laven JSE. Early menopause results from instead of causes premature general ageing. *Reprod Biomed Online* 2022;45:421-424. doi: 10.1016/j. rbmo.2022.02.027
- Tao XY, Zuo AZ, Wang JQ, Tao FB. Effect of primary ovarian insufficiency and early natural menopause on mortality: a meta-analysis. *Climacteric* 2016;19:27-36. doi: 10.3109/13697137.2015.1094784
- Ozcivit IB, Erel CT, Durmusoglu F. Can fibromyalgia be considered a characteristic symptom of climacterium? *Postgrad Med J* 2023;99: 244-251. doi: 10.1136/postgradmedj-2021-140336
- Gavilán-Carrera B, Delgado-Fernández M, Álvarez-Gallardo IC, et al. Longitudinal association of sedentary time and physical activity with pain and quality of life in fibromyalgia. *Scand J Med Sci Sports* 2023;33: 292-306. doi: 10.1111/sms.14258
- 32. Ouyang Y, Zhang X, Huang F, et al. Relationship between physical activity and muscle mass loss among people aged 60 and above in 15 provinces of China in 2015 [in Chinese]. *Wei Sheng Yan Jiu* 2023;52:528-540. doi: 10. 19813/j.cnki.weishengyanjiu.2023.04.002