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Short Communication

Role of serum estradiol and C-telopeptide on musculoskeletal pain in menopausal women

Muhammad FG. Siregar[1*], Masakazu Terauchi[2], Jonathan T. Lumbantobing[3], Hotma P. Pasaribu[4], Muhammad O. Prabudi[1], Edy Ardiansyah[5], Iman H. Effendi[6], Immanuel DL. Tobing[3], Selly Azmeila[7] and Nabila Nabila[3]

[1]Division of Fertility and Endocrinology Reproduction, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [2]Department of Women's Health, Tokyo Medical and Dental University, Tokyo, Japan; [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [4]Division of Fetomaternal, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [5]Division of Urogynecology and Reconstructive, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [6]Division of Social Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [7]Department of Physiology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

*Corresponding author: fgsiregar@gmail.com

Abstract

Musculoskeletal pain is one of the common symptoms of menopause syndrome throughout the world. Estradiol is the most potent and abundant derivative of estrogen and is associated with musculoskeletal pain, stiffness, and depressed mood during the menopausal transition. C-telopeptide is a molecule released during osteoclastic bone resorption and degradation of type I collagen, which is reported to have higher levels in individuals with musculoskeletal pain. An observational analytical study with a cross-sectional design was used in this research. Estradiol and C-telopeptide levels were measured in this study using enzyme-linked immunosorbent assay (ELISA). Musculoskeletal pain was assessed using the Nordic Musculoskeletal Questionnaire (NMQ) and the Menopause Quality of Life Questionnaire (MENQOL). Musculoskeletal pain was determined if the participant answered "yes" on questions number 12, 14 and 25 on the MENQOL. Data analysis was performed using the independent Student t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. A correlation test was performed using the Pearson correlation test for normally distributed data and the Spearman correlation test for non-normally distributed data. The results showed a non-significant relationship between estradiol and C-telopeptide levels with musculoskeletal pain assessed using the NMQ or MENQOL questionnaires. The correlation test also showed no correlation between estradiol and C-telopeptide levels in women with and without musculoskeletal pain.

Keywords: Estradiol, C-telopeptide, NMQ, MENQOL, musculoskeletal pain

Introduction

Menopause is defined as when a woman has undergone 12 consecutive months of amenorrhea without observable pathological or physiological causes [1]. Musculoskeletal pain is a prevalent symptom of menopausal syndrome globally, affecting approximately 40–60% of women, with about 20% experiencing it as the predominant menopausal symptom [2]. Decreased reproductive hormones are associated with increased pain perception [3]. During menopause, ovarian function decreases as estrogen levels reduce to 5–20 mcg/24 hours. Estradiol is the most abundant and potent estrogen derivative, with the highest number of receptors in various organs. Estradiol

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Received: March 5, 2024 - Accepted: July 26, 2024 - Published online: August 1, 2024

fluctuations have been associated with musculoskeletal and joint pain, stiffness, and depressed mood during the menopausal transition [4]. In addition, C-telopeptide, released during osteoclastic bone resorption and type I collagen breakdown, is reported to have higher levels in individuals with musculoskeletal pain [4]. However, its role in musculoskeletal pain among menopausal women is unknown.

Musculoskeletal pain in postmenopausal women could be measured using some tools, including the Nordic Musculoskeletal Questionnaire (NMQ) and the Menopause Quality of Life Questionnaire (MENQOL) [3]. No prior studies have explored the association between estradiol and C-telopeptide levels with musculoskeletal pain in menopausal women. The aim of this study was to determine the relationship between the levels of estradiol and C-telopeptide with musculoskeletal pain in menopausal women assessed using NMQ and MENQOL.

Methods

Study design and patients

A cross-sectional study was conducted at Prof. Dr. Chairuddin P. Lubis Hospital of Universitas Sumatera Utara, Medan, Indonesia, in 2023. Consecutive sampling was employed to recruit the menopausal women. This study included menopausal women who did not have menstruation for at least 12 consecutive months prior to the recruitment time, had no history of hysterectomy or oophorectomy, had not been treated with hormone replacement therapy, and had no history of metabolic, cardiovascular, or malignant diseases. Patients with damaged blood samples which was unsuitable for examination were excluded from the study.

Data collection and study variables

The characteristics of the participants, such as age, height, weight, body mass index (BMI), parity, and education level, were collected. The levels of C-telopeptide and estradiol were measured using venous blood samples and served as the independent variables. The dependent variable of the study was musculoskeletal pain, which was assessed using MENQOL and NMQ. Both questionnaires were asked directly to the participants.

Study instruments

The NMQ assesses pain in eleven body locations: neck, jaw, shoulders, upper back, elbows, wrists/hands, lower back, hips/thighs, knees, ankles/feet, and other areas of the body. Reported pain was rated based on pain intensity on a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable). Individuals reporting activity-limiting pain in at least one of eleven body areas were classified as having activity-limiting musculoskeletal pain. A total score of ≤28 indicated no pain, while a score of >28 indicated pain [5]. The NMQ has been validated in Indonesia with item validity test results ranging from 0.501 to 0.823 and a Cronbach's alpha reliability index of 0.726, indicating that the Indonesian version is valid and reliable for measuring musculoskeletal problems [6].

The MENQOL measures quality of life consisting of 29 items with four domains: vasomotor (three questions), psychosocial (seven questions), physical (16 questions), and sexual (three questions). For each MENQOL item, there are two possible answers: “yes” and “no,” with a score of 0 for “no.” In this study, musculoskeletal pain was assessed using three questions from the MENQOL questionnaire (items 12, 15 and 24). If the individual answered ‘yes’ to these questions, they were considered to have musculoskeletal pain [7].

Estradiol and C-telopeptide measurements

Blood samples were collected from the patients and processed in Prodia Laboratory, Medan, Indonesia. C-telopeptide levels were measured using the quantitative sandwich enzyme immunoassay technique with electrochemiluminescence immunoassay (ECLIA) using reagents and platform of Immunology Analyzer Cobas e 402 (Roche, Rotkreuz, Switzerland) with a normal range of 0.016–0.584 ng/mL. Estradiol levels were measured using enzyme-linked immunosorbent assay (ELISA) with a Human 17β Estradiol ELISA kit following the manufacturer’s recommendation (Bioassay Technology Laboratory) with a normal range from 0 to 30 pg/mL for postmenopausal women.

Statistical analysis

Data normality was tested using the Kolmogorov-Smirnov test. The difference in C-telopeptide and estradiol between those with and without musculoskeletal pain was assessed using the independent Student t-test or Mann-Whitney test, as appropriate, based on the data normality. The correlation between C-telopeptide and estradiol was also performed using Spearman correlation. All statistical analyses were conducted using SPSS version 26.0 (IBM, New York, USA).

Results

Characteristics of the patients

A total of 32 menopausal women were included in this study and the characteristics are presented in **Table 1**. The mean age was 57.41 years old, and the majority were aged ≥50 years (93.7%). Most of the women were obese (59.4%), and only ten had normal BMI. Based on parity, 23 women (71.9%) were categorized as multiparous. Among them, more than half had an education history of junior high school (56.3%). The mean of estradiol was 17.25±27.04 pg/mL, while the mean of C-telopeptide was 0.51±0.21 pg/mL.

Table 1. Characteristics of menopausal women (n=32)

Characteristics	Frequency (%)
Age	
<50 years	2 (6.3)
≥50 years	30 (93.7)
Height, cm	
Mean±SD	151.84±4.69
Median (min-max)	1505 (145–163)
Weight, kg	
Mean±SD	58.69±8.1
Median (min-max)	58.5 (45–73)
Body mass index	
Normal	10 (31.3)
Overweight	3 (9.4)
Obese	19 (59.4)
Parity	
Nulliparous	3 (9.4)
Primiparous	4 (12.5)
Multiparous	23 (71.9)
Grand multiparous	2 (6.3)
Education	
Elementary school	7 (21.9)
Junior high school	18 (56.3)
Senior high school	7 (21.9)
Estradiol, mean±SD (pg/mL)	17.25±27.04
Estradiol, median (min-max) (pg/mL)	9.0 (9.0–151.0)
C-telopeptide, mean±SD (pg/mL)	0.51±0.21
C-telopeptide, median (min-max) (pg/mL)	0.53 (0.14–0.98)

Relationship between serum estradiol and C-telopeptide levels with musculoskeletal pain based on NMQ

Based on the MNQ scores, 15 (46.9%) of the menopausal women had scores of ≤28, suggesting no musculoskeletal pain, while 17 (53.1%) had scores of >28, indicating the presence of musculoskeletal pain (**Table 2**). The median estradiol levels between the group of menopausal women with musculoskeletal pain and without pain were the same, both at 9 pg/mL (**Table 2**). There was no significant relationship was found between estradiol levels and musculoskeletal pain in menopausal subjects (p=0.542). The mean level of C-telopeptide in the group of menopausal women with musculoskeletal pain was 0.48 pg/mL, while in the group who did not experience musculoskeletal pain, it was 0.54 pg/mL, with no association between C-telopeptide levels and musculoskeletal pain in menopausal women (p=0.371) (**Table 2**).

Table 2. Relationship between serum estradiol and C-telopeptide levels with musculoskeletal pain based on NMQ in menopausal women (n=32)

Variables	Musculoskeletal pain		*p*-value
	Yes (n=17)	No (n=15)	
Estradiol, pg/mL			
Mean±SD	13.24±13.80	21.8±36.87	0.542[a]
Median (min-max)	9 (9–66)	9 (9–151)	
C-telopeptide, pg/mL			
Mean±SD	0.48±0.23	0.54±0.19	0.371[b]
Median (min-max)	0.41 (0.14–0.98)	0.59 (0.16–0.75)	

[a] Analyzed using Mann-Whitney test
[b] Analyzed using independent Student t-test

Relationship between serum estradiol and C-telopeptide levels with musculoskeletal pain based on MENQOL

Based on the MENQOL scores, 11 (34.4%) of the menopausal women were classified as having no musculoskeletal pain, while 21 (65.6%) were classified as having musculoskeletal pain (**Table 3**). The median estradiol levels between groups of menopausal women with and without musculoskeletal pain were the same, at 9 pg/mL. Our analysis suggested that C-telopeptide levels were also not related to musculoskeletal pain in menopausal women (p=0.509) (**Table 3**). The mean of C-telopeptide levels was 0.49±0.22 pg/mL in the group with musculoskeletal pain and 0.59±0.20 pg/mL in the group without pain (**Table 3**). No significant relationship was found between estradiol levels and musculoskeletal pain in menopausal women (p=0.459).

Table 2. Relationship of serum estradiol and C-telopeptide levels with musculoskeletal pain based on MENQOL in menopausal women (n=32)

Variables	Musculoskeletal pain		*p*-value
	Yes (n=21)	No (n=11)	
Estradiol, pg/mL			
Mean±SD	12.43±12.46	26.46±42.58	0.459[a]
Median (min-max)	9 (9–66)	9 (9–151)	
C-telopeptide, pg/mL			
Mean±SD	0.49±0.22	0.54±0.20	0.509[b]
Median (min-max)	0.49 (0.14–0.98)	0.59 (0.16–0.75)	

[a] Analyzed using Mann-Whitney test
[b] Analyzed using independent Student t-test

Correlation between estradiol and serum C-telopeptide levels

The Spearman's correlation test was conducted to assess the correlation between estradiol and C-telopeptide levels among all participants and those with and without musculoskeletal pain based on the NMQ questionnaire. Our data indicated weak correlations between estradiol and serum C-telopeptide levels among all participants (r=-0.294, p=0.103), those with musculoskeletal pain (r=-0.318, p=0.160) and those without musculoskeletal pain (r=-0.439, p=0.176) (**Table 4**).

Table 4. Correlation between estradiol and C-telopeptide serum in menopausal women

Estradiol levels	C-telopeptide levels	
	r	*p*-value [a]
All participants (n=32)	-0.294	0.103
Women with musculoskeletal pain	-0.318	0.160
Women without musculoskeletal pain	-0.439	0.176

[a] Analyzed using Spearman's correlation test

Discussion

Our study indicated that estradiol serum levels are lower in menopausal women experiencing musculoskeletal pain. However, the relationship between estradiol levels and musculoskeletal pain assessed using NMQ and MENQOL was not statistically significant. This finding contrasts with previous studies that identified a significant relationship between estradiol levels and musculoskeletal pain [8]. The lower estradiol serum levels in menopausal women with musculoskeletal pain could be explained by estrogen's role in maintaining joint homeostasis and

articular structures through the regulation of molecular pathways. Reduced estrogen levels lead to increased cartilage wear, joint surface erosion, decreased bone mineral density, loss of muscle mass and strength, and reduced collagen content in connective tissues [9]. These changes collectively contribute to decreased muscle performance and functional capacity, ultimately leading to premature degeneration and musculoskeletal pain in menopausal women [9]. The lack of a significant association between estradiol serum levels and musculoskeletal pain in our study may be due to the involvement of additional factors during menopause, such as fatigue, sleep disturbances, and mood changes, which could also influence pain perception [10].

Our study also found that serum C-telopeptide levels were lower in menopausal women with musculoskeletal pain, but this finding was not statistically significant. This result differs from previous studies, which reported significantly higher C-telopeptide levels, a biomarker of collagen metabolism, in cases of musculoskeletal pain [11]. The length of menopause in postmenopausal women was associated with C-telopeptide levels, potentially influencing the relationship between C-telopeptide and musculoskeletal pain [12]. In our study, most participants had been menopausal for more than five years, which may affect the results. The absence of an association between serum C-telopeptide levels and musculoskeletal pain could be explained by understanding that serum C-telopeptide is a marker of bone resorption during bone turnover. Menopausal women typically had increased bone resorption markers, including elevated serum C-telopeptide levels, compared to premenopausal women. However, the turnover process differs quantitatively from the premenopausal stage, as indicated by changes in the a/b C-telopeptide ratio [13].

Our study also showed no relationship between estradiol levels and serum C-telopeptide in menopausal women. This finding aligns with the previous study, which found no association between changes in bone resorption markers, such as C-telopeptide, and changes in estrogen levels [14]. Another study similarly reported no correlation between C-telopeptide and serum estradiol [15]. Jamka *et al.* provided an explanation for the lack of correlation between C-telopeptide and estradiol in menopausal women [16]. Their study suggested that balanced bone formation and resorption processes occur only in women with estradiol levels of ≥25 pg/mL. After menopause, the normal cycle of bone turnover is disrupted by estrogen deficiency, caused by the loss of ovarian hormonal function. This disruption leads to increased osteoclastic resorption activity and decreased osteoblastic activity. Although estrogen directly affects bone mineral density maintenance through various mechanisms involving osteoclasts, osteoblasts, and osteocytes by binding to estrogen receptors alpha (ERα) and beta (ERβ), the roles of these receptors in bone metabolism could differ significantly [16].

Conclusion

Most menopausal women experience musculoskeletal pain and experience a decrease in quality of life. There was no significant association between estradiol levels and C-telopeptide levels with musculoskeletal pain assessed using either the NMQ or MENQOL. Also, there was no correlation between estradiol and C-telopeptide levels in all menopausal women with and without musculoskeletal pain.

Ethics approval

The protocol of the study was reviewed and approved by the Health Research Ethical Committee, Universitas Sumatra Utara, Indonesia (1189/KEPK/USU/2023). All respondents provided informed consent to be included in the study.

Acknowledgments

None.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

Siregar MFG, Terauchi M, Lumbantobing JT, *et al*. Role of serum estradiol and C-telopeptide on musculoskeletal pain in menopausal women. Narra J 2024; 4 (2): e747 - http://doi.org/10.52225/narra.v4i2.747.

References

1. Takahashi TA, Johnson KM. Menopause. Med Clin North Am 2015;99(3):521-534.
2. Gulati M, Dursun E, Vincent K, *et al.* The influence of sex hormones on musculoskeletal pain and osteoarthritis. Lancet Rheumatol 2023;5(4):e225-e238.
3. Kulkarni S, Adhikari S, Kumar S. Prevalence of musculoskeletal disorder among postmenopausal women: A cross sectional study. Indian J Physiother Occup Ther 2020;14(2):278-282.
4. Fede C, Pirri C, De Caro R, *et al.* Myofascial pain in females and personalized care: The key role played by sex hormones. Eur J Pain Lond Engl 2022;26(4):939-940.
5. Weiss N, Skillgate E, Axén I. Psychological distress and musculoskeletal pain in manual therapists during the second wave of the COVID-19 pandemic in Sweden: A cross-sectional study. Chiropr Man Ther 2023;31(1):1-10.
6. Ramdan IM, Duma K, Setyowati DL. Reliability and validity test of the Indonesian version of the Nordic musculoskeletal questionnaire (NMQ) to measure musculoskeletal disorders (MSD) in traditional women weavers. Glob Med Heal Commun 2019;7(2):123-130.
7. Wong AYL. Musculoskeletal pain in postmenopausal women - implications for future research. Hong Kong Physiother J 2016;34:A1-A2.
8. Hyder T, Marino CC, Ahmad S, *et al.* Aromatase inhibitor-associated musculoskeletal syndrome: Understanding mechanisms and management. Front Endocrinol (Lausanne) 2021;12:713700.
9. Kang HK, Kaur A, Dhiman A. Menopause-specific quality of life of rural women. Indian J Community Med 2021;46(1):273-276.
10. Watt FE. Musculoskeletal pain and menopause. Post Reprod Health 2018;24(1):34-43.
11. Mourad BH. Prevalence of work-related musculoskeletal disorders among Egyptian printing workers evidenced by using serum biomarkers of inflammation, oxidative stress, muscle injury, and collagen type I turnover. Toxicol Ind Health 2021;37(1):9-22.
12. Pangestu W, Suparman E, Wagey F. Length of menopause has a positive correlation with C-Telopeptide plasma level in pascamenopause women. Indones J Obstet Gynecol 2014;2:82-86.
13. Gossiel F, Finigan J, Jacques R, *et al.* Establishing reference intervals for bone turnover markers in healthy postmenopausal women in a nonfasting state. Bonekey Rep 2014;3:573.
14. Taxel P, Kennedy DG, Fall PM, *et al.* The effect of aromatase inhibition on sex steroids, gonadotropins, and markers of bone turnover in older men. J Clin Endocrinol Metab 2001;86(6):2869-2874.
15. Banerjee S, Smith IE, Folkerd L, *et al.* Comparative effects of anastrozole, tamoxifen alone and in combination on plasma lipids and bone-derived resorption during neoadjuvant therapy in the impact trial. Ann Oncol 2005;16(10):1632-1638.
16. Jamka K, Adamczuk P, Skowrońska A, *et al.* Assessment of the effect of estradiol on biochemical bone turnover markers among postmenopausal women. Ann Agric Environ Med 2021;28(2):326-330.