ORIGINAL ARTICLE

Association of age at menopause and age at menarche with later-life skeletal fragility fractures in Bosnian postmenopausal women

Amila Kapetanović[1], Gordan Bajić[2], Sabina Sarić[1], Rubina Alimanović-Alagić[3], Martina Bonić[4], Dženan Pleho[1]

[1]Health Center of Sarajevo Canton, [2]Faculty of Health Studies, Pan European University Apeiron, Banja Luka, [3]Clinical Center University of Sarajevo; Bosnia and Herzegovina, [4]Therapiezentrum Unterhaching, Unterhaching, Kreis München, Germany

ABSTRACT

Aim To investigate the effects of estrogen-related events (age at menopause, age at menarche) on later-life skeletal fragility in Bosnian postmenopausal women.

Methods A total of 100 postmenopausal Bosnian women, aged between 55 and 75 years, were included. The women in the study group (n=50) had fragility fractures, and in the control group (n=50) were without fragility fractures. Bone mineral density (BMD) was measured using Dual Energy X-ray Absorptiometry (DXA) on the lumbar spine (L2-L4) and proximal femur.

Results No statistically significant difference relating to the age between the groups was found. The average age at menopause was 44.70 years in women with fragility fractures and 51.76 years in women without fragility fracture (p=0.0001). The average age at menarche was 14.30 years in women with fragility fractures and 13.70 years in women without fragility fractures (p=0.140). T score of ≤-2.5 SD was found in 40 (80%) women in the study group, and in eight (16%) women in the control group (p=0.0001).

Conclusions Age at menopause, but not age at menarche, was risk factors for later-life fragility fracture in postmenopausal Bosnian women. In addition, fragility fractures correlated with low BMD in this population group.

Key words: fragility fracture, menarche, menopause

Corresponding author:
Amila Kapetanović
Health Center of Sarajevo Canton
Vrazova 11, 71 000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 292 500
E-mail: amila.kapetanovicak@gmail.com
ORCID ID: https://orcid.org/0009-0005-9332-1704

Original submission:
30 October 2023;
Revised submission:
19 November 2023;
Accepted:
06 December 2023
doi: 10.17392/1692-23

Med Glas (Zenica) 2024; 21(1):154-158

INTRODUCTION

Estrogens are important hormones that directly and indirectly regulate the metabolism and function of bone and skeletal muscle via estrogen receptors (1). In osteoporosis quantitative and qualitative changes in density, geometry and microarchitecture modify the internal stress state predisposing to fragility fractures (2).

Clinically, a fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or lower, or no identifiable trauma (3). *An* injury that causes a fragility fracture would be insufficient to fracture normal bone.

Osteoporosis is the most common cause of bone fragility (4). Fragility fracture is a direct consequence of osteoporosis (5). In 2019, the average direct cost of osteoporotic fractures was €109.12 for each individual in the 27 countries of the European Union plus the UK and Switzerland (termed EU27+2), while in 2010 the average for the EU27 was €85.77 (after adjusting for inflation) (6).

Bone homeostasis depends on the precise balance between bone breakdown and formation, involves a series of complex and highly regulated steps and is dependent on the individual risk factors of each patient (7,8).

The female reproductive system profoundly affects the skeleton during longitudinal and radial growth during growth and development, and during modeling and remodeling throughout adult life (9). Estrogen promotes bone formation and suppresses bone resorption (10). A negative balance in the bone multicellular unit which causes bone loss, an increased remodeling rate, or both, compromises the strength of bone (11).

Many detailed cellular and molecular mechanisms underlying osteoporosis seem complicated and unexplored, and warrant further investigation (10).

The influence of estrogen-related events on the bone tissue are controversial. The results of scientific studies showed that the age at menarche and the age at menopause are not associated with fracture risk in a consistent manner (12-16).

The aim of this study was to investigate the effects of estrogen-related events (age at menarche, age at menopause) on later-life skeletal fragility in Bosnia and Herzegovina (B&H) postmenopausal women. The number of available studies in B&H is insufficient to make a conclusion based on the evidence about the influence of the age at menarche and the age at menopause on the fragility of the skeleton.

PATIENTS AND METHODS

Patients and study design

This case-control study was conducted at the Institute for Medical Rehabilitation and spa therapy Reumal, Fojnica. Medical documentation from January 2010 to April 2020 was analyzed.

The total of 100 Bosnian postmenopausal women, aged 55-75 years, selected for the study. The women in the study group (n=50) had fragility fractures, and in the control group (n=50) were without fragility fractures.

The inclusion criteria were: postmenopausal women with and without fragility fracture, aged 55-75 years, who do not use hormone replacement therapy. The exclusion criteria were women younger than 56 and older than 75 years, who are not postmenopausal, who use hormone replacement therapy, have a disease that can cause osteoporosis (endocrine diseases, rheumatic diseases, gastrointestinal diseases, renal diseases, neoplasme, etc), who use drugs that may cause osteoporosis.

Methods

The woman were divided in two groups, the study and control group. The women in the study group (n=50) had fragility fracture. The women in the control group (n=50) were without fragility fracture.

The values of BMD were obtained by DXA (Norland DXA scanner, USA) at the lumbar spine (L2-L4) and proximal femur.

According to the World Health Organization criteria (17), osteoporosis is defined as a BMD ranged 2.5 standard deviation (SD) or more below of the average value for young healthy women (T-score $\leq$-2.5 SD). Severe osteoporosis is defined as a value of BMD ranged 2.5 SD or more below the young adult mean in the presence of one or more fragility fractures. Low bone mass (osteopenia) is associated with a T-score between –1.0 SD and –2.5 SD (T-score < -1 SD and > -2.5 SD). Normal bone mineral density is defined as a value of BMD within 1 SD of the young adult reference mean (T-score $\geq$ -1 SD).

Table 1. Comparison of average age, age at menopause and age at menarche in the women with and without fracture

Age (years)	Mean±SD (min; max)			p
	Study group*	Control group*	Total	
Overall	64.0800±7.31462 (51.00;75.00)	63.8800±5.62661 (54.00;75.00)	63.9800±6.49317 (51.00;75.00)	p=0.879
At menopause	44.7000±3.64356 (36.00; 51.00)	51.7600±2.63849 (45.00; 55.00)	48.2300±4.75428 (36.00; 55.00)	p=0.0001
At menarche	14.3000±1.38873 (12.00;18.00)	13.7000±0.97416 (12.00;15.00)	14.0000±1.23091 (12.00;18.00)	p=0.140

*study group, women with fracture; control group, women without fracture;Min, minimum; max, maximum

Statistical analysis

To compare differences between groups, $\chi 2$ test and Student's t-test were used. Results were considered statistically significant at a confidence level of 95% ($p<0.05$).

RESULTS

There were no statistical significance between overall average age in the study and control group, 64.08±7.31462 (min. 51.00; max. 75.00) years, and 63.88±5.62661 (min. 54.00; max. 75.00) years, respectively (p=0.879). Statistical significance was found in an average age at menopause between the study and control group, 44.70±3.64356 (min. 36.00; max. 51.00) years, and 51.76±2.63849 (min. 45.00; max. 55.00) years, respectively (p=0.0001). No statistical significance between an average age at menarche between the study and control group was found, in the study group 14.30 years, and in the control group 13.70 years (p=0.140) (Table 1).

With statistical significance the women in the study group 40 (80%) had osteoporosis (T-score ≤-2.5 SD), comparing to the control group, eight (16%) (T-score ≤-2.5 SD) (p=0.0001) (Table 2).

Table 2. Comparison of bone mineral density (BMD) in the women with and without fracture

BMD (T score reference value) (T-score, SD)	No (%) of women in the group*		Total	p
	Study	Control		
Osteoporosis (≤-2.5)	40 (80.0)	8 (16.0)	48 (48.0)	p=0.0001
Osteopenia (< -1 SD and > -2.5) and normal (≥ -1) bone mineral density	10 (20.0)	42 (84.0)	52 (52.0)	
Total	50 (100.0)	50 (100.0)	100 (100.0)	

*study group, women with fracture; control group, women without fracture; SD, standard deviation;

DISCUSSION

The aim of this study was to examine the effects of estrogen-related events (age at menarche, age at menopause) on later-life skeletal fragility in Bosnian postmenopausal women because

the influence of estrogen-related events on the bone tissue are controversial (12-16), and data from B&H are insufficient. The results of our study showed that the age at menopause, but not the age at menarche, was risk factor for later-life fragility fracture in postmenopausal Bosnian women. In addition, fragility fractures correlated with low bone mineral density in this population group.

Anagnostis et al. has shown that early menopause (age at menopause < 45 years) is associated with increased fracture risk compared with age at menopause >45 years without any distinct effect on the site of the fracture (18). The results of our study confirm that the age of menopause is a risk factor for later-life skeletal fragility fractures in Bosnian postmenopausal women. Oophorectomy was associated with postoperative bone loss, especially among women who were premenopausal at the time of surgery that targeted management strategies should include routine bone mineral density assessment and hormone therapy use to improve management of bone health in this population (19). However, no evident effect of surgical menopause on BMD and fracture prevalence compared with natural menopause was found in the meta-analysis of Fakkert et al. (16).

Longer duration of endogenous estrogen exposure has a protective effect on fracture incidence in Iranian women; this point needs to be considered in fracture risk assessment (20). Vertebral fracture was prevalent among Egyptian females with osteoporotic hip fractures, and those who had later menarche, earlier menopause, and menstrual irregularities had a higher incidence of developing associated vertebral fracture (21). Female reproductive factors (age at menarche, age at menopause, parity, breastfeeding, and exogenous hormone use) were independent risk factors for fracture among postmenopausal women in Korea, with a higher risk associated with shorter lifetime endogenous estrogen exposure (22). In our study, the age of menarche was not found to be a risk factor for fragility fracture in Bosnian postmenopausal women.

Identification of patients who are at particularly high risk of fracture will help clinicians target

appropriate treatment more precisely and cost-effectively (23).

There are differences in the frequency of fragile fractures among racial groups, within the same race, as well as differences regarding gender and age.

Hip and vertebral fracture incidence increased steeply with age for both women and men (24). Ethnicity and race, like sex, influence the epidemiology of fractures, with highest fracture rates in white women (25). Gender- and ethnic-specific patterns in the incidence of hip fracture have been found among older US Asian and non-Hispanic white adults (26). There is a large variation in hip fracture incidence from different countries. Lifetime risk at the age of 50 years varies from 1% in women from Turkey to 28.5% in women from Sweden (27). Reasons for the large variation in fracture risk between countries are speculative (6). Ethnic differences in absolute fracture risk remain, which may warrant ethnic-specific clinical recommendations (28). Therefore, conducting scientific research related to the etiopathogenesis of skeletal fragility in certain population groups brings more evidence that will be useful for a better understanding of the problem.

The limitation of this study is that data were collected from only one rehabilitation institution. Future research should be extended to more institutions from different regions of B&H.

In conclusion, the results of this study showed the age at menopause has importance as a clinical factor in predicting skeletal fragility in Bosnian postmenopausal women. It will contribute to a better understanding of the etiopathogenesis of skeletal fragility in B&H women and it could be in the function of primary and secondary prevention and appropriate treatment of fragile fracture in Bosnian postmenopausal women.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Lu L, Tian L. Postmenopausal osteoporosis coexisting with sarcopenia: the role and mechanisms of estrogen. J Endocrinol 2023; 259:e230116.
2. Iolascon G, Paoletta M, Liguori S, Gimigliano F, Moretti A. Bone fragility: conceptual framework, therapeutic implications, and COVID-19-related issues. Ther Adv Musculoskelet Dis 2022;14:1759720X221133429.
3. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002; 167(10 Suppl):S1-34.
4. Ratti C, Vulcano E, Canton G, Marano M, Murena L, Cherubino P. Factors affecting bone strength other than osteoporosis. Aging Clin Exp Res 2013;25(Suppl 1):S9-11.
5. Tran T, Ho-Le T, Bliuc D, Abrahamsen B, Hansen L, Vestergaard P, Center JR, Nguyen TV. 'Skeletal Age' for mapping the impact of fracture on mortality. Elife 2023;12:e83888.
6. Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, McCloskey EV, Willer C, Borgström F. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos 2021;16:82.
7. Song S, Guo Y, Yang Y, Fu D. Advances in pathogenesis and therapeutic strategies for osteoporosis. Pharmacol Ther 2022; 237:108168.
8. Williams C, Sapra A. Osteoporosis markers. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK559306/ (11 November 2023)
9. Clarke BL, Khosla S. Female reproductive system and bone. Arch Biochem Biophys 2010; 503:118–28.
10. Wang LT, Chen LR, Chen KH. Hormone-related and drug-induced osteoporosis: a cellular and molecular overview. Int J Mol Sci 2023; 24:5814.
11. Seeman E, Delmas PD. Bone quality: the material and structural basis of bone strength and fragility. N Engl J Med 2006; 354:2250-61.
12. Long G, Liu C, Liang T, Zhang Z, Qin Z, Zhan X. Predictors of osteoporotic fracture in postmenopausal women: a meta-analysis. J Orthop Surg Res 2023;18:574.
13. Shieh A, Ruppert KM, Greendale GA, Lian Y, Cauley JA, Burnett-Bowie SA, Karvonen-Guttierez C, Karlamangla AS. Associations of age at menopause with postmenopausal bone mineral density and fracture risk in women. J Clin Endocrinol Metab 2022; 107:e561-9.
14. Paganini-Hill A, Atchison KA, Gornbein JA, Nattiv A, Service SK, White SC. Menstrual and reproductive factors and fracture risk: the leisure world cohort study. J Womens Health (Larchmt) 2005; 14:808-19.
15. Vesco KK, Marshall LM, Nelson HD, Humphrey L, Rizzo J, Pedula KL, Cauley JA, Ensrud KE, Hochberg MC, Antoniucci D, Hillier TA; Study of osteoporotic fractures. Surgical menopause and nonvertebral fracture risk among older US women. Menopause 2012; 19:510-6.
16. Fakkert IE, Teixeira N, Abma EM , Slart R, Mourits M, de Bock GH . Bone mineral density and fractures after surgical menopause: systematic review and meta-analysis. BJOG 2017; 124:1525-35.

17. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. Geneva, World Health Organization, 1994 (WHO Technical Report Series, No. 843).
18. Anagnostis P, Siolos P, Gkekas NK , Kosmidou N , Artzouchaltzi AM , Christou K , Paschou SA , Potoupnis M , Kenanidis E, Tsiridis E, Lambrinoudaki I , Stevenson JC , Goulis DG. Association between age at menopause and fracture risk: a systematic review and meta-analysis. Endocrine 2019; 63:213-24.
19. Kotsopoulos J, Hall E, Finch A, Hu H, Murphy J, Rosen B, Narod SA, Cheung AM. Changes in bone mineral density after prophylactic bilateral salpingo-oophorectomy in carriers of a BRCA mutation. Psychooncology 2013; 22:212-9.
20. Farahmand M, Rahmati M, Azizi F, Gandevani BS, Tehrani RF. The impact of endogenous estrogen exposure duration on fracture incidence: a longitudinal cohort study. J Clin Endocrinol Metab 2022; 107:e3321-9.
21. Abdelrahman Ali MA, Sweed HS, Allam MF, Aly WW, Mohamed Matter AH, Abdelalim Elshabrawy WE. Proportion and risk factors of silent vertebral fractures among Egyptian females with fragility hip fracture presenting to the emergency room of Ain Shams University Hospitals. Cureus 2023; 15:e46214.
22. Yoo JE, Shin DW, Han K, Kim D, Yoon JW, Lee DY. Association of female reproductive factors with incidence of fracture among postmenopausal women in Korea. JAMA Netw Open 2021; 4:e2030405.
23. Kanis JA, Cooper C, Rizzoli R, Abrahamsen B, Al-Daghri NM, Brandi ML, Cannata-Andia J, Cortet B, Dimai HP, Ferrari S, Hadji P, Harvey NC, Kraenzlin M, Kurth A, McCloskey E, Minisola S, Thomas T, Reginster JY; European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Identification and management of patients at increased risk of osteoporotic fracture: outcomes of an ESCEO expert consensus meeting. Osteoporos Int 2017; 28:2023-34.
24. Mayhew PM, Thomas CD, Clement JG, Loveridge N, Beck TJ, Bonfield W, Burgoyne CJ, Reeve J. Relation between age, femoral neck cortical stability, and hip fracture risk. Lancet 2005; 366:129-35.
25. Cauley JA. Defining ethnic and racial differences in osteoporosis and fragility fractures. Clin Orthop Relat Res 2011; 469:1891-9.
26. Lo JC, Chandra M, Lee DR, Darbinian JA, Gordon NP, Zeltser DW, Grimsrud CD, Lee C. Sex- and ethnic-specific patterns in the incidence of hip fracture among older US Asian and non-Hispanic white adults. J Am Geriatr Soc 2023; 71:1910-6.
27. Kanis JA, Johnell O, De Leat C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. J Bone Miner Res 2002; 17:1237-44.
28. Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, Santora AC, Sherwood LM. Osteoporosis and fracture risk in women of different ethnic groups. J Bone Miner Res 2005; 20:185-94.