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Original Article

Early Menopause and Risk of Fractures–A Preventable Gap

Ivana Minaković [1,2], Jelena Zvekić-Svorcan [1,3], Tanja Janković [1,3], Miljanka Vuksanović [4,5], Darko Mikić [6,7], Ksenija Bošković [1,8]

1. *Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia*
2. *Health Center Novi Sad, Novi Sad, Serbia*
3. *Special Hospital for Rheumatic Diseases, Novi Sad, Serbia*
4. *Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
5. *University Hospital Zvezdara, Belgrade, Serbia*
6. *Medical Faculty of the Military Medical Academy, University of Defence, Belgrade, Serbia*
7. *Pathology and Forensic Medicine Institute, Belgrade, Serbia*
8. *Clinic for Medical Rehabilitation, Clinical Center of Vojvodina, Novi Sad, Serbia*

***Corresponding Author:** Email: ivana.minakovic@uns.ac.rs

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Abstract

Background: Osteoporosis is a chronic disease that results in microarchitectural changes to the bone, thereby reducing its density and increasing the risk of fractures. This retrospective cross-sectional study aimed to examine the link between the risk of major osteoporotic fractures and hip fractures with the age of menopause onset, as well as the impact of menopause duration on fracture incidence.

Methods: This retrospective cross-sectional study was conducted at the Special Hospital for Rheumatic Diseases, Novi Sad, Serbia. The data required for meeting the study objectives were obtained from patients' medical records spanning the 2015-2018 period. The sample for the study comprised of 985 postmenopausal women aged ≥ 50 yr who underwent bone mineral densitometry examination and received a FRAX score for major osteoporotic fractures and hip fractures with and without bone mineral density. The obtained FRAX scores were compared across the subjects with respect to the age of menopause onset and menopause duration.

Results: The group that entered into menopause before the age of 45 had a high risk of hip fracture (OR: 1,652; 95% CI: 1,138 - 2,399; *P*<.01) and a higher mean FRAX score for hip fracture compared to women in whom menopause started after the age of 45 (Me=1.60 vs. 1.30, *P*<.004). FRAX scores were also correlated with menopause duration, and the difference between the groups with the longest (over 20 yr) and the shortest (1–10 yr) duration was statistically significant at *P*<.001.

Conclusion: As menopause duration could contribute to the prediction of fracture risk, its inclusion in the FRAX algorithm should be considered, while also taking into account the age of menopause onset.

Keywords: Menopause; Duration of menopause; Fracture risk assessment tool; Osteoporosis; Fracture risk

Introduction

Osteoporosis leads to skeletal fragility and thus increases the risk of fractures as well as associated morbidity and mortality, placing a significant burden on the healthcare system (1,2). This is a major public health problem, as osteoporosis often remains unrecognized or untreated until a

fracture occurs (3). Women start to lose bone mass around the age of 35, which can lead to a 35%–50% decline across their lifetime (4−6). As bone resorption accelerates during menopause while bone formation is reduced (5), the imbalance between these processes leads to osteoporosis (7). Consequently, the risk of osteoporosis increases in women that enter menopause early (8), as the catabolic effect of estrogen deficiency contributes to bone loss (3). Through induction of osteoclast apoptosis, estrogen directly inhibits osteoclastic bone resorption while also exerting anabolic effect on osteoblast function (9). In the last decade, age of menopause onset in Serbia is below the figures reported for other European countries (10).

As no universally accepted population screening policy for identifying patients with osteoporosis or those at a high risk of fracture presently exists in Europe, such assessments were previously based on bone mineral density (BMD), but increasingly tools such as the Fracture Risk Assessment Tool (FRAX) are being employed to enhance the screening accuracy (2). FRAX is a computer-based algorithm launched in 2008 that yields a 10–year probability of a major osteoporotic fracture (MOF) and hip fracture. As the probability of fracture varies across different populations, by 2018, 64 country-specific FRAX versions had been established, corresponding to the 80% global coverage (11).

In most countries, the average age of menopause onset is 51, ranging from 45 to 55 years. Thus, menopause that occurs at or before the age of 45 is considered early (12, 13), and is a phenomenon distinct from premature ovarian insufficiency (premature menopause) which occurs before the age of 40.

We aimed to examine the link between the risk of MOF and hip fractures with the age of menopause onset, as well as the impact of menopause duration on the fracture occurrence using the FRAX tool.

Methods

This retrospective cross-sectional study was conducted at the Special Hospital for Rheumatic Diseases, Novi Sad, Serbia, upon obtaining the approval of the institutional Ethics Committee.

The research sample comprised of 985 postmenopausal women aged ≥50, whereby women with previous traumatic fracture(s), osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism, chronic malnutrition, *malabsorption,* chronic liver disease, and premature menopause were excluded, as were those used hormone replacement therapy (HRT).

The data required for meeting the study objectives were obtained from patients' medical records spanning the 2015-2018 period and included menopausal status, age, sex, height, weight, history of fragility fractures, parental history of hip fractures, use of oral glucocorticoids, presence of secondary osteoporosis and rheumatoid arthritis, current smoking, and alcohol intake of three or more units daily. BMD was measured by dual-energy X-ray absorptiometry using the Lunar Prodigy Primo device, while age of menopause onset was self-reported by each patient.

Age of menopause onset was used to separate the sample into two groups, denoted as spontaneous early menopause (≤45 yr) and typical menopause (>45 yr). The FRAX algorithm adapted to Serbian population with and without BMD was also applied to the data retrieved from medical records to calculate the ten–year risk of MOF (FRAX–MOF) and hip fracture (FRAX–HIP) for each subject (14), whereby FRAX–MOF ≥20% and FRAX–HIP ≥3% indicated high fracture risk (15).

Statistical analyses

Statistical data processing and analyses were performed using the statistical package SPSS ver. 24 (IBM Corp., Armonk, NY, USA), whereby the Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to check the normality of distribution. As the distribution of numerical variables did not meet the normality criteria, findings related to continuous data were presented as medians and ranges. Differences between groups were examined by the Kruskal Wallis test, and Post Hoc Test was applied for subsequent comparisons. Categorical data were presented as absolute frequencies, and Chi-Squared test was adopted for assessing the differences between groups. Nonparametric Spearman correlation was employed for establishing correlations between numeri-

cal variables. Finally, logistic regression modeling was used to identify a multivariate association between the outcome variable (MOF FRAX + BMD and HIP FRAX + BMD) and explanatory variables (age of menopause onset and menopause duration).

Results

The study sample comprised of 985 women aged 50-86 yr with a median age of 64 yr. The sample was segregated into two groups based on the existence of previous fractures and then each group was segregated based on menopause onset. The difference was tested on the following variables: age, body weight, body height, BMI, BMI category, parent fractured hip, current smoking, alcohol intake, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, femoral neck BMD (g/cm2). In the first group a statistically significant difference between two subgroups were found on the variables: BMI category ($P<.05$), Secondary osteoporosis ($P<.05$) and Femoral neck BMD ($P<.05$). In a group composed of women without fractures, family history of parental hip fractures was more common in the typical (16.8%) compared to the early (7.4%) menopause group ($P<.001$), whereas the mean BMD of the femoral neck was statistically significantly lower in the latter subgroup (Me=0.81 vs. Me=0.84, $P<.01$), as shown in Table 1.

Table 1: Demographic and clinical characteristics of Serbian postmenopausal women with and without fracture stratified by age of menopause onset

Variable	*With Previous fracture* (*n* = 258)		*P-value*	*Without Previous fracture* (*n* = 727)		*P-value*	*All* (*n* = 985)
	Early menopause	**Typical menopause**		**Early menopause**	**Typical menopause**		
Age (yr), median (range)	67.00 (50 - 85)	68.00 (50 - 86)	0.196 [a]	64.00 (50 - 83)	63,00 (50 - 83)	0.462 [a]	64 (50 - 86)
Body weight (kg), median (range)	63.50 (41 - 100)	65.00 (36 - 97)	0.369 [a]	68.00 (40 - 100)	69.00 (33 - 114)	0.419 [a]	68.00 (33 - 114)
Body height (cm), median (range)	158.00(141 - 173)	158.00 (134 - 173)	0.911 [a]	160.00 (137 - 176)	159.00 (135 - 177)	0.931 [a]	159.00 (134 - 177)
BMI (kg/cm²), median (range)	25.60 (17.50 – 37.20)	26.50 (16,90 – 37.90)	0.302 [a]	27.30 (15.40 – 42.20)	27.30 (16.18 – 47.09)	0.685 [a]	27.00 (15.40 – 47.09)
BMI category, n (%)			**0.041** [b]			0.120 [b]	
underweight (< 18.5)	5 (6.4%)	1 (0.6%)		8 (4.2%)	9 (1.7%)		23 (2.3%)
normal weight (18.5−25)	27 (34.6%)	65 (36.1%)		60 (31.6%)	159 (29.6%)		311 (31.7%)
overweight (25–30)	34 (43.6%)	83 (46.1%)		71 (37.4%)	237 (44.1%)		425 (43.1%)
obese (>30)	12 (15.4%)	31 (17.2%)		51 (26.8%)	132 (24.6%)		226 (22.9%)
Parent fractured hip, n (%)			0.865 [b]			**0.001** [b]	
yes	15 (19.2%)	33 (18,3%)		14 (7.4%)	90 (16.8%)		152 (15.4%)
no	63 (80.8%)	147 (81.7%)		176 (92.6%)	447 (83.2%)		833 (84.6%)
Current smoking, n (%)			0.702 [b]			0.436 [b]	
yes	14 (17.9%)	36 (20.0%)		39 (20.5%)	125 (23.3%)		214 (21.7%)
no	64 (82.1%)	144 (80.0%)		151 (79.5%)	412 (76.7%)		771 (78.3%)
Alcohol intake (3 or more units/day), n (%)			/			0.093 [b]	
yes	0 (0%)	0 (0%)		1 (0.5%)	0 (0%)		1 (0.1%)
no	78 (100.0%)	180 (100.0%)		189 (99.5%)	537 (100.0%)		984 (99.9%)
Glucocorticoids, n (%)			0.082 [b]			0.625 [b]	
yes	4 (5.1%)	22 (12.2%)		20 (10.5%)	50 (9.3%)		96 (9.7%)
no	74 (94.9%)	158 (87.8%)		170 (89.5%)	487 (90.7%)		889 (90.3%)
Rheumatoid arthritis, n (%)			0.267 [b]			0.464 [b]	
yes	1 (1.3%)	7 (3.9%)		15 (7.9%)	52 (9.7%)		75 (7.6%)
no	77 (98.7%)	173 (96.1%)		175 (92.1%)	485 (90.3%)		910 (92.4%)
Secondary osteoporosis, n (%)			**0.028** [b]			0.441 [b]	
yes	6 (7.7%)	33 (18.3%)		34 (17.9%)	110 (20.5%)		183 (18.6%)
no	72 (92.3%)	147 (81.7%)		156 (82.1%)	427 (79.5%)		802 (81.4%)
Femoral neck BMD (g/cm²), median (range)	0.74 (0.51-0.95)	0.77 (0.47-1.15)	**0.029** [a]	0.81 (0.51-1.19)	0.84 (0.53-1.46)	**0.002** [a]	0.816 (0.47 – 1.46)

[a] Mann-Whitney U test, [b] χ^2 – chi-squared test. // Note: Early menopause is defined as menopause that commences at or before the age of 45.// Typical menopause occurs after the age of 45

The FRAX score for hip fracture calculated with the inclusion of BMD in the algorithm obtained for the early menopause group (Me=1.60) was statistically significantly lower (*P*<.01) than that for the typical menopause group (Me=1.30), while other FRAX scores were comparable, as was the percentage of women at a high risk for hip fracture or MOF, as shown in Table 2.

Table 2: Distribution of high and low ten–year risk of fracture

Variable	*Early menopause* (n = *268)*	*Typical menopause* (n = *717)*	***P-value***	*All* (n = *985)*
MOF FRAX – BMD median (range)	6.70 (1.80–31.00)	6.90 (1.80–46.00)	0.758[a]	6.80 (1.80–46.00)
high risk	13 (4.9%)	35 (4.9%)	0.984[b]	48 (4.9%)
low risk	255 (95.1%)	682 (95.1%)		937 (95.1%)
MOF FRAX + BMD median (range)	6.50 (1.90–43.00)	6.20 (1.40–59.00)	0.075[a]	6.30 (1.40–59.00)
high risk	15 (5.6%)	27 (3.8%)	0.206[b]	42 (4.3%)
low risk	253 (94.4%)	690 (96.2%)		943 (95.7%)
HIP FRAX – BMD median (range)	1.85 (0.10–64.00)	1.80 (0.10–33.00)	0.874[a]	1.80 (0.10–64.00)
high risk	81 (30.2%)	218 (30.4%)	0.956[b]	299 (30.4%)
low risk	187 (69.8%)	499 (69.6%)		686 (69.6%)
HIP FRAX + BMD median (range)	1.60 (0.00–32.00)	1.30 (0.00–54.00)	0.004[a]	1.30 (0.00–54.00)
high risk	73 (27.2%)	162 (22.6%)	0.128[b]	235 (23.9%)
low risk	195 (72.8%)	555 (77.4%)		750 (76.1%)

[a] Mann-Whitney U test; [b] χ^2 – chi-squared test.
Note: For hip fracture, high risk is indicated by a ≥3% ten–year fracture probability.
For MOF fracture, high risk is indicated by a ≥20% ten–year fracture probability.
FRAX MOF – BMD = FRAX score for major osteoporotic fracture without bone mineral density (BMD).
FRAX MOF + BMD = FRAX score for major osteoporotic fracture with BMD.
FRAX HIP – BMD = FRAX score for hip fracture without BMD.
FRAX HIP + BMD = FRAX score for hip fracture with BMD

In the full sample, the shortest and the longest menopause duration was 12 months and 41 yr, respectively, with an average of 16 yr. The Spearman's correlation coefficient indicated a moderate and statistically significant positive correlation between menopause duration and the FRAX scores for hip fracture calculated without BMD (r=0.443, *P*<.001), whereby the strength of the correlation declined when the FRAX scores were calculated with BMD (r=0.270, *P*<.001). A moderately high positive correlation was also obtained between the FRAX scores for MOF (with and without BMD) and menopause duration. When the sample was segregated into three groups based on menopause duration (1−10 yr, 29.5%; 11−20 yr, 37.4%; and >20 yr, 33.1%) the FRAX scores for hip fracture (with and without BMD) were statistically significantly different (*P*<.001) across the groups and were the highest (lowest) in the groups with the longest (shortest) menopause duration. Similar trend was noted for the FRAX scores for MOF (with or without BMD), and the difference was statistically significant (*P*< .001) (Table 3).

The duration of menopause is a predictor of high risk for major osteoporotic fractures (OR: 1.054; 95% CI: 1.015-1.095; *P*<.05) and for hip fractures (OR: 1.098; 95% CI: 1.076 - 1.119; *P*<.05). Women who entered menopause early have a high risk of hip fractures (OR: 1,652; 95% CI: 1,138 - 2,399; *P*<.01) (Table 4).

Table 3: Menopause duration and FRAX scores

Variable	*Hip fracture*		*MOF fracture*	
	FRAX–BMD	FRAX+BMD	FRAX–BMD	FRAX+BMD
	0.443[a]	0.270[a]	0.512[a]	0.371[a]
Menopause duration (years), categories				
A: 1–10	0.70 (0.10–33.00)	0.70 (0.00–18.00)	4.30 (1.80–26.00)	4.50 (1.90–32.00)
B: 11–20	1.70 (0.20–26.00)	1.30 (0.00–48.00)	6.95 (2.00–46.00)	6.35 (1.40–38.00)
C: > 20	3.25 (0.30–64.00)	2.30 (0.00–54.00)	8.65 (2.70–40.00)	7.90 (1.90–59.00)
P-value	0.000[b]	0.000[b]	0.000[b]	0.000[b]
A *vs.* B	0.000[c]	0.000[c]	0.000[c]	0.000[c]
A *vs.* C	0.000[c]	0.000[c]	0.000[c]	0.000[c]
B *vs.* C	0.000[c]	0.000[c]	0.000[c]	0.000[c]

[a] Spearman's correlation coefficient. All presented correlation coefficients were statistically significant at the level of $P<.01$.
[b] Kruskal Wallis Test // [c] Post Hoc Test // Note: Menopause duration = current age – age at the menopause onset

Table 4: Early menopause and duration of menopause as predictors of FRAX score

Variable	*Multivariate logistic regression analysis: Odds Ratio (95% Confidence Interval)*	
	MOF FRAX+BMD (high risk=1, low risk=0)	**HIP FRAX+BMD (high risk=1, low risk=0)**
Age of menopause onset		
Early menopause	1.023 (0.497-2.105)	1.652 (1.138 - 2.399) **
Typical menopause	reference	reference
Menopause duration, years (continuous)	1.054 (1.015-1.095) **	1.098 (1.076 - 1.119) *

*$P<0.05$; ** $P<0.01$; Reference category=0.
Note: Independent variables were used in the regression model: Age of menopause onset and Menopause duration. Other research variables (age, BMI, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, femoral neck BMD) were used to calculate FRAX values, and calculating their predictive value is not justified

Discussion

The findings of this study indicate that menopause duration is associated with the risk of hip fracture and MOF. Likewise, an association was observed between the risk of hip fracture and earlier age at menopause onset. Most of the respondents in our study were overweight or obese (66%), which is in line with the findings reported for the Serbian adult population (≥20 yr old), indicating that 56.3% of adults are overweight (16), and that a greater percentage of women are obese compared to men (17). Our finding showed that the average BMD of the femoral neck was statistically significantly lower in the early menopause group is also supported by current literature (18−20).

However, available data on the association between early menopause and osteoporotic fractures is inconsistent, as both strong (21,22) and weak (23,24) association between early menopause and hip fractures or MOF has been reported by other authors. A meta-analysis of studies published prior to 2018, compared to normal menopause, early menopause is associated with an increased risk of fractures (8). Our analyses revealed a statistically significant difference between the two groups only in relation to FRAX scores for hip fracture including BMD, which is in line with the results reported for a Chinese sample (25). Conversely, the FRAX scores for MOF with and without BMD, as well as FRAX score for hip fractures without BMD, were com-

parable across the two groups, as were percentages of women at high risk for hip fractures or MOF. Similar conclusions were reached by (20), while early menopause seemed to increase these risks, the difference between early and normal menopause group was not statistically significant (P>.05). As FRAX has some limitations, these results need to be interpreted with caution. In particular, dietary factors and chronic diseases that can potentially affect bone quality and mass are not included in the FRAX algorithm (3). Likewise, dose response for certain risk factors (including number of fractures, glucocorticoid exposure, cigarette smoking, alcohol intake) is not incorporated into FRAX (2,11). Women that enter into menopause before the age of 45 have different comorbidities than those with later menopause onset, and are more likely to be smokers and have lower socioeconomic status (24).

Our analyses further indicate that menopause duration is statistically significantly correlated with FRAX scores, which were the highest in the group with the longest menopause duration (over 20 yr). Similar observations were made for Moroccan women, indicating that menopause duration is significantly negatively correlated with the lumbar spine BMD, leading the authors to conclude that menopause duration and the lumbar spine T score are the best predictors of vertebral fractures (26). Likewise, the number of years women had experienced estrogen deficiency is linked to the risk of BMD reduction (27). In particular, a linear relationship was reported between menopause duration and hip fracture risk in the first 20 years following the menopause onset, after which this upward trend becomes less pronounced, suggesting that the decline in BMD and estrogen plateaus about 20 years after menopause onset (25). In Brazilian women, menopause duration was positively associated with osteoporosis and this link was the strongest after 20 years of menopause. However, the risk increases every five years since the onset of menopause (28). These findings are supported by the results reported by Silva et al. (29) indicating that menopausal duration of more than five years is linked to a higher prevalence of osteoporosis compared to shorter duration of menopause.

Conclusion

Appropriate management of osteoporosis is necessary to reduce the risk of fragility fractures, which necessitates more frequent risk assessments and timely disease diagnosis. Moreover, as our analyses revealed that menopause duration could be a valuable indicator of fracture risk, its inclusion in the FRAX algorithm should be considered. In addition, women that enter into early menopause should be offered HRT to reduce their risk of future fractures. Greater recognition of the association between early menopause onset and osteoporotic fractures could benefit the affected women as they would be offered more intensive treatment. Therefore, it is necessary to raise awareness of the importance of HRT for women that enter into menopause before the age of 45 to prevent accelerated loss of BMD and delay the consequences of osteoporosis.

Journalism Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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