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Relationship between reduced exposure to estrogen over a lifetime and bone mineral density in postmenopausal women

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ABSTRACT

Introduction: The influence and interactions of various genetic, hormonal, environmental and nutritional factors, and risks for decreased bone mineral density in older age are not yet clear. The aim of this study was to examine the relationship between reduced exposure to estrogen over a lifetime (early age at menopause, shorter period between menarche and menopause) and bone mineral density in older postmenopausal women.

Methods: A total of 60 women, aged 60–75 years, were included and assigned to osteoporosis group (n = 30) or control group with normal bone mineral density or osteopenia (n = 30). The values of bone mineral density were obtained by dual-energy X-ray absorptiometry at the lumbar spine (L2-L4) and proximal femur.

Results: Women with osteoporosis entered the menopause at a younger age (43.03 ± 3.18 years) compared to women without osteoporosis (51.93 ± 2.30 years), and the difference was statistically significant, $p = 0.0001$. In addition, women with osteoporosis had shorter timespan between menarche and menopause (28.33 ± 3.31 years), compared to women without osteoporosis (38.43 ± 2.48 years), which was statistically significant, $p = 0.0001$.

Conclusion: Reduced exposure to estrogen over a lifetime because of early menopause, and shorter timespan between menarche and menopause may be associated with decreased bone mineral density and osteoporosis in older postmenopausal women.

Key words: Estrogen; osteoporosis; bone mineral density; older postmenopausal women

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which depends on bone density. Bone quality refers to bone architecture, metabolic turnover, damage accumulation, and demineralization and if low may present increased risk of fracture (1). In 2010, 22 million women and 5.5 million men from the 27 countries of the European Union (EU27) were estimated to have osteoporosis, with the incidence of 3.5 million fragility fractures, of which 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures, and 1,800,000 other fractures (pelvis, rib, humerus, tibia, fibula,

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clavicle, scapula, sternum, and other femoral fractures) (2). Older patients are much more susceptible to fracture at any given bone mineral density than are younger patients because of various factors including the quality of aging bone, which involves more factors than bone mineral density (3). Osteoporosis-related fractures can increase pain, disability, nursing home placement, total health-care costs, and mortality (4). Causally related deaths comprised 17–32% of all deaths associated with hip fracture (depending on age) and accounted for more than 1.5% of all deaths in the population aged 50 years or more (5). Consequences of vertebral fracture, even asymptomatic ones, include loss of height, back pain, kyphosis, protuberant abdomen, and decreased lung vital capacity, loss of self-esteem, sleep disorders, and depression, further fractures and increased mortality (6). The results of the study by Ong et al. showed that inpatient and 1-year mortality after vertebral fragility fracture was between 0.9 and 3.5%, and 20 and 27%, respectively, between 34 and 50% were discharged from hospital to a care facility. Older age and increasing comorbidities were associated with longer hospital stay and higher mortality (7).

Osteoporosis has a complex etiology and is considered a multifactorial polygenic disease in which genetic determinants are modulated by hormonal, environmental, and nutritional factors (8). The female reproductive system plays a major role in regulating the acquisition and loss of bone by the skeleton from menarche through senescence (9). Menopause and the accompanying loss of ovarian estrogens are associated with declines in bone mineral density (10). Estrogen deficiency increases the high turnover, increases the lifespan of osteoclasts, and promotes osteoblastic apoptosis (11). At menopause, decreased gonadal sex steroid production normally leads to rapid bone loss - the most rapid bone loss associated with decreased estrogen levels occurs in the first 8–10 years after menopause, with slower age-related bone loss occurring during later life (9). Age-related bone loss, in both men and women, results when bone remodeling becomes uncoupled and bone resorption exceeds bone formation - the roles and interactions of various hormonal, genetic, and other factors in bone loss and risk for decreased bone health are not yet clear (12). The incidence of osteoporotic fracture starts to increase in older age. Further, understanding of the relative contributions of the female reproductive system and each of the other factors to development and maintenance of the female skeleton, bone loss, and fracture risk will lead to improved approaches for prevention and treatment of osteoporosis (9).

The aim of this study was to examine association between reduced exposure to estrogen over a lifetime, reflected as early menopause, and shorter timespan between menarche and menopause, and bone mineral density in older postmenopausal women.

METHODS

Study design

A total of 60 women, aged 60–75 years, were included in this study. The women who met following criteria were included in the study: Women aged 60–75 years, women who do not use hormone replacement therapy, women whose finding of bone densitometry was at the level of osteoporosis, and women whose finding of bone densitometry was at the level of osteopenia or normal. The exclusion criteria were: Women younger than 60 and older than 75 years, women who use hormone replacement therapy, women who have a disease that can cause osteoporosis, and women who use drugs that may cause osteoporosis.

Two groups of women were formed based on bone mineral density values. In the study group (n = 30) was included women whose bone mineral density was at the level of osteoporosis, and in the control group (n = 30) was women with bone mineral density at the normal level or at the level of osteopenia.

The values of bone mineral density were obtained by measuring bone mineral density using dual-energy X-ray absorptiometry at the lumbar spine (L2-L4) and proximal femur.

Statistical analysis

Results of the analysis are presented in the tables and graphs. To compare differences between groups, Chi-square test and Student's t-test were used. Results of these tests were considered statistically significant at a confidence level of 95% or in $p < 0.05$. Statistical analysis was done using the statistical package MedCalc v12.7 (Antwerp, Belgia).

RESULTS

The average age of women in the study group was 68.1 years and in the control group was 68.7 years (Figure 1). There were no statistically significant differences between these two groups, t = 0.031; p = 0.975 (Table 1).

The average age of menopause in the study group was 43.0333 years and in the control group was 51.9333 years (Figure 2). There were statistically significant differences between these two groups, t = −12.419; p = 0.0001 (Table 2).

There were statistically significant differences in age of menopause expressed in decades of life between the study group and the control group, χ^2 = 33.818; p = 0.0001 (Table 3).

The average period between menarche and menopause in the study group was 28.3333 years and in the control group was 38.4333 years (Figure 3). There were statistically significant differences between these two groups, t = 7.198; p = 0.0001 (Table 4).

There were statistically significant differences in period between menarche and menopause expressed in range of years between the study group and the control group, χ^2 = 36.533; p = 0.0001 (Table 5).

DISCUSSION

Estrogen is the key regulator of bone metabolism in both men and women (10). Estrogen exposures occur throughout life, including prenatally, and change with reproductive events such as menarche and menopause (13).

In this study was examined the relationship between reduced exposure to estrogen over a lifetime and bone mineral density in postmenopausal women aged 60-75 years.

The studies have discrepant results about the relation between estrogen-related events and osteoporosis.

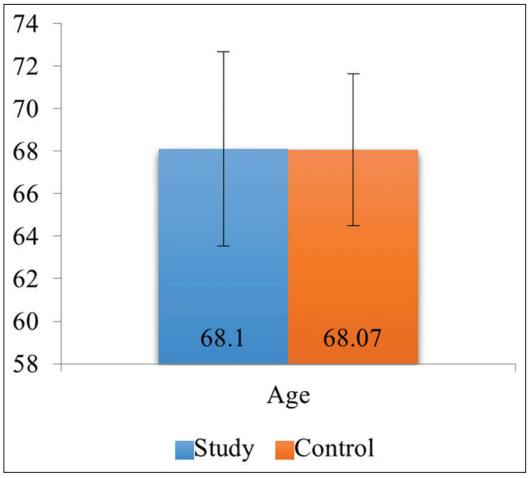

FIGURE 1. The average age of women in the study and in the control group.

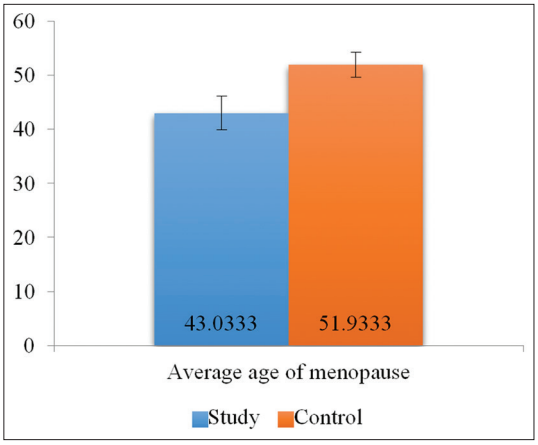

FIGURE 2. The average age of menopause.

TABLE 1. Comparison of average age by groups

Age	N (%)	SD	SE	Minimum	Maximum
Study	30 (68.10)	4.581	0.836	60	75
Control	30 (68.07)	3.581	0.654	63	75
Total	60 (68.08)	4.077	0.526	60	75

t=0.031; *p*=0.975. SD: Standard deviation, SE: Standard error

TABLE 2. Comparison of average age of menopause by groups

Age of menopause (years)	N (%	SD	SE	Minimum	Maximum
Study	30 (43.0333)	3.17841	0.58030	35.00	50.00
Control	30 (51.9333)	2.30342	0.42055	48.00	56.00
Total	60 (47.4833)	5.26418	0.67960	35.00	56.00

t=−12.419; *P*=0.0001. SD: Standard deviation, SE: Standard error

The aim of prospective population-based observational study by Svejme et al. was to evaluate of the long-term effects of early menopause on mortality, risk of fragility fracture, and osteoporosis. Menopause before age 47 years was associated with increased mortality risk and increased risk of sustaining fragility fractures and of osteoporosis at age 77 years. Women with early menopause had a risk ratio of 1.83 (95% confidence interval [CI] = 1.22–2.74) for osteoporosis at age 77 years, a risk ratio of 1.68 (95% CI = 1.05–2.57) for fragility fracture, and a mortality risk of 1.59 (95% CI = 1.04–2.36) (14). The result by Sullivan et al. study showed that whole-body bone mineral density was lower in women who reported menopause before age 40 years than in women who reported menopause at ages 40–49 years and women who reported menopause at age 50 years or older. The left hip bone mineral density was lower in women who underwent menopause before age 40 years than in women who underwent menopause at age 50 years or older, and total spine bone mineral density was lower in women who underwent menopause before age 40 years than in women who underwent menopause at age 50 years or older and women who underwent menopause at ages 40–49 years (15). In the study by Cavkaytar et al., fertility duration over 33 years (years of menstruation) had a statistically significant protective effect against osteoporosis in women with spontaneous menopause (16). The result of the study by Parker et al. supports the hypothesis that lifetime cumulative exposure to estrogens is protective against osteoporosis (13).

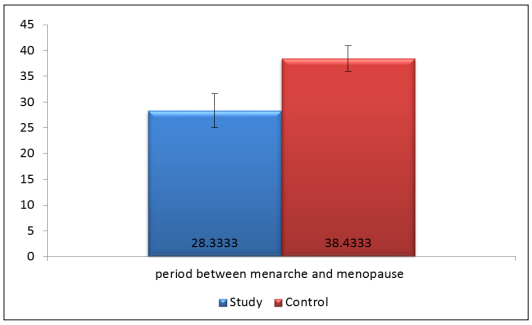

FIGURE 3. The average period between menarche and menopause.

TABLE 3. Comparison of age of menopause expressed in decades of life by groups

Age of menopause (decades of life)	Group		Total
	Study	Control	
30–40 years N (%)	6 (20.0)	0 (0.0)	6 (10.0)
41–50 years N (%)	24 (80.0)	9 (30.0)	33 (55.0)
51–60 years N (%)	0 (0.0)	21 (70.0)	21 (35.0)
Total N (%)	30 (100.0)	30 (100.0)	60 (100.0)

χ^2=33.818; *P*=0.0001

TABLE 4. Comparison of average period between menarche and menopause by groups

Average period between menarche and menopause (years)	N (%)	SD	SE	Minimum	Maximum
Study	30 (28.3333)	3.31489	0.60521	21.00	37.00
Control	30 (38.4333)	2.48698	0.45406	35.00	43.00
Total	60 (33.3833)	5.86310	0.75692	21.00	43.00

t=7.198; *p*=0.0001. SD: Standard deviation, SE: Standard error

TABLE 5. Comparison of period between menarche and menopause expressed in range of years by groups

Period between menarche and menopause (range of years)	Group		Total
	Study	Control	
20–25 years	6 (20.0)	0 (0.0)	6 (10.0)
26–30 years	16 (53.3)	0 (0.0)	16 (26.7)
31–40 years	8 (26.7)	22 (73.3)	30 (50.0)
40–45 years	0 (0.0)	8 (26.7)	8 (13.3)
Total	30 (100.0)	30 (100.0)	60 (100.0)

χ^2=36.533; *p*=0.0001

Sioka et al. found that in postmenopausal women the cumulative exposure to endogenous estrogens, measured as years of menstruation, seems to be a significant protective factor against the development of postmenopausal osteoporosis. Age at menopause between 40 and 45 years correlated with low bone mineral density (17). The result of the study by Comim et al. suggests that premenopausal hirsutism and/or oligomenorrhea may be associated with an increased risk of fracture postmenopause, particularly in the humerus and lower leg (18). The study by Mohammadi et al. examined the relationship between reproductive characteristics and bone mineral density in postmenopausal women aged 45–71 years. Age at menopause was not significantly correlated with bone mineral density (19). In the study by Gerdhem and Obrant was found that age at menarche or menopause seems to be of limited or no importance as a risk factor for osteoporosis when subjects are age 75 years or older (20).

The aim of this study was to examine the relationship between reduced exposure to estrogen over a lifetime (early age at menopause, shorter period between menarche and menopause) and bone mineral density in older postmenopausal women. There was a statistically significant difference related to age of menopause between the women with osteoporosis and women without osteoporosis. Furthermore, there was registered statistically significant difference related to the period between menarche and menopause, between the women with osteoporosis and women without osteoporosis. Average age of menopause in the women with osteoporosis was 43.03 ± 3.18 years and in women without osteoporosis 51.93 ± 2.30 years. Average period between menarche and menopause in the women with osteoporosis was 28.33 ± 3.31 years and in women without osteoporosis was 38.43 ± 2.48 years.

The result of this study showed that the deficit of estrogen over a lifetime is associated with a decrease in bone mineral density. Kapetanović and Advić found that healthy lifestyle has positive impact on bone tissue and has the potential to preserve bone mass in postmenopausal women with estrogen deficiency in their menstrual history (21,22).

CONCLUSION

Reduced exposure to estrogen over a lifetime because of early menopause, and shorter timespan between menarche and menopause may be associated with decreased bone mineral density and osteoporosis in older postmenopausal women.

CONFLICTS OF INTEREST

The authors declare that have no conflicts of interest.

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