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Serum estradiol levels and bone mineral density in postmenopausal women

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ABSTRACT

Postmenopausal women are at high risk of disease, such as coronary heart disease, stroke, malignancies, dementia and osteoporosis. This is due to decreased levels of estrogen/estradiol, produced mainly in the ovaries, leading to reduced bone mineral density (BMD), which is the gold standard for diagnosis of osteoporosis. The purpose of the present study was to determine the relationship between serum estradiol levels and BMD in postmenopausal women. The study, which was of cross-sectional design, involved 184 postmenopausal women meeting the inclusion criteria, viz. healthy postmenopausal women aged between 47 and 60 years having taken no hormonal medications in the previous 3 years. The subjects were assessed for anthropometric and biochemical characteristics, including BMD and serum estradiol levels. BMD was measured at the lumbar spine, right femoral neck and at the distal radius by the dual-energy X-ray absorptiometry (DXA) instrument. The mean serum estradiol concentration was 7.54 ± 4.65 pg/ml, while in 49.5% of the subjects the estradiol concentration was ≤ 5 pg/ml. In postmenopausal women with estradiol concentrations of > 5 pg/ml, a significant positive relationship was found between BMD and the T-scores for the femoral neck. Thus the higher the serum estradiol levels, the higher the BMD values for femoral neck region. In conclusion, the results of this study point to estradiol levels as a major factor in determining the BMD values in postmenopausal women.

Keywords: Postmenopausal, estradiol, bone mineral density, femoral neck

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INTRODUCTION

With the increased longevity there is a concomitant increase in the numbers of the elderly, particularly postmenopausal women, in developed as well as developing countries. According to World Health Organization (WHO) estimates the number of postmenopausal women in the year 2025 will be around 60–70 million.[1] Postmenopausal women are at high risk of disease, such as osteoporosis, hypertension, coronary heart disease, and stroke.[2] The menopause is the 12-month period after cessation of menstruation, while the postmenopausal is the period after menopause onwards.[1] In the postmenopausal period the ovaries as main producers of estradiol are no longer functional, leading to

decreased levels of estradiol.[3,4] In the postmenopausal period there is degeneration of the ovaries, resulting in cessation of estradiol production by these organs. The remaining sources of estradiol are the adrenals, adipose tissue, and muscles through aromatization of androstenedione.[5-7] Estradiol is synthesized in osteoblasts and chondrocytes in osseous tissue from circulatory androgens, particularly testosterone followed by dehydroepiandrosterone and androtenedione.[5] The reduction in bone mass is significantly associated with decreased androgen levels in perimenopausal and postmenopausal women.[8] Testosterone level is positively associated with BMD, and circulatory androgens play an important role in maintaining estrogen levels in osseous tissue.[9]

In young adults the processes of bone formation and absorption are closely associated to one another. After the age of 30 years there is a gradual diminution of bone mass, which is most clearly seen in women, who experience a significant decrease in bone mass. This is associated with lowered estrogen production several years prior to the onset of the menopause and continues for a period of up to 5 years, followed by a slow decrease in bone mass for the remaining life span of the women.[10] Osteoporosis is a condition of diminished bone mass and changes in bone architecture up to the fracture threshold without clinical signs or symptoms.[12] In this disorder the rate of bone formation is frequently normal, but the rate of bone absorption is increased. Bone loss occurs more frequently in trabecular bone, such as in the vertebrae, femoral neck and distal radius.[11] The rate of bone loss is 2-2.5% in the first 5 post-menopausal years, 39% in the age range of 70-79 years and 70% at age 80^{+} years.[12] The WHO has estimated the prevalence of osteoporosis among white postmenopausal women in the US to be 14% at age 50-59 years, 22% at 60-69 years, 39% at age 70-79 years and 70% at age 80^{+} years.[13]

Unmodifiable risk factors for osteoporosis are gender (women are of lesser weight and have smaller bones than men), advanced age, family history of osteoporosis, race (Asian and Caucasian women are at greater risk of osteoporosis than African women), body build (thin and small women are at higher risk of osteoporosis), and a number of disorders (anorexia, diabetes, chronic diarrhea, renal and hepatic disorders). Modifiable risk factors are smoking, alcohol consumption, low calcium intake, lack of exercise, underweight and use of medications (steroids, phenobarbital and phenytoin).[10] The objective of this study was to determine serum estradiol levels and their relationship with BMD values in postmenopausal women.

METHODS

Research design

The present study was of cross-sectional design in order to determine serum estradiol levels and their relationship with BMD values in postmenopausal women.

Study subjects

The study subjects were randomly selected postmenopausal women aged 47 up to 60 years from four villages *(kelurahan)* in the Mampang Prapatan subdistrict, South Jakarta, namely the villages of Kuningan Barat, Mampang Prapatan, Tegal Parang and Pela Mampang.

Inclusion criteria for this study were: postmenopausal women, duration of menopause of more than one year, age 47 up to 60 years, willing to participate in the study and sign informed consent, able to actively communicate, and actively mobile (requiring no walking aids).

The exclusion criteria were women with hysterectomy or bilateral oophorectomy, acute infections, diabetes mellitus, diseases of the kidneys, lungs and liver, malignancies, and those consuming hormonal medications in the last 3 years. The respondents were interviewed

from February to April 2010 by 14 health center cadres, using a questionnaire that included items on age and duration of menopause. All participating women signed an informed consent form.

Assessment of physical characteristics

The physical characteristics assessed were height, weight, and body mass index (BMI). Height was measured to the nearest 0.1 cm with the subjects in the upright position without shoes. Body weight was determined to the nearest 0.1 kg with the subjects wearing indoor clothes but no shoes. BMI was calculated as weight (kg)/ height $(m)^2$. BMI is classified into the following categories: underweight (< 18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23.0-27.5 kg/m^2), and obese (≥ 27.6 kg/m^2).[14]

Biochemical measurements

Blood samples for biochemical measurements were drawn by venipuncture after a fast of 12-14 hours. Subsequently the serum was separated and stored at $–70^0C$ until needed for examination.

Determination of serum estradiol concentration (coefficient of variation = 3.2%) was performed at Prodia Laboratories, Jakarta, using Roche reagents (catalog no. 03000079122, lot no.154701-04 ED). The detection range of the serum estradiol determinations was 5.00 - 4300.00 pg/ml.

BMD measurements

BMD of the lumbar spine (first to fourth lumbar vertebrae), the right femoral neck, and the distal left radius was determined by dual-energy X-ray absorptiometry (DXA), using a Lunar DPX Bravo Nomusa densitometer (GE Medical Systems) at Budi Jaya Hospital, Jakarta.

According to definitions of diagnostic categories suggested by a WHO study group in 1994, the normal category has a BMD within 1 SD of the reference mean (young adults). In osteopenia the BMD value is more than 1 SD below the reference mean, whereas in osteoporosis the BMD is 2.5 SD or more below the reference mean.[16] Expressed as T-scores: normal if T-score > -1; osteopenia if -2.5 < T-score < -1; osteoporosis if T-score < -2.5.[15]

Ethics

Ethical clearance was provided by the Research Ethics Commission of the Medical Faculty, Trisakti University.

Data analysis

Subsequent to coding of the collected data, data entry was performed using Statistical Package for Social Science (SPSS) version 15 for Windows. Initially a test of normality was done by means of the Komogorov-Smirnov test. Since the data were non-normally distributed, correlation analysis was performed by calculating Spearman's rho in order to determine correlations between BMI and serum estradiol levels. The level of statistical significance was set at $p < 0.05$.

RESULTS

Among 215 subjects aged 47-60 years, 31 (31/125 = 0.25%) did not meet the inclusion criteria of whom 20 subjects were on biochemical testing revealed to have diabetes mellitus and 11 did not show up for laboratory tests. A total of 184 women meeting the inclusion criteria participated in this study. Mean age of the subjects was 53.58 ± 3.53 years, with age range of 47 – 60 years. Mean BMI was 26.75 ± 4.68 kg/m^2. The majority of postmenopausal women (65.3%) were overweight and 30.4% were in the normal category. Mean estradiol concentration was 7.54 ± 4.65 pg/ml, while 46.5% of women were in the low estradiol category (≤ 5 pg/ml). Mean lumbar T-score was –1.63 ± 1.04, mean femoral neck T-score was –0.99 ± 0.96, and mean distal radial T-score was –1.95 ± 1.17. Mean duration of menopause was 4.47 ± 2.24 years, with a range of 2 to 11 years (Table 1).

Table 1. Mean values for age, BMI, lumbar, femoral and radial T-scores, estradiol level and duration of menopause in postmenopausal women (n=184)

General characteristics	Mean ± SD
Age (years)	53.58 ± 3.53
Body mass index (kg/m^2)	26.74 ± 4.68
Underweight	8 (4.3%)
Normal	56 (30.4%)
Overweight	120 (65.3%)
Lumbar T-score	-1.63 ± 1.04
Right femoral T-score	-0.99 ± 0.96
Left radial T-score	- 1.95 ± 1.17
Estradiol (pg/ml)	36.14 ± 16.14
≤ 5.0	91 (46.5%)
> 5.0	93 (50.5%
Duration of menopause (years)	4.47 ± 2.24

In this study, the highest prevalence of osteopenia was for the lumbar vertebrae (50%), while the prevalence of osteoporosis was highest in the left distal radius (35.3%) (Table 2).

The Kolmogorov-Smirnov test of normality showed that serum estradiol was not normally distributed. Nonparametric correlation according to Spearman rho showed a positive correlation between serum estradiol and BMD of the femoral neck (r=0.021;p=0.042) (Table 3). Thus the higher the serum estradiol levels, the higher the BMD values for the femoral neck region.

DISCUSSION

In the present study 49.5% of postmenopausal women had estradiol concentrations of ≤ 5 pg/ml. In postmenopausal women aged between 47 and 60 years the estradiol concentration was ≥ 5 pg/ml, this study showed a significant positive relationship between estradiol levels and T-scores for the femoral neck region. Essentially similar results were found by Bagur et al. in postmenopausal women < 65 years of age, who had estradiol levels of > 10 pg/ml and higher BMD values in all skeletal sites examined, in comparison with women whose estradiol levels were < 10 pg/ml.[5] A study involving 370 postmenopausal women aged between 55 and 85 years found a significant positive relationship between serum estradiol levels and BMD values for the lumbar spine and the femoral neck.[16]

In postmenopausal women, the ovaries as the main producers of estradiol undergo degeneration resulting in diminished estradiol levels, which may lead to osteopenia and

Table 2. Distribution of osteopenia and osteoporosis by BMD site in postmenopausal women (n=184)

BMD site	Osteopenia (n,%)	Osteoporosis (n,%)
Lumbar vertebrae 1-4	92 (50.0)	43 (23.4)
Right femoral neck	91 (49.5)	9 (2.2)
Left distal radius	77 (41.8)	63 (35.3)

Table 3. Correlation between serum estradiol and bone mineral density in postmenopausal women with estradiol concentrations of > 5 pg/ml (n=93)

	BMD		
	Lumbar spine	Femoral neck	Distal radius
Estradiol (pg/ml)	r=0.080	r=0.211*	r=0.063

*p=0.042

osteoporosis. Extragonadal sources of estradiol are the adrenals, adipose tissue, liver, kidney and muscle, where estradiol is synthesized through aromatization of andrestenedione.[7] The critical role of estrogens in bone homeostasis is widely recognized, and one of its consequences is the loss of bone occurring after the menopause, when the gonadal function ceases.[17] Extragonadal aromatization is affected by age, gender, and body weight. Overweight women have higher estrogen conversion and circulation rates than underweight women.[1,2]

Lack of estrogen also causes osteoporosis, as in the case of women athletes in whom menstruation is delayed, resulting in less than normal estrogen levels. One in three women and one in twelve men will suffer from osteoporosis throughout their lives, particularly after the age of 50 years. Osteoporosis may occur at age under 45 years in women who have undergone hysterectomy and oophorectomy.[1,2]

Osteoporosis is a common disorder of old age, creating a worldwide health problem, as the aged tend to suffer from bone fractures from mild injury or even without injury. These fractures increase the morbidity and mortality rates, and health funding, and reduce the quality of life of the patients.[10,18] In the study by Morton et al. it was found that BMD decreased with advancing age, whereas BMD was proportional to BMI.[19] In the present study, it is unclear whether the extremely low estradiol level (≤5 pg/ml) in the majority of the respondents was caused by lack of dietary cholesterol (fat), since estrogen is synthesized in the liver and some is of dietary origin.

Osteoporosis may also be caused by low calcium, low vitamin D and lack of exercise, which affects bone density. It is reported that osteoporosis in Asia is intimately associated with low calcium and lack of vitamin D. Around 35% of postmenopausal women in Asia have osteoporosis and 50% osteopenia. In postmenopausal women, the most frequently affected by osteoporosis are the trabecular bones (spongious bones).[1] As is well-known, two risk factors for osteoporosis are age and menopause. With advancing age there is increased resorption of old bone in comparison to new bone formation, so that the bones weaken and fracture easily at the slightest injury or even spontaneously. The most common fractures are those of the hip, vertebrae and wrist.[20] The reduction in bone mineral mass of the radius in men occurs after the age of 60 years. However, in women bone loss commences around the age of 50 years, is most rapid 3 or 4 years after menopause, and on average continues at a greater rate from the age of 67 years upwards.[19,20] In approximately half of white postmenopausal women the radial mineral mass is below normal.

In the study by Rogers et al. a positive association was found between estradiol and bone density at all body sites examined.[21] In another study, it was found that increased age was associated with decreased estradiol and BMD, because reduced serum estradiol concentrations increased bone turnover, which is a risk factor for fractures.[16] Zarrabeitia et al. revealed a significant correlation of serum estradiol concentration with BMD of the spine in postmenopausal women. In addition, the investigators also found in subjects with high BMI that body weight and estradiol concentration were the principal factors determining BMD.[22]

This study was subject to some limitations. First, as this was a cross-sectional community-based study, no conclusions can be drawn as regards the cause-effect relationship between estradiol levels and BMD, and longitudinal studies will be necessary to confirm our conclusions. Secondly, the women in this study were aged between 47 and 60 years, for whom no BMD data were available. Thirdly, no measured values of free estrogen were available.

CONCLUSIONS

Postmenopausal women aged 47 to 60 years 49.5% had serum estradiol levels of ≤ 5 pg/ml. There was a significant correlation between estradiol and femoral neck BMD values in postmenopausal women with estradiol levels of > 5 pg/ml.

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