ORIGINAL ARTICLE

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Serum follicle-stimulating hormone level is a predictor of bone mineral density in patients with hormone replacement therapy

Abstract *Methods:* A retrospective study regarding the relationship between serum hormonal levels and bone mineral density (BMD) was performed in 125 women with hormone replacement therapy (HRT). Serum estradiol (E_2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and BMD were evaluated before and at 12 and 24 months of HRT. *Results:* There was a significant increase in E_2 and decrease in FSH at both 12 (E_2, 39.3±76.6 pg/ml to 71.0±67.9 pg/ml; FSH, 67.9±36.3 mIU/ml to 47.9±29.0 mIU/ml) and 24 months (E_2, 68.3±54.5 pg/ml; FSH, 45.3±24.4 mIU/ml). LH level was high at baseline (26.5±16.1 mIU/ml) and decreased at 12 months (22.9±14.0 mIU/ml). On the contrary, it increased from 12 to 24 months (27.4±14.9 mIU/ml). In the lumbar spine BMD, a significant rise was seen only in the first 12 months (0.933±0.157 g/cm^2 to 0.938±0.152 g/cm^2). When percentage change was analyzed, a significant positive correlation was found between E_2 and BMD and a negative correlation between gonadotropin levels and BMD. *Conclusion:* These data demonstrate that serum gonadotropin levels, especially FSH, are a good marker to predict BMD in women with HRT.

Keywords Estradiol · Luteinizing hormone · Follicle-stimulating hormone · Bone mineral density · Hormone replacement therapy

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Introduction

The menopause is the permanent cessation of menstruation resulting from loss of ovarian follicular activity [22]. To alleviate the symptoms of menopause such as hot flashes, many postmenopausal women have been treated with ovarian hormones, namely hormone replacement therapy (HRT). It has been generally accepted that HRT with estrogen alone or estrogen and progestin slow or prevent bone loss in women who are deficient in estrogen after oophorectomies or natural menopause [1]. However, a subgroup of postmenopausal women with HRT lose bone mass, although more slowly than untreated patients. Thus, monitoring bone mass is recommended to assess the effect of HRT. Bone mass can be measured safely, accurately, and precisely by using techniques such as single-photon absorptiometry, dual-energy photon absorptiometry, dual-energy X-ray absorptiometry, and quantitative computed tomography [10]. Unfortunately, these techniques are not always available in regular clinical practice, where alternative and convenient method is required. Because estrogens are associated with bone mineral density (BMD), bone loss, and fractures [5, 6, 13], we tested the hypothesis that the serum levels of estradiol (E_2) and gonadotropins might be predictors for BMD.

Materials and methods

We did a retrospective survey of all patients with HRT at Handa City Hospital between January 1995 and December 2000. HRT was performed as follows: 0.625 mg of oral conjugated estrogen (Wyeth Pharmaceuticals, Collegeville, PA, USA) daily, transdermal E_2 patches (72 μg 17-β E_2, Japan Ciba-Geigy, Takarazuka, Japan) every other day, or 0.625 mg of oral conjugated estrogen for the first 21 days of the cycle (28 days). In patients without hysterectomy, medroxyprogesterone acetate (Wyeth Pharmaceuticals) 2.5 mg daily or 5 mg/day on days 11 to 21 was administered. Of the first selection of 155 women, we excluded 30 women who were missing data for hormones and BMD. One hundred and twenty-five women were included in this study, consisting of 82 postmenopausal and 43 perimenopausal women. Age, gravida, paragravida, height, weight, and BMI of the study population are presented in

Table 1 Characteristics of the study population

	Mean ± SD	Range
Age (years)	52.3±6.1	31–67
Gravida	3.0±1.6	0–7
Paragravida	1.9±0.9	0–4
Height (cm)	154.2±5.0	141–169
Weight (kg)	53.9±7.9	34.5–78.0
BMI (kg/m^2)	22.5±1.9	17.4–28.6

Table 1. Basal serum hormone levels and BMD were evaluated before and at 12 and 24 months of HRT. The blood samples were drawn in the morning after overnight fast and 30-min rest in the supine position. Serum was separated immediately and frozen at −80°C for future analysis. The hormonal levels were measured by using commercial radioimmunoassay kits; Coat-A-Count Estradiol Kit (Diagnostic Products Corporation, Los Angels, CA, USA) for E_2, SPAC-S LH Kit (Daiichi Radioisotope Laboratory, Tokyo, Japan) for LH, and SPAC-S FSH Kit (Daiichi Radioisotope Laboratory) for FSH. The sensitivity, expressed as minimal detectable dose, was 8 pg/ml, 0.5 mIU/ml, and 0.5 mIU/ml for E_2, LH, and FSH, respectively. Intra- and interassay coefficients of variation were 7.0% and 8.1% for E_2, 5.3% and 9.0% for LH, and 4.6% and 2.8% for FSH. BMD at the lumbar spine (L2–L4 in anteroposterior projection) was determined on each subject by use of dual-energy X-ray absorptiometry (DEXA; QDR-2000, Hologic, Bedford, MA, USA). The precision error (% coefficient of variation) was 0.23%. Percentage change was computed by dividing the difference by basal level and multiplying the result by 100. All statistical analyses were performed using the commercially available statistical software for Microsoft Excel. The Student t-test was used for comparisons between group means. Associations are given as Pearson's correlation coefficients. A p value of <0.05 was considered significant.

Results

Table 2 summarizes the hormonal characteristics of the study population before and during HRT. There was a significant increase in E_2 and decrease in FSH at both 12 and 24 months. LH decreased at 12 months ($p<0.01$), and then increased to the basal level at 24 months. In the lumbar spine BMD, a significant rise was seen only in the first 12 months. Correlation coefficients of each hormonal percentage change with that of BMD are shown in Table 3. Positive correlation was found between E_2 and BMD at both 12 and 24 months. Correlation coefficients of FSH (−0.27 at 12 months and −0.28 at 24 months) were greater than those of LH (−0.23 at 12 months and −0.21 at 24 months), although both LH and FSH were negatively correlated with BMD.

Table 3 Correlations with BMD

	r	p
E_2 (12 months/before)	0.196	0.031
E_2 (24 months/before)	0.234	0.010
LH (12 months/before)	−0.229	0.012
LH (24 months/before)	−0.205	0.025
FSH (12 months/before)	−0.271	0.003
FSH (24 months/before)	−0.283	0.002

Correlation coefficients of each hormonal percentage change with that of BMD are calculated at 12 and 24 months during HRT

Discussion

Although several investigators have shown that E_2 is a predictor of bone loss [19, 20], there is a conflicting report that correlation of E_2 levels was not significant with BMD [2]. Some issues should be taken into account in evaluating the E_2 value in patients with HRT. Oral administration of estrogen leads to hormone concentrations in hepatic sinusoidal blood that are four to five times higher than those in peripheral blood [12]. This so-called first-pass makes orally ingested E_2 be metabolized to estrone (E_1), resulting in higher E_1 and lower E_2 concentrations. Because the metabolic capacity of the liver may be influenced by diet and possibly stress, large variations in E_1 and E_2 levels can be observed in an individual woman from day to day or from hour to hour. Although E_1 itself is a weak estrogen, it is in reversible equilibrium with E_2 and thus acts as a source of E_2 despite the virtual absence of ovarian E_2 secretion in postmenopausal women. The equilibrium condition also affects the serum E_2 level. Peripheral levels of E_2 may not necessarily represent E_2 levels in target tissues such as bone. Furthermore, the biological effectiveness of the circulating estrogens is affected by binding to sex hormone binding globulin. These physiological mechanisms may complicate the association between serum E_2 level and BMD.

The hypothalamic-pituitary-ovarian axis has been well documented in women with regular cycles, whereas less is known of its axis in postmenopausal women with HRT. Recent reports have demonstrated that mean LH and FSH levels decreased during HRT in women with premature ovarian failure and natural menopause [3, 16, 17], indicating the negative feedback mechanism. Thus, we hypothesized that the change of gonadotropin levels may substitute the E_2 level to predict BMD. In the present study, the percentage change of LH and FSH negatively associated with that of BMD. The correlation

Table 2 Changes in serum estradiol (E_2) and gonadotropin levels and lumbar spine bone mineral density (*BMD*) during hormone replacement therapy (*HRT*). *LH* luteinizing hormone, *FSH* follicle-stimulating hormone

	Before	12 months	24 months
E_2 (pg/ml)	39.3±76.6	71.0±67.9*	68.3±54.5*
LH (mIU/ml)	26.5±16.1	22.9±14.0*	27.4±14.9
FSH (mIU/ml)	67.9±36.3	47.9±29.0*	45.3±24.4*
Lumbar spine BMD (g/cm^2)	0.933±0.157	0.938±0.152**	0.936±0.150

Data are presented as mean ± SD
*$p<0.01$ and **$p<0.05$ compared with the values before HRT

coefficient of LH was comparative to and that of FSH was greater than that of E_2 at both 12 and 24 months. Since gonadotropins are known to be secreted in an episodic fashion, the validity of gonadotropin determinations based on a single blood measure may be questioned. Rossmanith et al. [15] has shown that the pulse amplitude of postmenopausal women with HRT was 4.8±0.7 mIU/ml and 5.7±1.0 mIU/ml for LH and FSH, respectively. The attenuated serum gonadotropin pulsatility has been found in older postmenopausal women [16]. Furthermore, recent reports have shown that the half-life of both LH and FSH was prolonged in postmenopausal women [18, 21]. Taken together, the pulse secretion seems to be negligible to determine the mean gonadotropin levels.

In the present study, both LH and FSH were suppressed at 12 months during HRT, but their levels did not reach to the levels of women with regular cycles. This finding supports that the sensitivity to negative ovarian steroid feedback diminished with age [14]. It is of interest that the negative feedback was removed at 24 months in LH but not in FSH. Aging was associated with a lack of concordance between LH and FSH release and it was no more synchronized by hypothalamic gonadotropin-releasing hormone (GnRH) [8]. FSH but not LH was episodically secreted in postmenopausal women when a GnRH analogue was administered [7]. It has been also shown that hypothalamic changes occurred with aging that were independent of the changes in gonadal hormones [9]. These reports suggest different mechanisms for secretion of LH and FSH in aged women, which in turn may explain the different dynamic state of LH and FSH in patients with HRT.

Bone turnover markers have not been shown their usefulness in predicting BMD [11]. Recently, Chung et al. [4] has reported that pyridinoline and osteocalcin are good markers in correlation with BMD in women −5~0 years since menopause (YSM) and women 0–10 YSM, respectively, indicating that these markers are useful when YSM is considered. Although subjects in our study were women with HRT, the long-term follow-up will be necessary to see how long the measurement of gonadotropin levels is useful to predict BMD, because aging itself affects the sensitivity to sex steroid feedback [16].

In conclusion, the strong relation between the percentage change of BMD and serum gonadotropin levels, especially FSH, was shown. This indicates that the serial measurements of serum FSH levels are useful to predict the change of bone mass in cases where it cannot be monitored directly.

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