

# Effect of Transdermal Estrogen Therapy on Bone Mineral Density in Postmenopausal Korean Women

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**Objectives:** To evaluate the effects of transdermal estrogen therapy on bone mineral density (BMD) in postmenopausal Korean women.

**Methods:** A total of 149 healthy postmenopausal women were retrospectively evaluated: 100 were on hormone therapy (HT) and 49 were the control group. For the HT group, 54 applied estrogen transdermally using either a patch (n = 21) or gel (n = 33), and 46 took estrogen orally (conjugated estrogen 0.625 mg or equivalent). Demographic profiles and changes in BMD over two years were compared according to the route of the estrogen.

**Results:** No differences were found in age, age at menopause, parity, body mass index, and type of menopause among the oral, transdermal and control groups. Compared with controls, HT significantly increased BMD after 2 years in both the lumbar spine and the total hip. The increases in BMD at both lumbar spine and hip were comparable between the oral and transdermal groups. There were also no differences in BMD changes according to progestogen addition in either the oral or transdermal groups.

**Conclusion:** Transdermal estrogen therapy increases BMD, comparable to oral estrogen, in postmenopausal Korean women. (J Menopausal Med 2014;20:111-117)

**Key Words:** Administration cutaneous, Bone density, Hormone replacement therapy, Postmenopause

Menopause, the permanent cessation of menstruation, occurs at the mean age of 49.7 years in Korea.<sup>1</sup> Although the age at menopause has remained remarkably constant, the postmenopausal period has been elongated due to the great increase in the life expectancy of women. In this circumstance, osteoporosis is becoming a major health problem which affects one third of women aged over 50.<sup>2</sup> Meanwhile, osteoporosis can lead to increased medical and social costs, impaired quality of life and higher mortality rate related to fractures.

After menopause, estrogen deficiency results in the accelerated bone loss and increased the risk for fractures. Hormone therapy (HT) has established beneficial effect

on bone loss as well as relief of menopausal symptoms.<sup>3-7</sup> Although oral route is most commonly used for administration of HT, several adverse effects could be a barrier for the treatment, since oral estrogen affects liver function, increases clotting factors or inflammatory markers, and may cause gastrointestinal problems.<sup>8-10</sup> In these aspects, there have been attempts to use non-oral route for estrogen administration. Since transdermal route bypasses the gastrointestinal tract and first hepatic metabolism in contrast to oral route,<sup>9,10</sup> it maintains more constant level of serum estrogen, and alters liver function, clotting, and inflammatory markers less than oral estrogen.<sup>8-10</sup>

Previous studies demonstrated comparable effects of

Received: February 20, 2014 Revised: October 30, 2014 Accepted: November 25, 2014

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transdermal estrogen over oral administration on relief of vasomotor symptoms and protection of bone loss in postmenopausal women.<sup>11,12</sup> However, in Korea, there have been only a few reports on effects of transdermal estrogen in postmenopausal women, and most of them were regarding the effects on symptom relief or lipid metabolism, and skeletal protective effect was rarely addressed.<sup>13-18</sup> The aim of the present study was to compare the effects of estrogen on bone according to route of administration in postmenopausal Korean women.

## Materials and Methods

This retrospective study included 149 healthy postmenopausal women: 100 women who received HT at Samsung Medical Center Menopause Clinic, and 49 women who had annual routine checkups at Samsung Medical Center for Health Promotion. Women without menstruation for at least 12 months or those with serum level of follicle stimulating hormone over 40 mIU/mL were defined as postmenopausal. Only women with baseline and annual follow up results of bone mineral density (BMD) for two years were eligible for this study. Exclusion criteria were prior exposure to HT within 6 months from the baseline and a history of diseases or medications that can affect BMD. In addition, women who changed the route of estrogen administration during the follow up were also excluded.

Women in HT group were treated with either oral (*n* = 46) or transdermal estrogen (*n* = 54). Oral estrogens were conjugated equine estrogen (CEE) 0.625 mg or equivalent, and transdermal estrogens were a patch (estradiol 1.5 mg patch, Estran-50 patch, [Handok Inc., Seoul, Korea] twice a week, *n* = 21) or gel (0.1% estradiol gel, Estreva gel [Samil Pharm Co., Ltd., Seoul, Korea] 1.5 mg once daily, *n* = 33). In oral estrogen group, 16 were treated with estrogen alone, 30 with estrogen combined with progestogen. In transdermal estrogen group, 15 were treated with estrogen alone, and 39 with estrogen combined with progestogen.

BMDs were measured annually using dual energy X-ray absorptiometry (DXA) at the lumbar spine (L2-4) and the total hip. Since there were two types of scan system used for DXA at our center, Hologic system (Hologic Inc.,

Bedford, MA, USA), and Lunar DXA system (GE Healthcare, Madison, WI, USA), standardized BMD were calculated by universal BMD standardization equations to compare BMDs from different system. The equation that used in the present study as follows: sBMD at the spine = 1,0550 X (BMD measured by Hologic system - 0.972) + 1,0436 = 0,9683 X (BMD measured by Lunar system - 1,1) + 1,0436; sBMD at the total hip = (1,008 × BMD measured by Hologic system) + 0,006 = (0,979 × BMD measured by Lunar system - 0,031).<sup>19-21</sup>

Baseline characteristics in oral estrogen, transdermal estrogen and control groups were compared by one-way analysis of variance (ANOVA) for continuous variables and Pearson's chi-square test for categorical variables. BMD changes during the follow up period were compared by repeated measures ANOVA. In addition, independent-sample t test was used to compare the differences between the groups at each time point. Data were analysed with a standard statistical package (PASW 18.0; SPSS, Inc., Chicago, IL, USA), and *P* values less than 0,05 were regarded as statistically significant.

## Results

Table 1 presents clinical characteristics at the baseline. There were no differences in age, age at menarche, age at menopause, parity, body mass index (BMI), and type of menopause among the oral or transdermal estrogen, and the control groups. Standardized baseline BMD at both the lumbar spine and the total hip also did not differ by group (Table 1).

BMD increased after HT (oral or transdermal), while it decreased in control group during the follow up period, showing significant differences at both the lumbar spine and the total hip, respectively (*P* < 0,05 and *P* < 0,01; Fig. 1).

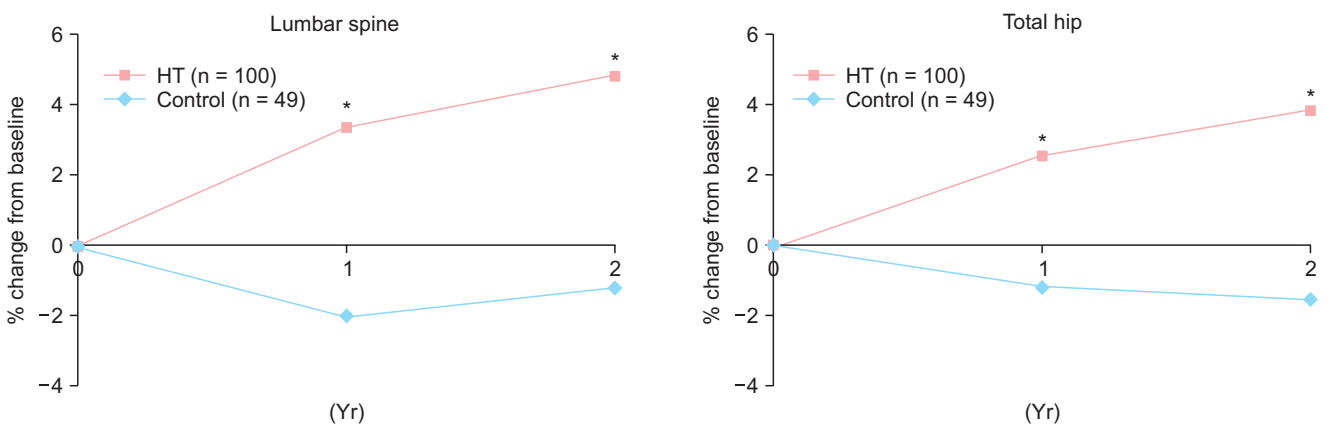
In women who received estrogen alone (*n* = 31), the changes of BMD were not significantly different between the oral (*n* = 16) and transdermal (*n* = 15) route (Fig. 2).

Changes in BMD were compared according to the addition of progestogen. Figure 3 shows the changes in BMD between estrogen alone and estrogen combined with progestogen groups within oral HT group. BMDs increased

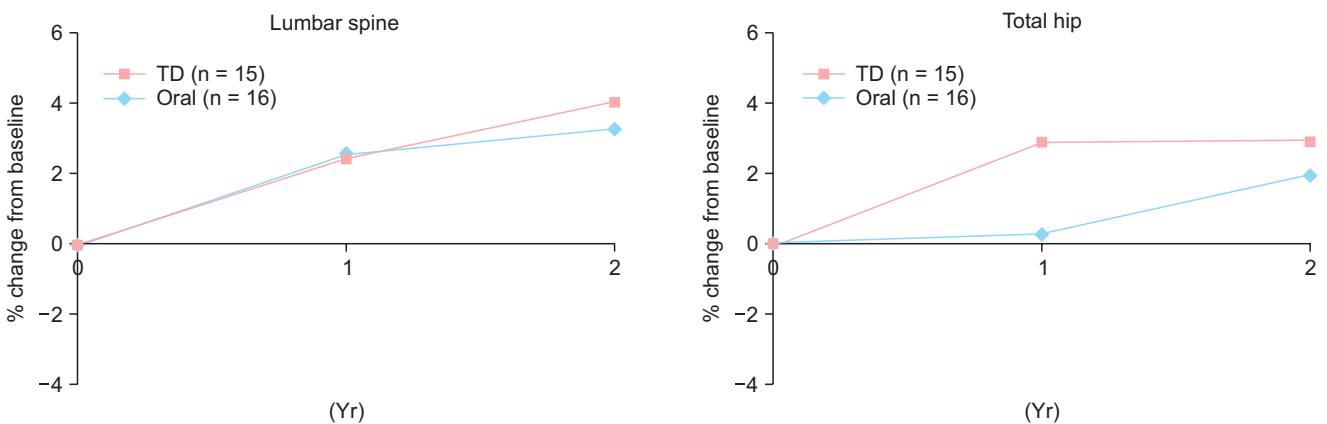
**Table 1.** Baseline characteristics of the study participants

	Oral (n = 46)	Transdermal (n = 54)	Control (n = 49)	P value
Age (years)	53.6 ± 5.9	52.2 ± 5.8	54.6 ± 3.8	0.069
Age at menarche (years)	15.5 ± 1.7	15.6 ± 1.2	15.2 ± 1.7	0.434
Age at menopause (years)	47.6 ± 4.7	46.7 ± 3.4	48.2 ± 5.0	0.192
Parity (n)	2.6 ± 1.3	2.3 ± 1.2	2.5 ± 1.0	0.312
Body mass index (kg/m <sup>2</sup> )	22.8 ± 2.0	23.4 ± 3.1	22.4 ± 2.4	0.115
Type of menopause				0.108
Natural	30 (65.2%)	38 (70.4%)	41 (83.7%)	
Surgical	16 (34.8%)	16 (29.6%)	8 (16.3%)	
Baseline bone mineral density (g/cm <sup>2</sup> )				
Lumbar spine (L2-4)	1.007 ± 0.139	0.996 ± 0.163	1.042 ± 0.155	0.285
Total hip	0.804 ± 0.101	0.791 ± 0.113	0.839 ± 0.100	0.061

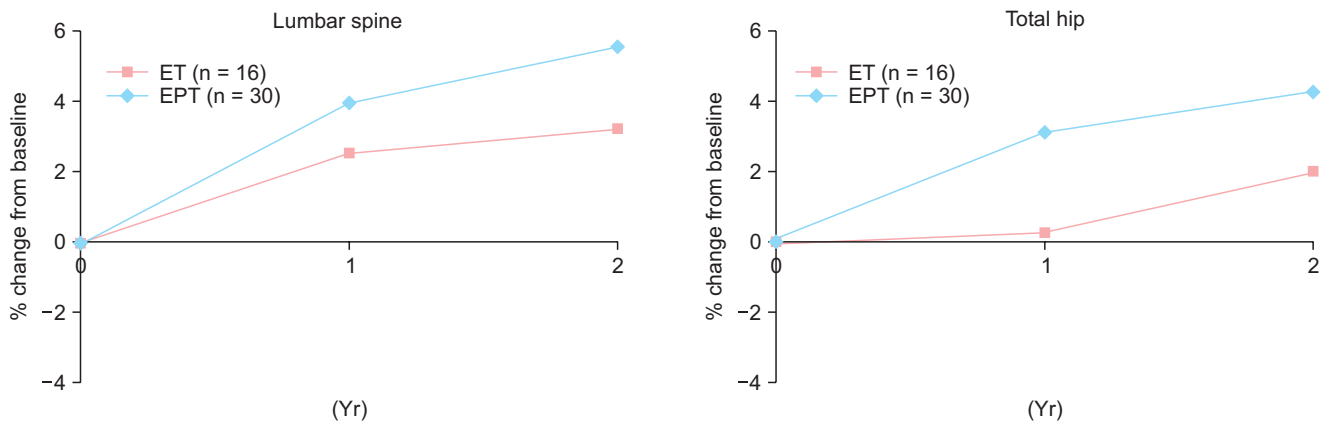
Data are presented as mean ± standard deviation (SD) (P values by one-way analysis of variances) or n (%) (P values by Pearson's chi-square test)



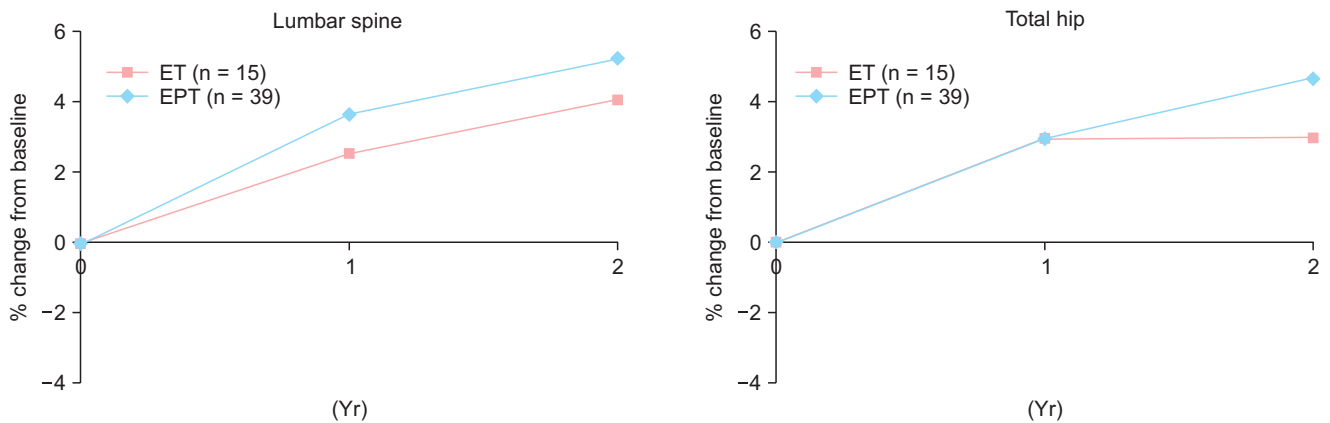
**Fig. 1.** Bone mineral density changes between hormone therapy and control groups. HT: hormonal therapy. \**P* < 0.05, †*P* < 0.01 by independent sample t test.



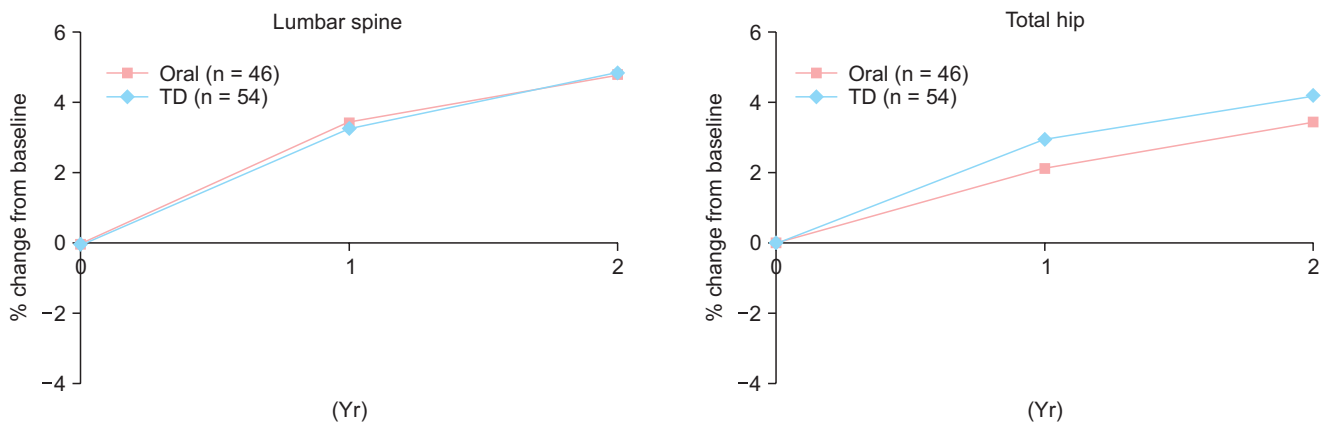
**Fig. 2.** Changes in bone mineral density in women taking estrogen-alone according to route of administration. TD: transdermal.



**Fig. 3.** Changes in bone mineral density in women taking receiving hormone therapy using through oral estrogen. ET: estrogen therapy, EPT: estrogen plus progestogen therapy.



**Fig. 4.** Changes in bone mineral density in women taking hormone therapy using transdermal estrogen. ET: estrogen therapy, EPT: estrogen plus progestogen therapy.



**Fig. 5.** Changes in bone mineral density in women taking hormone therapy according to the route of estrogen administration – pooled analysis. TD: transdermal.

in both groups without significant differences. In addition, within transdermal estrogen group, the pattern of BMD changes was also not different between estrogen alone and estrogen combined with progestogen groups (Fig. 4). Based on these findings, data on estrogen alone and estrogen combined with progestogen were pooled in the subsequent analysis, and comparisons were made only according to the route of estrogen administration.

Figure 5 shows the changes in BMD after 2 years of HT. BMD at the lumbar spine increased by 4.8% in the oral estrogen group (n = 46) and 4.9 % in the transdermal estrogen group (n = 54) after 2 years of treatment. At the total hip, the BMD increased by 3.5 % in the oral estrogen group and 4.2 % in the transdermal estrogen group after 2 years. The changes in BMD at both the lumbar spine and the total hip according to the route of estrogen were comparable.

In addition, within transdermal group, the changes of BMD were not different according to the type of transdermal estrogen – gel or patch (data not shown).

## Discussion

The present study compared changes in BMD according to the route of estrogen in postmenopausal Korean women, and demonstrated a positive effect of transdermal estrogen therapy on BMD, which was comparable to that of oral estrogen therapy.

Changes of BMD did not differ by addition of progestogen in both oral and transdermal estrogen groups, which is consistent with the results of a previous study showing no significant differences in BMD according to progestogen addition.<sup>11</sup> Checa and colleagues<sup>22</sup> also reported comparable odds ratios for bone loss in both the estrogen and estrogen–progestogen therapy. However, there are still conflicting results about the effect of progestogen addition on bone mass. A previous randomized trial reported that addition of medroxyprogesterone acetate (MPA) to CEE showed greater increase in spine BMD than CEE–alone.<sup>23</sup> In addition, another randomized trial also showed additional gain in BMD within the group of CEE 0.625 mg combined with MPA 2.5 mg daily,<sup>24,25</sup> and Dresner–Pollak and colleagues<sup>26</sup>

demonstrated positive effects on bone when norethindrone acetate was added to estradiol in postmenopausal women. To determine the effects of progestogen on bone, further studies are needed

Several studies have proposed ethnic differences on estrogen metabolism. Kim et al.<sup>27</sup> reported different levels of sex hormones in postmenopausal women in different ethnicities. In addition, Caucasian women had higher bioavailable estradiol levels than African–American or Hispanic women, and the changes in estradiol levels among estrogen users were larger in Caucasian women than in African–American women. Huddleston and colleagues<sup>28</sup> reported higher serum estradiol level in Asian after transdermal estradiol, which also suggests differences in metabolic clearance of sex hormones in different ethnic groups. In a similar way, bone metabolism also can be different according to the ethnicity.<sup>29–31</sup> Elevation of bone resorption marker was greater in Japanese women than in African–American or Caucasian women,<sup>32</sup> and BMDs in postmenopausal Caucasian women were higher than those in Asian women at the total hip and spine, but lower than those in African–American women at the hip.<sup>29,33</sup> Consequently, the prevalence of osteoporosis (37.0%) in Korea is higher than in Caucasian women.<sup>34,35</sup> However, fracture rates were lower in Asian women than Caucasian women, and this discrepancy might also be explained by ethnic differences in bone microarchitecture or thickness and density of cortex.<sup>36,37</sup>

In spite of ethnic differences in bone metabolism, there have been limited reports regarding transdermal estrogen in Korean women. Transdermal estrogen was effective for relief of menopausal symptoms, and improvement of lipid profiles,<sup>15–18</sup> but only few reports showed the increase in BMD with transdermal estrogen. A previous study evaluated the effects of transdermal estrogen in 30 postmenopausal Korean women, and reported 4.8% gain of BMD at the lumbar spine, showing consistency with our results. However, effects was not compared according to the route.<sup>16</sup> To the best of our knowledge, this is the first report that compared beneficial effect of transdermal estrogen on bone with oral route in postmenopausal Korean women.

Nevertheless, the present study has some limitations mostly stemming from small sample size and retrospective design. In addition, fracture risk was not assessed.

Use of two different DXA systems might affect precise comparisons, although BMD measurement was converted into standardized BMD for comparison.<sup>19-21</sup>

In conclusion, transdermal estrogen therapy increases BMD, to a similar degree with oral estrogen in postmenopausal Korean women.

## Acknowledgement

This work has been supported in part by Sungkyunkwan University Foundation for Corporate Collaboration (S-2010-0228-000) and Samsung Medical Center Research Fund (PH01040831 and PH01095801).

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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