Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2025**; 52(9): 26546
https://doi.org/10.31083/CEOG26546

Original Research

Differences Between Oral Tibolone and Estradiol Plus Dydrogesterone in Improving Bone Mineral Density in Peri- and Post-menopausal Women

Yan Zhou[1], Yang Zhou[1], Changbing Li[1], Huaping Li[1,*], Minfang Tao[1,*]

[1]Department of Gynecology and Obstetrics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 200233 Shanghai, China

*Correspondence: lihp@sjtu.edu.cn (Huaping Li); taomf@sjtu.edu.cn (Minfang Tao)

Academic Editor: Dah-Ching Ding

Submitted: 12 September 2024 Revised: 10 March 2025 Accepted: 24 June 2025 Published: 29 September 2025

Abstract

Background: To retrospectively investigate the efficacy and influencing factors of tibolone and estradiol plus dydrogesterone in improving bone mineral density (BMD) in peri- and post-menopausal women, to provide a basis for clinical management. **Methods**: Women aged 40–60 years who were undergoing menopausal transition or were post-menopausal, and who attended the menopause clinic at the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, between January 3, 2011, and May 11, 2020, were included in this study. Participants received tibolone or estradiol plus dydrogesterone for the management of menopause-related symptoms. Demographic characteristics were recorded, and BMD was measured using dual-energy X-ray absorptiometry at baseline and at 1, 2, and 3 years post-treatment to compare the efficacy of the two treatments in improving BMD. **Results**: The use of estradiol plus dydrogesterone showed an increasing trend in the BMD of the lumbar spine, total hip, and femoral neck after 1 and 2 years of treatment, with a decrease in the third year. Tibolone treatment showed a decreasing trend in BMD after 1, 2, and 3 years, indicating that estradiol plus dydrogesterone is superior to tibolone in improving BMD. After 3 years of tibolone treatment, changes in BMD were correlated with age, height, weight, and body mass index (BMI), whereas after 3 years of estradiol plus dydrogesterone treatment, changes in BMD showed no significant correlation with age, height, weight, and BMI. **Conclusions**: Both estradiol plus dydrogesterone and tibolone are beneficial for maintaining BMD in peri- and post-menopausal women, with estradiol plus dydrogesterone demonstrating greater advantage over tibolone.

Keywords: menopause; tibolone; estradiol + dydrogesterone; bone mineral density

1. Introduction

As the world population ages, the incidence of osteoporosis (OP) increases, becoming a serious health threat to the middle-aged and older populations, with post-menopausal women being the most significantly affected group. OP is a skeletal system disease characterized by decreased bone strength and an increased risk of fractures [1]. The latest epidemiological survey in China reported that the prevalence of OP among people >60 years old has reached 32.0% (10.7% and 51.6% in men and women, respectively), with majority of them being post-menopausal women [2]. Bone mass loss in post-menopausal women is related to estrogen deficiency and is a major factor in post-menopausal OP [3]. The declining estrogen levels disrupt the dynamic balance between bone formation—primarily by osteoblasts—and bone resorption—mainly by osteoclasts—leading to bone loss [4]. Therefore, post-menopausal estrogen therapy is one of the main measures for post-menopausal OP. Hormone replacement therapy is highly effective in slowing bone loss and preventing fractures in women aged <60 years or <10 years of menopause [5].

At present, several medications for menopausal hormone therapy (MHT) are available, with clinical applications in China primarily focusing on tibolone and estradiol + dydrogesterone; the main component of tibolone is 7α-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one [6]. Following drug metabolism, it exhibits distinct effects in various organs, manifesting as estrogenic, progestagenic, and androgenic activities. Its estrogenically active metabolites have an osteogenic effect, which increases bone mineral density (BMD) and improves menopausal symptoms [7]. 17β-estradiol and dydrogesterone are the main components of estradiol + dydrogesterone, and 17β-Estradiol can improve menopausal symptoms and OP.

MHT formulations vary in their ability to improve BMD. This study aimed to compare the changes in BMD and its differences pretreatment and at 1, 2, and 3 years post-treatment with tibolone and estradiol + dydrogesterone in women during menopausal transition and after menopause; explore the similarities and differences in the efficacy of the two drugs in improving the BMD of women; and provide clinical evidence for evaluating the effectiveness of prevention and treatment of post-menopausal OP.

2. Participants and Methods

2.1 Participants

We conducted a retrospective review of the medical records of peri- and post-menopausal women who visited the menopause clinic of the Department of Gynecology and Obstetrics at Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, between January 3, 2011, and May 11, 2020. Participants aged 40–60 years, in the menopausal transition and post-menopausal stages according to the criteria of reproductive aging +10 [8], with normal liver and kidney functions, who did not undergo hormonal therapy in the past 6 months, with no contraindications to MHT and willing to undergo MHT, and consistently taking medications as prescribed were included in the study. However, those who have already received antibone resorption treatment, have undergone hysterectomy and oophorectomy, are involved in high-intensity physical activity, are smokers, and did not undergo follow-up <1 year post-treatment were excluded. Overall, this study included 362 eligible participants and was approved by the Ethics Committee of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Approval number: 2023-R02).

2.2 Grouping

According to the principles of MHT and considering participants' wishes, if menstruation is desired during peri-menopause, estradiol + dydrogesterone is prescribed. However, if menstruation is not desired during peri-menopause, tibolone is recommended—similar to when menstruation is not desired post-menopause. When a woman aged <50 years strongly desires menstruation within 2 years post-menopause, estradiol + dydrogesterone is prescribed. A single oral tibolone (1012869, NV Organon, Oss, Netherlands), with each tablet containing tibolone 2.5 mg tablet was administered once every day; 240 participants were included in the tibolone group. Similarly, a single estradiol + dydrogesterone (362939, Abbott Biologicals B.V., Olst, Overijssel, Netherlands), with each tablet containing 17β-estradiol 2.0 mg and dydrogesterone 10 mg tablet was administered once every day; 122 participants were included in the estradiol + dydrogesterone group.

2.3 Study Methods

The demographic characteristics of the participants, including age, height, and weight, were collected using a self-designed questionnaire [9]. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). The modified Kupperman menopause index (KMI) was used for assessing menopausal symptoms [10], which includes 13 items. Total scores of $\leq$6, 7–15, 16–30, and $>$30 indicate no, mild, moderate, and severe symptoms, respectively. Dual-energy X-ray absorptiometry (Hologic) was used for measuring the lumbar spine (L1–L4), left femoral neck, and total hip BMD of the participants. Changes in BMD values and differences from baseline to 1, 2, and 3 years post-treatment were compared between the two groups.

2.4 Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software version 26.0 (IBM Corporation, Armonk, NY, USA). BMD was normally distributed (Kolmogorow-Smironov, KS test) and expressed as ($\bar{x} \pm$ s); pre- and post-treatment comparisons were conducted using independent sample *t*-tests. In the demographic data, height was normally distributed and analyzed using independent sample *t*-tests. Age, weight, and BMI were approximately normal distribution and are analyzed using an independent sample *t*-test. Quantitative and categorical data were compared using analysis of variance (ANOVA) and chi-square tests, respectively. Age, height, weight, and BMI data did not follow normal distribution. Thus, Spearman's correlation was used to test associations. A *p*-value of <0.05 was considered statistically significant, and a *p*-value of <0.01 was considered highly statistically significant.

3 Results

3.1 Demographic Characteristics

The average age of the participants was 50.905 $\pm$ 5.159 years. The tibolone group included 240 participants with an average age of 53.008 $\pm$ 4.005 years. The estradiol + dydrogesterone group encompassed 122 participants with an average age of 46.812 $\pm$ 4.707 years, which was lower than that of the tibolone group. Significant statistical differences were observed between the two groups regarding age, duration of education, employment status, and KMI scores ($p < 0.001$, $p = 0.008$, $p = 0.000$, and $p = 0.000$, respectively; $p < 0.01$). No significant statistical differences were noted between the two groups regarding height, weight, BMI, marital status, and fertility status ($p = 0.292$, $p = 0.350$, $p = 0.585$, $p = 0.093$, and $p = 0.064$, respectively; $p > 0.05$) (Table 1).

3.2 Analysis of BMD Values Pre- and Post-Treatment In Both Groups

3.2.1 Changes in Total Hip BMD Pre- and Post-Treatment in Both Groups

No statistically significant differences were noted between the total hip BMD and baseline for the 2-year treatment. In the estradiol + dydrogesterone group, total hip BMD slightly increased by 0.87% and 1.3% after 1- and 2 years of treatment, respectively, compared to baseline, with a partial decrease (0.43%) after 3 years (Fig. 1). Conversely, in the tibolone group, the total hip BMD decreased by 0.22%, 0.67%, and 1.01% after 1, 2 and 3 years of treatment (Fig. 1), respectively. The differences in total hip BMD values between the two groups were statistically sig-

Table 1. Analysis of demographic characteristics between the two groups ($\bar{x} \pm s$).

Item		Total (362)	Estradiol + Dydrogesterone (122)	Tibolone (240)	*p*-value
		Value/cases (%)	Value/cases (%)	Value/cases (%)	
Age (years)		50.905 ± 5.159	46.812 ± 4.707	53.008 ± 4.005	<0.001
Height (cm)		158.886 ± 5.477	158.475 ± 5.671	159.110 ± 5.375	0.292
Weight (kg)		57.028 ± 7.762	56.486 ± 8.331	57.319 ± 7.459	0.350
BMI (kg/m²)		22.571 ± 2.682	22.458 ± 2.661	22.628 ± 2.696	0.585
Marital status	Married	352 (100.0)	116 (33.0)	236 (67.0)	0.093
	Unmarried (including divorced)	10 (100.0)	6 (60.0)	4 (40.0)	
Education duration	≤9 years	58 (100.0)	18 (31.0)	40 (69.0)	0.008
	10 years ≤ Duration < 14 years	121 (100.0)	29 (24.0)	92 (76.0)	
	≥14 years	183 (100.0)	75 (41.0)	108 (59.0)	
Fertility status	Childless	28 (100.0)	13 (46.4)	15 (53.6)	0.064
	1 Child	297 (100.0)	92 (31.0)	205 (69.0)	
	>1 Child	37 (100.0)	17 (45.9)	20 (54.1)	
Employment status	Employed	210 (100.0)	107 (50.9)	103 (49.1)	0.000
	Not employed (retired + unemployed)	152 (100.0)	15 (9.9)	137 (90.1)	
KMI score	KMI total score <6 Score	30 (100.0)	19 (63.3)	11 (36.7)	0.000
	KMI total score 6–15	121 (100.0)	50 (41.3)	71 (58.7)	
	KMI total score 16–30	177 (100.0)	46 (26.0)	131 (74.0)	
	KMI total score >30	34 (100.0)	7 (20.6)	27 (79.4)	

Note: the data for height follow a normal distribution and are analyzed using an independent sample *t*-test. Age, weight, and BMI were approximately normal distribution and were analyzed using an independent sample *t*-test. The remaining data, including marital status, and employment status, are analyzed using the continuity correction chi-square tests. Education Duration, total KMI scores are analyzed using chi-square tests. BMI, body mass index; KMI, Kupperman menopause index.

nificant after 1, 2, and 3 years of treatment ($p = 0.013$, $p = 0.020$, and $p = 0.024$, respectively; $p < 0.05$). The differences in the increase in total hip BMD values between the two groups were statistically significant after 1 and 2 years of treatment ($p = 0.048$ and $p = 0.020$, respectively; $p < 0.05$). A statistically significant difference in baseline total hip BMD values was observed in both groups, but no statistical difference was found in the increase in these values after 3 years of treatment ($p > 0.05$) (Table 2).

3.2.2 Changes in Femoral Neck BMD Before and After Treatment in Both Groups

No statistically significant differences were observed between the two groups regarding the initial baseline femoral neck BMD and baseline for 2 years of treatment ($p = 0.200$ and $p = 0.302$, respectively). The estradiol + dydrogesterone group showed a slight increase in femoral neck BMD after 1 and 2 years compared with that at baseline (0.95% and 0.46%), whereas a slight decrease was noted after 3 years (1.68%) (Fig. 2). In contrast, the tibolone group exhibited a slight decrease in femoral neck BMD after 1, 2, and 3 years (0.95%, 1.77%, and 2.13%) (Fig. 2). Differences in the increase in femoral neck BMD after 1 and 2 years of treatment were observed between the two groups ($p = 0.010$ and $p = 0.011$, respectively; $p < 0.05$); however, no statistically significant difference in the increase after the 3-year treatment was noted ($p = 0.646$; $p > 0.05$) (Table 3).

3.2.3 Changes in Lumbar Spine (L1–L4) BMD Pre- and Post-Treatment in the Two Groups

No statistically significant differences were noted between the two groups regarding the initial baseline lumbar spine BMD for the 2-year treatment ($p = 0.165$). The estradiol + dydrogesterone group showed increased lumbar spine (L1–L4) BMD after 1 and 2 years (1.45% and 1.40%) (Fig. 3). After 3 years of treatment, a slight decrease in lumbar spine (L1–L4) BMD was observed (0.18%) (Fig. 3). The tibolone group exhibited a decrease in lumbar spine (L1–L4) BMD after 1, 2, and 3 years (0.097%, 0.67%, and 1.26%) (Fig. 3). The difference in the increase in lumbar spine (L1–L4) BMD between the two groups after 2 years of treatment was statistically significant ($p = 0.013$; $p < 0.05$). No statistically significant difference in the increase in lumbar spine (L1–L4) BMD after 1 and 3 years of treatment was observed ($p = 0.076$ and $p = 0.447$, respectively; $p > 0.05$) (Table 4).

3.3 Analysis of Factors Related to Changes in BMD After the 3-Year Treatment

3.3.1 Analysis of Factors Related to Changes in BMD at Different Sites After the 3-Year Treatment

The ANOVA results indicated that marital status ($p = 0.139$, $p = 0.164$, and $p = 0.604$), duration of education ($p = 0.756$, $p = 0.282$, and $p = 0.432$), fertility status ($p = 0.404$ and $p = 0.939$, $p = 0.926$), KMI score ($p = 0.954$, $p = 0.726$, and $p = 0.836$), and employment status ($p = 0.772$, p

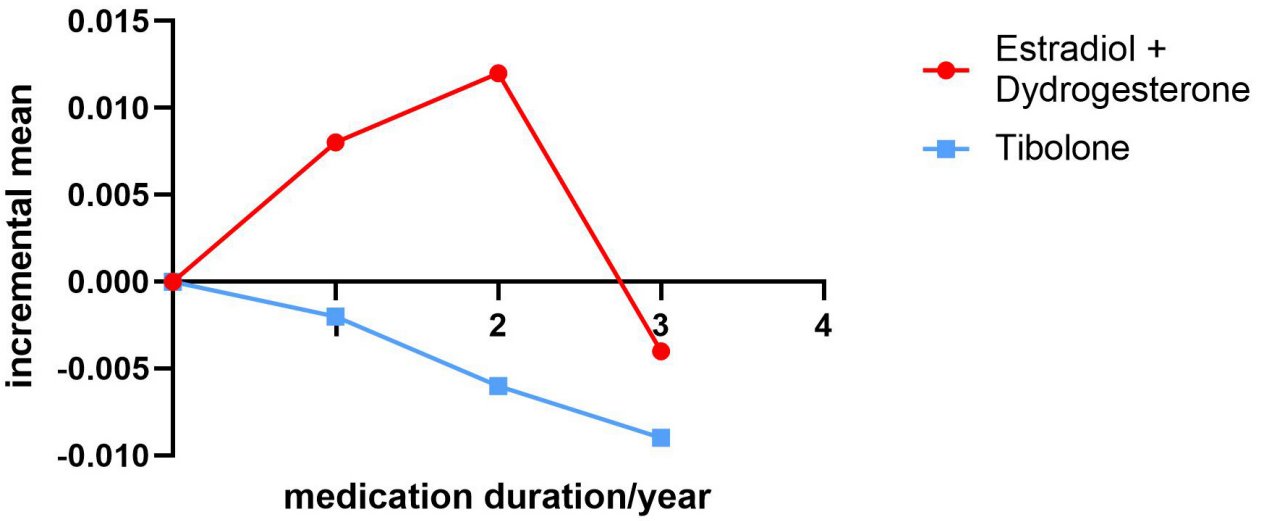

Fig. 1. Comparison of total hip bone mineral increments between the estradiol + dydrogesterone and tibolone groups.

Table 2. Changes in total hip BMD Pre- and Post-treatment in both groups ($\bar{x} \pm s$).

Total Hip Bone Mineral Density	Total	Estradiol + Dydrogesterone	Tibolone	*p*-value
Number of Cases	362	122	240	
Before Treatment	0.903 ± 0.124	0.917 ± 0.129	0.895 ± 0.121	0.109
After 1 Year of Treatment	0.904 ± 0.118	0.926 ± 0.118	0.893 ± 0.117	0.013
Increase After 1 Year of Treatment	0.001 ± 0.047	0.008 ± 0.053	–0.002 ± 0.044	0.048
Number of Cases	241	84	157	
Baseline for 2-Year Treatment Cases	0.902 ± 0.133	0.914 ± 0.139	0.895 ± 0.129	0.274
After 2 Years of Treatment	0.902 ± 0.121	0.927 ± 0.117	0.889 ± 0.122	0.020
Increase in 2-Year Treatment Cases	0.0002 ± 0.058	0.012 ± 0.069	–0.006 ± 0.051	0.020
Number of Cases	172	44	128	
Baseline for 3-Year Treatment Cases	0.906 ± 0.126	0.938 ± 0.119	0.895 ± 0.126	0.047
After 3 Years of Treatment	0.899 ± 0.122	0.934 ± 0.117	0.886 ± 0.122	0.024
Increase After 3 Years of Treatment	–0.008 ± 0.045	–0.004 ± 0.033	–0.009 ± 0.048	0.574

Note: The increments in total hip BMD after 1, 2, and 3 years are the differences in BMD values at 1, 2, and 3 years post-treatment compared with the baseline total hip BMD at the first diagnosis, 2 years prior, and 3 years prior, respectively. The total hip BMD values conform to a normal distribution. Comparisons of BMD between the estradiol + dydrogesterone and tibolone groups are performed using an independent sample *t*-test for computational analysis. BMD, bone mineral density.

= 0.604, and $p = 0.962$) were not associated with changes in BMD at various sites after 3 years ($p > 0.05$; **Supplementary Table 1**). Furthermore, marital status ($p = 0.798$, $p = 0.630$, and $p = 0.268$), duration of education ($p = 0.801$, $p = 0.396$, and $p = 0.217$), fertility status ($p = 0.803$, $p = 0.780$, and $p = 0.551$), KMI score ($p = 0.596$, $p = 0.723$, and $p = 0.300$), and employment status ($p = 0.410$, $p = 0.309$, and $p = 0.305$) were not associated with the increase in BMD at various sites after 3 years ($p > 0.05$, **Supplementary Table 2**). Spearman's correlation showed that age influenced changes in total hip and lumbar spine (L1–L4) BMD after 3 years of treatment ($p = 0.040$ and $p = 0.044$, respectively; $p < 0.05$; **Supplementary Table 3**). Furthermore, height was correlated with changes in femoral neck, total hip, and lumbar spine (L1–L4) BMD after 3 years of treatment ($p = 0.008$, $p = 0.014$, and $p = 0.002$, respectively; $p < 0.05$; **Supplementary Table 3**). Weight was correlated with the increase in femoral neck, total hip, and lumbar spine (L1–L4) BMD after 3 years of treatment ($p = 0.018$, $p = 0.022$, and $p = 0.011$, respectively; $p < 0.05$; **Supplementary Table 3**). BMIs were correlated with the increase in femoral neck, total hip, and lumbar spine (L1–L4) BMD after 3 years of treatment ($p = 0.003$, $p = 0.002$, and $p = 0.004$, respectively; $p < 0.05$; **Supplementary Table 3**). No patients with nontraumatic fractures were observed during this period.

3.3.2 Analysis of Factors Related to Changes in BMD at Different Sites After 3 Years of Estradiol + Dydrogesterone Treatment

ANOVA results indicated that fertility status affected total hip BMD ($p = 0.048$; $p < 0.05$; **Supplementary Table**

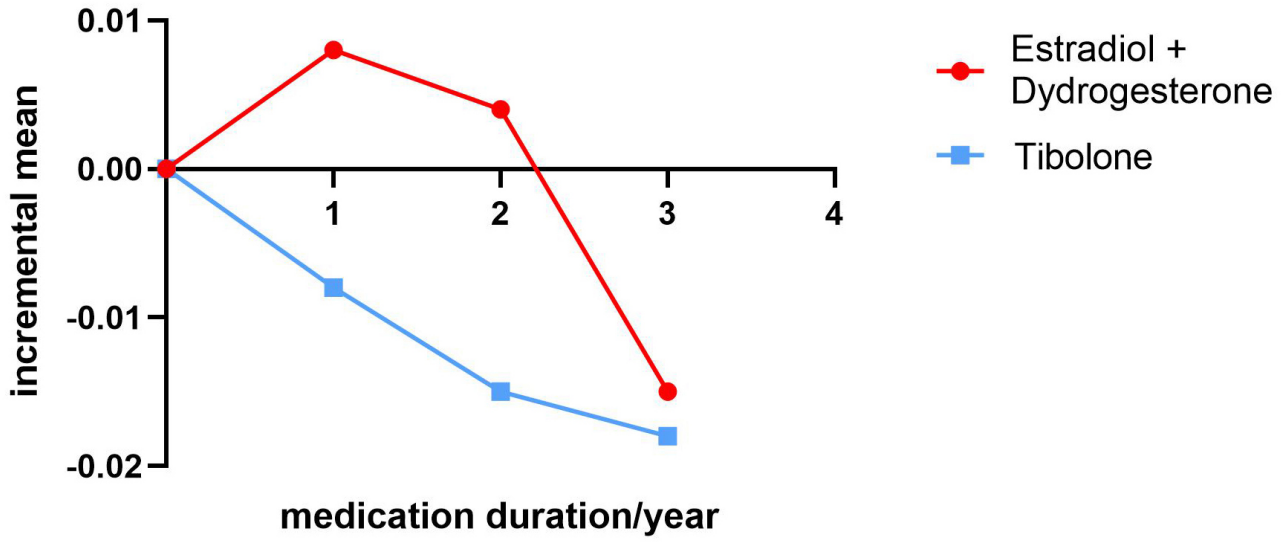

Fig. 2. Comparison of femoral neck bone mineral density increments between the estradiol + dydrogesterone and tibolone groups.

Table 3. Changes in femoral neck BMD pre- and post-treatment in both groups ($\bar{x} \pm s$).

Femoral neck bone mineral density	Total	Estradiol + Dydrogesterone	Tibolone	*p*-value
Number of Cases	362	122	240	
Before Treatment	0.846 ± 0.127	0.858 ± 0.134	0.840 ± 0.123	0.200
After 1 Year of Treatment	0.842 ± 0.121	0.862 ± 0.126	0.832 ± 0.118	0.025
Increase After 1 Year of Treatment	–0.002 ± 0.056	0.008 ± 0.058	–0.008 ± 0.054	0.010
Number of Cases	241	84	157	
Baseline for 2-Year Treatment Cases	0.852 ± 0.128	0.864 ± 0.139	0.846 ± 0.122	0.302
After 2 Years of Treatment	0.845 ± 0.117	0.869 ± 0.117	0.832 ± 0.116	0.017
Increase in 2-Year Treatment Cases	–0.007 ± 0.057	0.004 ± 0.063	–0.015 ± 0.053	0.011
Number of Cases	172	44	128	
Baseline for 3-Year Treatment Cases	0.859 ± 0.117	0.894 ± 0.110	0.846 ± 0.118	0.020
After 3 Years of Treatment	0.841 ± 0.115	0.879 ± 0.114	0.828 ± 0.113	0.011
Increase After 3 Years of Treatment	–0.017 ± 0.045	–0.015 ± 0.038	–0.018 ± 0.047	0.646

The increments in femoral neck BMD at 1, 2, and 3 years post-treatment are the differences between the femoral neck BMD values at these respective timepoints and the initial femoral neck BMD at diagnosis, and at 2 and 3 years prior. Femoral neck BMD values are normally distributed. Comparisons of bone density between the estradiol + dydrogesterone and tibolone groups are performed using an independent sample *t*-test for calculation and analysis.

4). Education duration was related to the increment in lumbar spine (L1–L4) BMD after 3 years ($p = 0.02$; $p < 0.05$; **Supplementary Table 5**). Spearman's correlation analysis showed that age, height, weight, and BMI were not significantly correlated with the changes in the femoral neck, total hip, and lumbar spine (L1–L4) BMD or their increments after 3 years ($p > 0.05$; **Supplementary Table 6**).

3.3.3 Analysis of Factors Related to Changes in BMD at Different Sites After 3 Years of Tibolone Treatment

The ANOVA results indicated that marital status influenced the femoral neck and total hip BMD ($p < 0.05$); however, education duration, reproductive history, KMI score, and occupational status were not significantly related to the changes in BMD at different sites after 3 years ($p > 0.05$; **Supplementary Tables 7,8**). Spearman's correlation analysis showed that age was significantly correlated with the increment in the lumbar spine (L1–L4) BMD ($p < 0.05$; **Supplementary Table 9**). Height affected the femoral neck, total hip, and lumbar spine (L1–L4) BMD after 3 years ($p < 0.05$; **Supplementary Table 9**). Weight and BMI were significantly correlated with the changes and increments in the femoral neck, total hip, and lumbar spine (L1–L4) BMD after 3 years ($p < 0.05$; **Supplementary Table 9**).

4. Discussion

Estrogen is closely associated with bone metabolism [11]. Following the menopausal transition, estrogen levels rapidly decrease with decreasing ovarian function, directly

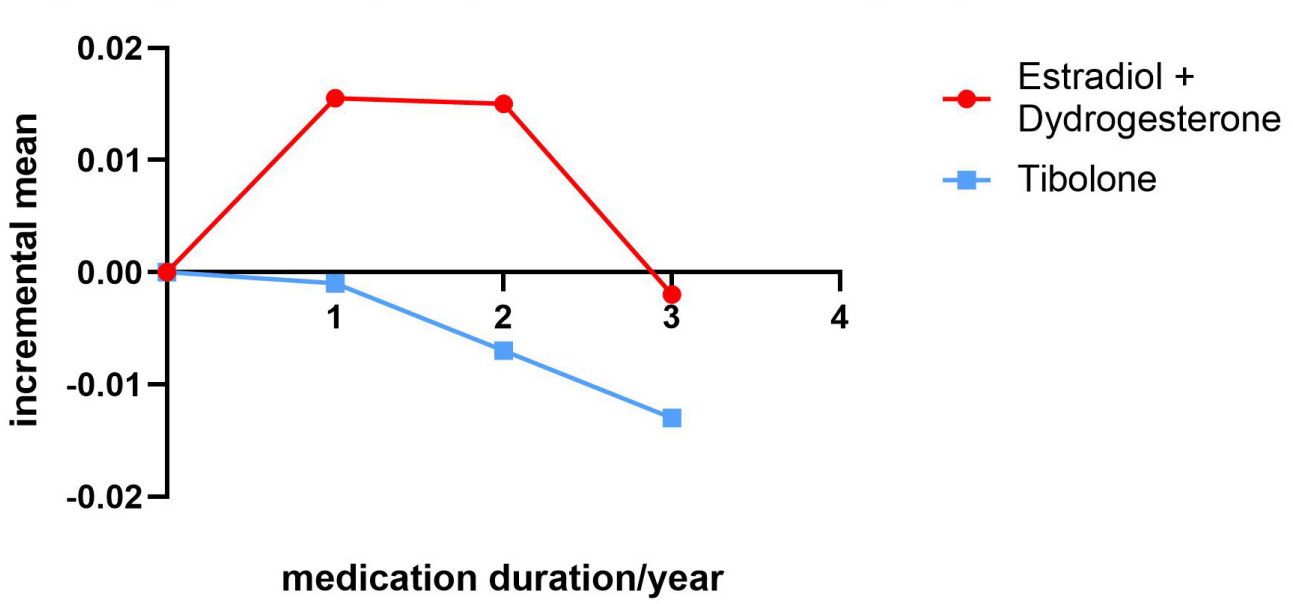

Fig. 3. Comparison of lumbar spine (L1–L4) bone mineral density increments between the estradiol + dydrogesterone and tibolone groups.

Table 4. Changes in lumbar spine (L1–L4) BMD pre- and post-treatment in both groups ($\bar{x} \pm s$).

Lumbar 1~4 bone mineral density	Total	Estradiol + Dydrogesterone	Tibolone	*p*-value
Number of Cases	362	122	240	
Before Treatment	1.044 ± 0.163	1.068 ± 0.163	1.031 ± 0.162	0.039
After 1 Year of Treatment	1.048 ± 0.161	1.084 ± 0.168	1.030 ± 0.154	0.002
Increase After 1 Year of Treatment	0.004 ± 0.084	0.0155 ± 0.110	–0.001 ± 0.067	0.076
Number of Cases	241	84	157	
Baseline for 2-Year Treatment Cases	1.049 ± 0.164	1.069 ± 0.169	1.038 ± 0.161	0.165
After 2 Years of Treatment	1.049 ± 0.157	1.083 ± 0.161	1.031 ± 0.152	0.013
Increase in 2-Year Treatment Cases	0.0005 ± 0.073	0.015 ± 0.066	–0.007 ± 0.075	0.025
Number of Cases	172	44	128	
Baseline for 3-Year Treatment Cases	1.049 ± 0.163	1.093 ± 0.162	1.034 ± 0.162	0.038
After 3 Years of Treatment	1.039 ± 0.160	1.09 ± 0.159	1.021 ± 0.157	0.013
Increase After 3 Years of Treatment	–0.010 ± 0.074	–0.002 ± 0.059	–0.013 ± 0.079	0.447

The increments in lumbar spine (L1–L4) BMD after 1, 2, and 3 years are the differences between the BMD values at those timepoints and the initial values at diagnosis, 2 years prior, and 3 years prior, respectively. Lumbar spine (L1–L4) BMD values follow a normal distribution, and comparisons of BMD between the estradiol + dydrogesterone and tibolone groups are performed using independent sample *t*-tests for computational analysis.

leading to bone loss. Reportedly, the cumulative loss rate of lumbar spine BMD over a 10-year post-menopause is 10.6%, of which 7.38% is lost during the menopausal transition [12]. Moreover, the loss of BMD in the femoral neck is 9.1%; of which 5.8% occurs during the transition period [12]. Therefore, preventing and treating menopause-related OP during and after the menopausal transition is essential. Since the 1930s, estrogen can reportedly be used to treat bone loss due to declining ovarian function and improve other menopause-related issues [13]. With the continuous development of estrogen preparations and decades of clinical practice, MHT has become an integral part of the health strategy for women during and after the menopausal transition [14]. Menopausal estrogen therapy can reduce fractures in the lumbar spine, total hip, and other areas prone to post-menopausal OP—a considerable disease affecting the health of middle-aged and older women [15].

However, different formulations and dosages of estrogen vary in effectiveness for treating and preventing post-menopausal OP. Currently, frequently used menopausal estrogen therapy formulations in China include 17β-estradiol + dydrogesterone and tibolone; although tibolone is not an estrogen–progestogen therapy, it exerts estrogenic, progestogenic, and androgenic effects following metabolism. 17β-estradiol + dydrogesterone is the preferred choice for peri-menopausal women and can also be used by post-

menopausal women who desire "menstrual" bleeding. Tibolone is the preferred choice for post-menopausal women; in addition, it can be used by peri-menopausal women who do not wish to have menstrual bleeding. A study has reported that using 17β-estradiol + dydrogesterone 2 mg can increase vertebral and femoral neck BMD by 6.7% and 2.5%, respectively [15]. After 8 years of using tibolone, compared with the baseline, the average lumbar spine and femoral neck BMD increased by 4.1% and 4.6%, respectively [16]. However, clinical evidence on the impact of 17β-estradiol + dydrogesterone and tibolone on the BMD of women in China during and after the menopausal transition is yet to be determined.

We accomplished this by conducting a real-world clinical study. This study is a real-world clinical trial based on the principles of MHT and preferences of women, treating those in peri- and post-menopause with 17β-estradiol + dydrogesterone and tibolone. According to the therapeutic regimen, we divided them into two groups: estradiol + dydrogesterone and tibolone. Although age discrepancies were noted, no significant difference was observed in their baseline total hip and femoral neck BMD. Changes in BMD indicated that the estradiol + dydrogesterone group showed increases in lumbar (1.45% and 1.40%), total hip (0.87% and 1.3%), and femoral neck (0.95% and 0.46%) BMD after 1 and 2 years of treatment; however, the declines in the third year were 0.18%, 0.43%, and 1.68%, respectively (Figs. 1,2,3). Overall, the tibolone group showed a decrease, indicating that estradiol + dydrogesterone treatment is superior to tibolone treatment in improving femoral neck and lumbar spine BMD in peri- and post-menopausal women. Although the tibolone group exhibited a decreasing trend in lumbar spine and hip BMD, the magnitude of the decrease in lumbar spine and hip BMD after menopause was significantly reduced compared with those reported in previous studies. Lester and Coleman [17] reported that menopause is linked to a swift decline in bone mass, leading to a reduction of up to 3% per year during the first 5 years following its occurrence. This study showed that both drugs were beneficial for post-menopausal OP.

To analyze the efficacy and dosage, we used 17β-estradiol 2 mg, which is the standard dosage for peri-menopausal women. Although tibolone 2.5 mg is a standard dose, it is primarily intended for the post-menopausal population, suggesting that its estrogenic effect should be lower than that of 17β-estradiol 2 mg; therefore, its BMD improvement is less than that of 17β-estradiol 2 mg. This study indirectly demonstrated the impact of drug dosage on BMD improvement; however, further high-level and large-sample studies are required to confirm this.

Considering the treatment duration, 17β-estradiol 2 mg showed an increasing trend 1 and 2 years post-treatment; however, a decreasing trend was observed in the third year of treatment, indicating that the effective duration of menopausal estrogen therapy is 1–2 years. As age increases and treatment duration extends, BMD shows a declining trend, suggesting that this finding may be related to patient aging; however, further studies are necessary.

Correlation analysis showed that the treatment effect of the 17β-estradiol + dydrogesterone group was not related to major indicators, such as age and BMI. The treatment effect of the tibolone group was related to age and BMI. This study, which is based on real-world data and involves a small sample size, employed a retrospective design and, thus, inherently carries certain limitations. Furthermore, the absence of multivariate analysis in this study precluded the exclusion of potential confounding factors that may have concurrently influenced the independent and dependent variables, introducing bias into the results. Consequently, we recommend that future research adopt a prospective study design and expand the sample size to further explore the relationship and impact of the two drugs on BMD for clinical guidance in post-menopausal OP prevention and treatment.

5. Conclusions

We found that estradiol + dydrogesterone is superior to tibolone in improving BMD. After 3 years of tibolone treatment, changes in BMD were correlated with age, height, weight, and BMI, whereas after 3 years of estradiol + dydrogesterone treatment, changes in BMD showed no significant correlation with age, height, weight, and BMI.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contributions

The study's conception and design were undertaken by MFT. YanZ, YangZ, CBL, HPL were contributed to the research's data acquisition. The data analysis and interpretation were shouldered by YanZ and MFT. YanZ were responsible for the manuscript's initial drafting, while MFT critically revised the manuscript for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (2023-R02) and all the researchers collected data in strict accordance with the ethical requirements through-

out the study. All subjects gave their informed consent for inclusion before they participated in the study.

Acknowledgment

We would like to express my gratitude to all those who helped me during the writing of this manuscript.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG26546.

References

[1] Li J, Chen X, Lu L, Yu X. The relationship between bone marrow adipose tissue and bone metabolism in postmenopausal osteoporosis. Cytokine & Growth Factor Reviews. 2020; 52: 88–98. https://doi.org/10.1016/j.cytogfr.2020.02.003.

[2] Brown JP. Long-Term Treatment of Postmenopausal Osteoporosis. Endocrinology and Metabolism (Seoul, Korea). 2021; 36: 544–552. https://doi.org/10.3803/EnM.2021.301.

[3] Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause (New York, N.Y.). 2021; 28: 973–997. https://doi.org/10.1097/GME.0000000000001831.

[4] Zhang L, Zheng YL, Wang R, Wang XQ, Zhang H. Exercise for osteoporosis: A literature review of pathology and mechanism. Frontiers in Immunology. 2022; 13: 1005665. https://doi.org/10.3389/fimmu.2022.1005665.

[5] "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause (New York, N.Y.). 2022; 29: 767–794. https://doi.org/10.1097/GME.0000000000002028.

[6] Verheul HAM, Timmer CJ, Kloosterboer HJ. Pharmacokinetic parameters of sulfated tibolone metabolites in postmenopausal women after single and multiple doses of tibolone. Clinical Pharmacology and Therapeutics. 2007; 81: 573–579. https://doi.org/10.1038/sj.clpt.6100094.

[7] Castrejón-Delgado L, Castelán-Martínez OD, Clark P, Garduño-Espinosa J, Mendoza-Núñez VM, Sánchez-Rodríguez MA. Effect of Tibolone on Bone Mineral Density in Postmenopausal Women: Systematic Review and Meta-Analysis. Biology. 2021; 10: 211. https://doi.org/10.3390/biology10030211.

[8] Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, *et al*. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. The Journal of Clinical Endocrinology and Metabolism. 2012; 97: 1159–1168. https://doi.org/10.1210/jc.2011-3362.

[9] Zhou Y, Zheng Y, Li C, Hu J, Zhou Y, Geng L, *et al*. Association of body composition with menopausal symptoms in (peri-)menopausal women. Climacteric: the Journal of the International Menopause Society. 2018; 21: 179–183. https://doi.org/10.1080/13697137.2018.1428295.

[10] Wang X, Juan J, Gao D, Song B, Zhang X. Associations between menopausal symptoms and cardiovascular disease in middle-aged Chinese women. Climacteric: the Journal of the International Menopause Society. 2024; 27: 413–420. https://doi.org/10.1080/13697137.2024.2368479.

[11] Tomczyk-Warunek A, Winiarska-Mieczan A, Blicharski T, Blicharski R, Kowal F, Pano IT, *et al*. Consumption of Phytoestrogens Affects Bone Health by Regulating Estrogen Metabolism. The Journal of Nutrition. 2024; 154: 2611–2627. https://doi.org/10.1016/j.tjnut.2024.05.026.

[12] Cauley JA. Estrogen and bone health in men and women. Steroids. 2015; 99: 11–15. https://doi.org/10.1016/j.steroids.2014.12.010.

[13] SELEY AD, BAUMGOLD D, VERNICK S. Oral estrogen therapy during menopause. The Journal of Clinical Endocrinology and Metabolism. 1947; 7: 451.

[14] Baber RJ, Panay N, Fenton A, IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric: the Journal of the International Menopause Society. 2016; 19: 109–150. https://doi.org/10.3109/13697137.2015.1129166.

[15] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288: 321–333. https://doi.org/10.1001/jama.288.3.321.

[16] Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 beta and dydrogesterone. Osteoporosis International: a Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2001; 12: 251–258. https://doi.org/10.1007/s001980170113.

[17] Lester J, Coleman R. Bone loss and the aromatase inhibitors. British Journal of Cancer. 2005; 93 Suppl 1: S16–22. https://doi.org/10.1038/sj.bjc.6602691.