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Original Article

Effect of Tibolone on Postmenopausal Bone Loss

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Abstract. A 2-year non-randomized prospective study was carried out in a teaching hospital menopause clinic to assess the effect on the skeleton of tibolone (Livial, Organon) 2.5 mg daily in recently postmenopausal women. One hundred women who were between 6 and 36 months since their last menstrual period and had raised gonadotrophin levels consistent with the menopause were allocated into two groups. One group received 2.5 mg tibolone daily and the other group no medication. Bone densitometry of the spine and femur was performed at 0, 6, 12 and 24 months and biochemical markers of bone metabolism were assessed at these points. Severity of hypo-oestrogenic symptoms was assessed at baseline and at 1 and 2 years. After 2 years there was a significant increase in bone mass as measured by dual energy X-ray absorptiometry (DXA) of 2.5% in the spine, and 3.5% in the neck of femur in the women who took tibolone ($n = 46$), whereas in the control group ($n = 45$) bone loss occurred (spine, 2.9%; femur, 3.7%). When these changes were compared they were significantly different for both sites ($p < 0.001$). In the treatment group the urinary hydroxyproline/creatinine and calcium/creatinine ratios fell from 0.014 (0.002–0.027) to 0.010 (0.000–0.111) (mol/l) (mmol/l) ($p < 0.01$) and 0.47 (0.08–0.96) to 0.33 (0.09–1.20) (mmol/l) (mmol/l) ($p < 0.001$) respectively, while the serum osteocalcin and alkaline phosphatase decreased from 1.90 (0.20–4.70) to 1.00 (0.00–3.00) mmol/l ($p < 0.01$) and 190 (92–301) to 138 (91–283) mmol/l ($p < 0.001$) respectively. In conclusion we have found that tibolone given in the early postmenopausal years suppresses skeletal metabolism and prevents bone loss in both spine and femur. Tibolone therefore has a potentially important long-term role in the reduction of the incidence of osteoporotic fractures, particularly in view of the compliance that 'bleed-free' therapy will encourage.

Keywords: Bleed-free HRT; Prevention of bone loss; Tibolone

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Introduction

At the menopause, in the presence of declining ovarian function and diminishing oestrogen levels, the female skeleton undergoes increased bone remodelling [1,2] and the rate of bone loss is increased [3,4]. The role of oestrogen replacement therapy in preventing postmenopausal bone loss has been well documented [5–9]. However, while to protect the skeleton long-term use is necessary, there is a reluctance among women to continue hormone replacement therapy. Mean duration of use is in the order of months rather than years [10], with the commonest reason for cessation of therapy being the withdrawal bleeding which is required to protect the endometrium in conventional combined therapies [11].

Tibolone ((7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one; Livial) is a synthetic compound with weak hormonal properties. Comparative animal studies have demonstrated that tibolone's oestrogenic potency is about one-fiftieth that of ethinyl oestradiol, its progestagenic potency is one-eighth that of norethisterone and its androgenic potency is one-third that of norethisterone [12]. The appealing clinical feature of tibolone is that it does not stimulate the endometrium [13–15], thus eliminating the need for women to have a progestagen-induced withdrawal bleed.

Previous studies of tibolone using single-photon absorptiometry [16] to measure the metacarpal mineral bone content demonstrated that tibolone was protective against postmenopausal bone loss. With the advent of more sophisticated techniques for measuring bone density the sites of clinical relevance, i.e. spine and hip, can now be measured directly.

In the present study of recently postmenopausal women we have investigated the effect of tibolone on bone density by using dual energy X-ray absorptiometry (DXA) to measure the lumbar spine and three sites in the femur, i.e. the neck of femur, the trochanter and Ward's triangle.

Subjects and Methods

One hundred healthy women (mean age 49.5 years, SD 4.2 years) who were between 6 and 36 months postmenopause (as documented by time since last menstrual period and raised gonadatrophin levels) were recruited into a 2-year non-randomized study of the effect of tibolone on bone density. The women were given the choice of receiving hormone replacement therapy (HRT) or not. Recruitment took place over a period of 18 months. If women withdrew during this period they were replaced. After 2 years 46 women remained in the tibolone group and 45 in the control group. None had any history of metabolic bone disease, were taking drugs or had coexistent diseases known to affect bone and mineral metabolism. All recruits were either non-smokers or smoked fewer than 10 cigarettes per day. The groups were compared (unpaired *t*-test) for age, body mass index, months since menopause, and parity (Table 1). Women were excluded if they had previously been on HRT or if they had had a hysterectomy or endometrial ablation. Informed consent was obtained from all subjects and the protocol was approved by the Guy's Hospital Ethics Committee.

At the initial visit all women underwent a full physical examination and endometrial biopsies (Gynocheck, Roussell Laboratories, UK) were taken. Tibolone (2.5 mg) was prescribed in the treatment group. The control group had no medication. Subsequent follow-up was 3-monthly for 2 years. Prior to the commencement of the study all patients had a lateral radiograph of the lumbar spine to exclude vertebral fractures. The women were given questionnaires prior to the study and at 1 and 2 years to evaluate the average number of hot flushes per day they were experiencing.

Table 1. Baseline demographic characteristics of the tibolone and control groups

	Tibolone (n = 46)	Control (n = 45)
Age at menopause (yr)	48.4±4.2	50.4±3.2
Months since LMP	21.0±9.6	20.9±9.7
Parity	2.3±1.3	2.2±1.2
Body mass index	25.6±6.0	25.0±4.0

Values are the mean ± SD.
An unpaired *t*-test was used to compare the groups and there was no significant difference for all of the parameters stated.
LMP, last menstrual period.

Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DXA; Hologic 1000) in the lumbar spine (L1–4), proximal neck of femur, the trochanter and Ward's triangle at 0, 6, 12, and 24 months. All scans were performed and analyzed by one operator. The long-term precision error of the daily BMD measurements of the anthropomorphic spine phantom was 0.38%. In vivo precision on subjects with repeated measurements was on average 1.2% for the hip and 1.1% for the spine. Height and weight were measured at the time of each bone densitometry measurement and the body mass index calculated (body mass index = weight/height^2).

Blood samples were obtained from all women at 0, 6, 12 and 24 months. Serum concentrations of calcium and phosphate and alkaline phosphatase were measured using a Hitachi 737 autoanalyzer. Serum concentrations of FSH and LH were measured by radioimmunoassay (RIA) (Chelsea Hospital for Women Kit) and oestradiol by the DPC Coat-a-Count Oestradiol kit (DPL Diagnostic Products). Serum osteocalcin was measured by RIA (Incstar, Winnersh, Berkshire, UK).

Fasting urine concentrations of hydroxyproline and creatinine were measured (0, 6, 12 and 24 months) and the ratio used as an index of bone resorption. Twenty-four hour collections of urine were analyzed for calcium and creatinine levels and the ratio used as an index of bone resorption. Urinary calcium concentration was measured with a Greiner G-300 analyzer using the O-cresolpthalein complexone-DEA method and creatinine concentration also with a Greiner G-300 but using the Jaffe (kinetic) method. Urinary hydroxyproline concentration was analyzed as described by Bergman and Loxley [17] using spectrophotometry.

Endometrial biopsies were performed at 0, 12 and 24 months, and analyzed both cytologically and histologically. If entry to the endometrial cavity was not possible, vaginal ultrasound of the endometrium was performed.

Drug compliance was checked by the return of all tablet bottles and the remaining tablets correlated with consumption. If more than 6 tablets had been missed over a 3-month period the patient was excluded from the trial.

Statistical Analyses

The baseline demographic characteristics were compared using an unpaired *t*-test.

The bone densities were found to have a normal distribution so the baseline differences were compared using an unpaired *t*-test and within the two groups the measurements over the 2 years were compared with their baseline values by paired *t*-tests.

The percentage changes in bone mass were compared

by unpaired t-test for the lumbar spine and neck of femur.

The serum and urinary measurements were not normally distributed so the baseline differences were compared using the Mann–Whitney U-test and the within-group changes were analysed with the Wilcoxon matched-pairs signed-rank test.

The baseline number of flushes in each group were compared with an unpaired t-test. The changes within the groups were compared by paired t-tests.

Results

The two groups were matched in terms of demographic characteristics (Table 1). FSH and LH serum levels remained >20 iu/l and >50 iu/l respectively in all patients. Serum oestradiol levels were within the post-menopausal range throughout the trial at each assessment point.

Histological and cytological analysis of the endometrial samples showed no evidence of endometrial stimulation in any samples. In 2 patients in the treatment group and 5 in the control group the cavity was not entered, but vaginal ultrasound of the endometrium did not demonstrate thickening.

Bone densitometry values are presented in Table 2. The baseline values between the two groups at all sites were not significantly different. The tibolone-treated group at 2 years showed significant increases from the baseline assessment in the lumbar spine (p <0.001), the neck of femur (p <0.05), Ward's triangle (p <0.05) and the trochanter (p <0.01). The control group showed a significant decrease in bone density in the lumbar spine

Table 2. Bone density (DXA) values in the tibolone and control groups over 2 years

	Months	Tibolone (n = 46)	Control (n = 45)
Lumbar spine (g/cm^2)	0	0.970±0.152 ~	0.990±0.156
	6	0.981±0.152***	0.981±0.158*
	12	0.986±0.147***	0.977±0.165**
	24	0.993±0.153***	0.962±0.163***
Neck of femur (g/cm^2)	0	0.783±0.122 ~	0.786±0.108
	6	0.793±0.117 NS	0.783±0.111 NS
	12	0.797±0.102 NS	0.777±0.104 NS
	24	0.807±0.108*	0.764±0.124***
Ward's triangle (g/cm^2)	0	0.596±0.101 ~	0.590±0.106
	6	0.586±0.106 NS	0.581±0.104 NS
	12	0.605±0.098 NS	0.577±0.110 NS
	24	0.616±0.100*	0.576±0.119*
Trochanter (g/cm^2)	0	0.680±0.103 ~	0.705±0.108
	6	0.689±0.108 NS	0.692±0.103*
	12	0.687±0.104 NS	0.684±0.112**
	24	0.697±0.096**	0.670±0.096**

Values are the mean ± SD.
The differences in baseline measurements were compared by an unpaired t-test; measurements within each group were compared by a paired t-test.
*p <0.05; **p <0.01; ***p <0.001. NS, not significant; ~, not significantly different at baseline.

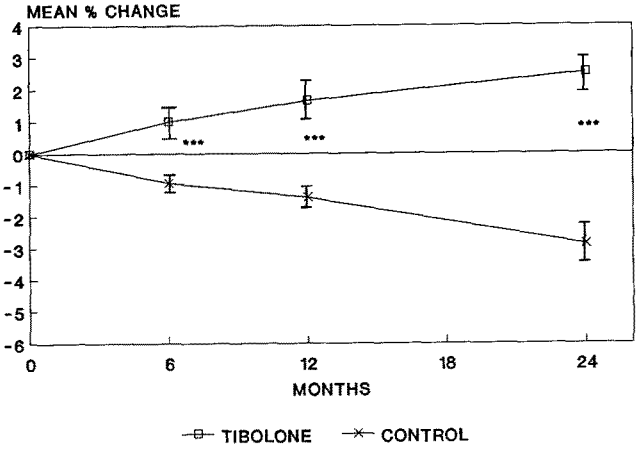

Fig. 1. Bone density changes (mean percentage initial value with standard error of the mean) in lumbar spine. The two groups were compared with an unpaired t-test. Tibolone group, n = 46; control group, n = 45. ***p <0.001.

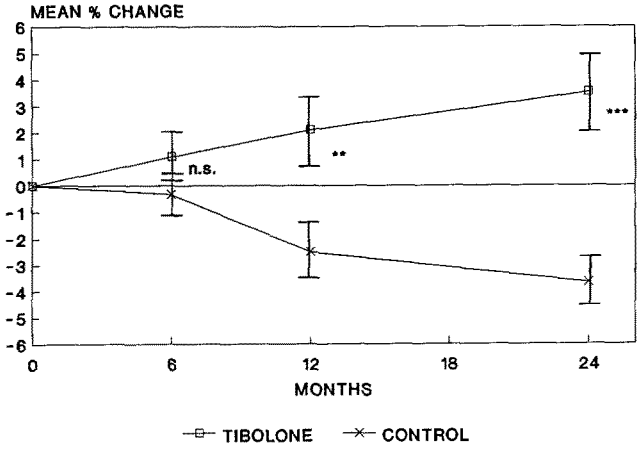

Fig. 2. Bone density changes (mean percentage initial value with standard error of the mean) in neck of femur. The two groups were compared with an unpaired t-test. Tibolone group, n = 46; control group, n = 45. n.s. = not significant; **p <0.01; ***p <0.001.

(p <0.001), the neck of femur (p <0.001), Ward's triangle (p <0.05) and trochanter (p <0.01).

When the percentage change in bone loss for the lumbar spine and neck of femur were directly compared between the two groups the results at 2 years were highly significant for both sites (p <0.001) (Figs 1, 2).

In the tibolone group review of individual patient results over 2 years showed that 39 of 46 (85%) had increased bone density in the spine and 33 of 45 (75%) increased bone density in the femur.

The biochemical values are presented in Table 3. The baseline biochemical parameters between groups were not significantly different. Significant reductions in serum calcium, (p <0.001), phosphorus (p <0.01), alkaline phosphatase (p <0.001) and serum osteocalcin (p <0.01) occurred in the tibolone group over the 2 years of treatment. The control group showed an increase in serum phosphorus (p <0.001) and serum

Table 3. Serum alkaline phosphatase, calcium, phosphorus and osteocalcin in the tibolone and control groups over 2 years

	Months	Tibolone (n = 46)	Control (n = 45)
Alkaline phosphatase (mmol/l)	0	190 (92–301) ~	173 (79–430)
	6	152 (91–287)***	172 (82–392) NS
	12	145 (92–374)***	176 (82–400) NS
	24	138 (91–283)***	169 (98–398) NS
Calcium (mmol/l)	0	2.40 (2.20–2.60) ~	2.40 (2.20–3.10)
	6	2.40 (2.20–2.50) NS	2.40 (2.20–2.66) NS
	12	2.30 (2.10–2.60)***	2.40 (2.11–2.57) NS
	24	2.22 (2.08–2.54)***	2.38 (2.09–2.61) NS
Phosphorus (mmol/l)	0	1.10 (0.80–1.66) ~	1.09 (0.70–1.40)
	6	0.90 (0.40–2.26)***	1.10 (0.88–1.50) NS
	12	0.90 (0.50–1.40)***	1.10 (0.80–1.31)***
	24	0.94 (0.54–1.50)**	1.11 (0.87–1.64)***
Osteocalcin (mmol/l)	0	1.90 (0.20–4.70) ~	1.25 (0.02–4.20)
	6	1.40 (0.20–4.00)*	1.50 (0.20–7.60)*
	12	1.00 (0.20–3.10)**	1.50 (0.20–6.60)**
	24	1.00 (0.00–3.00)**	1.50 (0.10–7.30)*

Values are the mean (range).
The differences in baseline measurements were compared with the Mann–Whitney U-test; the Wilcoxon matched-pairs signed-rank test was used to compare changes within the groups.
*p <0.05; **p <0.01; ***p <0.001. NS, not significant; ~, not significantly different at baseline.

Table 4. Urinary hydroxyproline/creatinine and calcium/creatinine ratios in the tibolone and control groups over 2 years

	Months	Tibolone (n = 46)	Control (n = 45)
Hydroxy-proline/ creatinine ratios[a]	0	0.014 (0.002–0.027) ~	0.011 (0.001–0.088)
	6	0.013 (0.003–0.050) NS	0.012 (0.0000.065) NS
	12	0.009 (0.020–0.050)***	0.015 (0.0000.052) NS
	24	0.010 (0.000–0.111)**	0.012 (0.0000.050) NS
Calcium/ creatinine ratios[b]	0	0.47 (0.08–0.96) ~	0.51 (0.01–1.23)
	6	0.39 (0.06–1.17)***	0.48 (0.09–1.30) NS
	12	0.31 (0.10–0.97)**	0.46 (0.12–1.23) NS
	24	0.33 (0.09–1.20)***	0.46 (0.11–1.25) NS

[a](μmol/l)/(mmol/l); [b](mmol/l)/(mmol/l).
Values are the median (range).
The differences in baseline measurements were compared with the Mann–Whitney U-test; the Wilcoxon matched-pairs signed-rank test was used to compare changes within the groups.
**p <0.01; ***p <0.001. NS, not significant; ~, not significantly different at baseline.

osteocalcin (p <0.05), whereas the other parameters showed no change (Table 3).

There was a significant fall in urinary calcium/creatinine ratios (p <0.001) and hydroxyproline/creatinine ratios (p <0.01) in the tibolone-treated group while in the control group there was no significant change (Table 4).

Throughout the 2-year observation period there were no statistically significant changes in height or weight.

During the trial, 12 women withdrew from the tibolone group. One woman had persistent bleeding, 1 woman felt 'hungover', 1 felt no dramatic change in wellbeing, 2 developed acne, 2 gained weight (5 pounds in 2 months), 4 did not attend follow-up, and 1 was advised to stop tibolone by a vascular surgeon prior to having her varicose veins stripped. In the control group 11 women withdrew: 6 wished to commence HRT and 5 did not attend for follow-up. No women were withdrawn for lack of medication compliance.

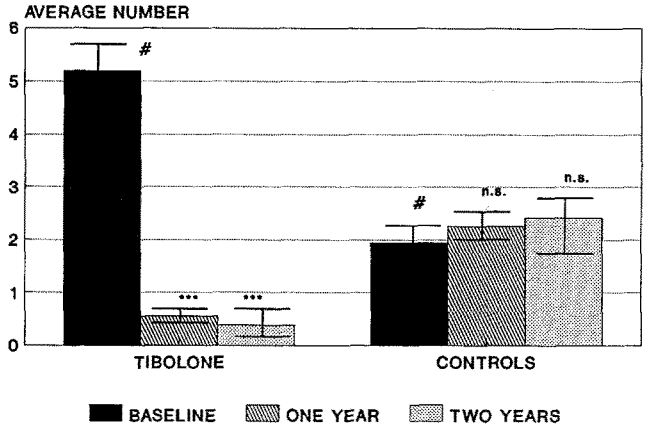

Fig. 3. The average number of hot flushes per day in the tibolone and control groups over the 2 years. The baseline number in each group were compared with an unpaired t-test; the changes within the groups were compared with paired t-tests. Tibolone group, n = 46; control group, n = 45. n.s, not significant; #p <0.01; ***p < 0.001.

Twelve women in the treated group (and 5 in the control group) experienced vaginal bleeding, and all but 1 continued on tibolone treatment without further bleeding. Formal dilatation and curettage in all these patients showed no evidence of endometrial proliferation.

There was a significant difference (p <0.01) between the baseline number of flushes per day in the tibolone group (5.2 ± 4.1) compared with the control group (1.9 ± 1.2). Over the 2 years the number of flushes in the tibolone group decreased significantly (p <0.001) whereas there was no significant change in the reference group (Fig. 3).

Discussion

The concept of bleed-free HRT is a goal that the majority of women in the postmenopausal years would appreciate [18]. From our experience [19] and previous work [15] tibolone would appear to provide such a therapy. Whilst the relief of climacteric symptoms is the basic aim of HRT, the rationale for its long-term use is the prevention of osteoporosis and benefits in relation to cardiovascular disease. This study addresses the effect of tibolone on bone density.

We have demonstrated that tibolone at a dose of 2.5 mg/day does prevent bone loss in postmenopausal women. The control group showed the expected reduction in bone density in the spine and neck of femur of 2.9% and 3.7% respectively. The tibolone-treated patients not only maintained their bone mass but gained 2.5% in the spine and 3.5% in the femoral neck over the 2 years of the study. These data are further supported by

a recent study of women with established osteoporosis which showed that tibolone inhibited bone loss and induced an increase in bone mass [20]. Moreover the gain in axial bone density was apparently not at the expense of any cortical bone loss.

The biochemical data indicate the effect of tibolone to be due to suppression of bone remodelling. Urinary calcium/creatinine and hydroxyproline/creatinine ratios were suppressed in the therapy group in keeping with inhibition of bone resorption. The reduction in serum alkaline phosphatase and osteocalcin, markers of bone formation, were also suppressed, reflecting an overall reduction in bone remodelling secondary to inhibition of bone resorption. As expected the control group showed increases in these biochemical parameters due to the increased bone resorption and remodelling which occurs in the early postmenopausal years. Although there are no histomorphometric data available relating to tibolone use, it would seem that this compound behaves similarly to oestrogen with regard to its effect on biochemistry and bone density measurements.

This very positive effect of tibolone on bone density would lead us to believe that in the long term tibolone will significantly decrease fracture risk. The increase in bone density in the femur with tibolone use is particularly reassuring as fractures of the femur are associated with greater morbidity and mortality than spinal fracture. The overall pattern of global skeletal protection is similar to that found with oestrogen. This is important as it is possible for a therapeutic agent to protect against spinal bone loss but to have little or no effect on the peripheral skeleton [21]. In the case of fluoride it has even been suggested that while there can be dramatic increases in spinal bone mass there may be loss of bone density in the femur [22]. Increase in bone mass with tibolone use is likely to be due to inhibition of bone resorption with subsequent continuation of osteoblastic activity leading to filling in of resorption cavities [23]. It is unlikely that there is a true anabolic effect, although as yet there are no long-term data relating to the skeletal effects of tibolone.

Some women do lose bone while receiving tibolone therapy, which is in accordance with the findings of other investigators who have observed this with oestrogen therapy [19]. However, it may be that bone loss would have been greater in the absence of therapy.

At entry into the study the women in the tibolone group were experiencing a higher number of flushes per day than the control group. It is thus possible that there was an element of bias for women with more severe hypo-oestrogenism to select treatment with tibolone. Naessen et al. [24] reported that women with severe climacteric symptoms may have an excessive rate of bone loss. In this context it is of interest that at baseline the tibolone group had lower spinal bone density than the control group and the baseline biochemical markers of bone turnover were higher than in the control group, although these differences were not significantly different.

There seems little doubt that for skeletal protection long-term use of HRT or other anti-resorptive agents is necessary, perhaps in the order of 10–15 years. Compliance is therefore a major issue in achieving this goal. Both our own studies and those of others [14,15, 16,19,20] have found that tibolone overcomes one of the serious drawbacks of conventional combined therapies with oestrogen and progestagens, i.e. regular withdrawal bleeding. The subjects in our study had only 23 episodes of bleeding in over 1000 months of usage. Endometrial biopsies at 1 and 2 years did not reveal stimulation.

As with all hormone replacement therapies, cessation of therapy for a variety of reasons does occur. A major problem with conventional combined treatment is breast tenderness and premenstrual symptoms. These did not occur with tibolone.

Thus our study has shown that tibolone prevents postmenopausal bone loss at the key sites of spine and femur. The drug is well-tolerated and effective in controlling menopausal symptoms. Compliance for a non-bleeding form of HRT is likely to be improved when compared with conventional therapies. Tibolone therefore has exciting potential as a therapeutic agent in the prevention of osteoporosis.

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