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Mammographic Density in Postmenopausal Women Treated with Tibolone, Estriol or Conventional Hormone Replacement Therapy

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Abstract

Objective: To compare the effects of tibolone, estriol and conventional hormone replacement therapy (HRT) on mammographic parenchymal density in postmenopausal women.

Design and Setting: This was a non-randomised, prospective, longitudinal, comparative study conducted at two specialist outpatient clinics in Chile.

Patients and Participants: 210 non-obese, postmenopausal women aged <65 years with a normal mammogram at baseline.

Methods: Participants received one of seven oral HRT regimens for 1 year. Treatments (daily doses) were: (i) estradiol 2mg; (ii) estradiol 2mg plus sequential medroxyprogesterone acetate (MPA) 5mg for 10 to 16 days/cycle; (iii) estradiol 2mg plus continuous MPA 2.5mg; (iv) combined equine estrogens (CEE) 0.625mg; (v) CEE 0.625mg plus sequential MPA 5mg; (vi) estriol 2mg; or (vii) tibolone 2.5mg. In addition, an age-matched group of 30 untreated control individuals was studied.

Results: Increased mammographic density occurred in 67, 57, 30, 43 and 27% of patients receiving regimens (i) to (v), respectively. No patients receiving tibolone or estriol experienced increases (both $p < 0.05$ *vs* conventional HRT). Overall, 67 of 210 treated patients [31.9%; 95% confidence interval (CI) 25.7%, 38.6%] experienced increases, compared with one of 30 controls (3.3%; 95% CI 0%, 17.2%).

Conclusions: Neither the tissue-specific agent tibolone nor the short-acting estrogen estriol induced any breast density increase. Increased breast density was more frequent with regimens containing estradiol than CEE, and with unopposed rather than opposed regimens. Tibolone (or estriol, if suitable) may be a preferable HRT for women in whom this is a concern.

Hormone replacement therapy (HRT) provides undoubted benefits to postmenopausal women by alleviating vasomotor and urogenital symptoms and by preventing osteoporosis. However, there is still some concern about the effects on breast tissue of conventional HRT regimens (i.e. those containing estradiol or estrogens, alone or with progestogens), in particular in view of recent indications of an association between long-term HRT use and the diagnosis of breast cancer.[1,2]

Studies have indicated that various conventional HRT regimens are associated with an increase in mammographic parenchymal density.[3,4] Increased density in itself has been shown to correlate with increased risk of breast cancer.[5,6] In addition, increased density can impair interpretation of mammograms, increasing the failure rate of screening programmes.[7,8] Therefore, a lack of increase in mammographic density with treatment should be an important consideration for the prescribing physician.

We wished to compare the effects on mammographic density of the tissue-specific HRT tibolone, and the weakly estrogenic hormone estriol, with those of conventional estradiol- and estrogen-containing HRT regimens. Although previous studies have examined the effect of HRT on breast density, many of these were small or uncontrolled,[9,10] did not distinguish between regimens,[4,10] or studied only one type of estrogen.[9,11] Tibolone has been shown to be effective in treating climacteric symptoms[12,13] and preventing bone loss.[14,15] In addition, compared with HRT containing estradiol or combined equine estrogens (CEE), there is a significantly lower incidence of vaginal bleeding and breast tenderness.[12,13] *In vitro* and *in vivo* studies indicate that tibolone does not have an estrogenic effect on breast cells: it inhibits both the local production of estradiol in breast tissue and the growth and development of mammary tumours in rats.[16,17] This study was designed to compare changes in the mammographic density patterns of postmenopausal women after 1 year of treatment with tibolone, estriol or conventional HRT.

Materials and Methods

This non-randomised, prospective, longitudinal, comparative study was conducted at two specialist outpatient clinics in Chile. Women eligible for selection were required to be postmenopausal, defined as being aged >50 years and either amenhorreic for >12 months or with follicle-stimulating hormone (FSH) levels of >40 mIU/ml. Eligible women had undergone a routine mammogram (baseline) at one of the study centres, subsequently received HRT prescribed by their general practitioner for 1 year, and then received a second (follow-up) mammogram at the same centre. The baseline mammogram was required to show no signs indicative of tumour presence.

Obese women [i.e. with body mass index (BMI) >30 kg/m^2], those aged >65 years, with previous breast surgery or with risk factors for breast cancer at baseline were excluded. Women who had received concomitant therapy for hyperprolactinaemia or had taken HRT for >6 months before the baseline mammogram were also excluded.

As the study was observational with anonymous evaluation of the results and no publication of any identifiying features, no ethical approval or consent was required.

Data were compared from patients receiving the following seven HRT regimens containing estradiol, CEE, estriol or tibolone:

- estradiol 2mg daily;
- estradiol 2mg daily plus medroxyprogesterone acetate (MPA) 5mg sequentially;
- estradiol 2mg daily plus MPA 2.5mg daily;
- CEE 0.625mg daily;
- CEE 0.625mg daily plus MPA 5mg sequentially;
- tibolone (Livial®, Organon) 2.5mg daily;
- estriol (Ovestin®, Organon) 2mg daily.

In sequential regimens, MPA was taken for 10 to 16 days per cycle, depending on the prescribing doctor and individual patient. For women who received sequential regimens, the mammogram was taken after the occurrence of withdrawal bleeding, following the last MPA intake of the cycle.

Data from seven groups of 30 women, each receiving one of the above HRT regimens, were

analysed. An additional 30 age-matched, postmenopausal women attending the study centres for routine annual mammography served as a control group, giving a total study population of 240 women. As with the actively treated women, mammograms from the control group were also taken 12 months apart. The control group did not have increased risk factors for breast cancer.

Two radiologists evaluated each mammogram in an anonymous, double-blind manner, without being aware of whether the film was taken at baseline or follow-up. Mammographic density was classified according to Wolfe's four parenchymal patterns:

- N1: no visible ducts, some residual fibrous tracts, primarily fat;
- P1: prominent ducts (observed as high-density linear or nodular regions) affecting <25% of the mammary parenchyma;
- P2: prominent ducts occupying >25% of the mammary parenchyma;
- Dy: diffuse, high-density parenchyma, with difficult differentiation between ducts and fat.[18]

A change in Wolfe pattern was classed as +1 for each grade increase, and –1 for each decrease. The number of women showing increased density in the various HRT groups and control group were compared by analysis of variance (ANOVA) using Wilcoxon's test. The 95% confidence interval (CI) was calculated for the proportion of women showing increased density in each treatment group.

Results

Mean baseline demographic data for all the analysed women are summarised in table I. At baseline, mammograms from 81% of patients were classified as N1 or P1.

The proportion of HRT users who experienced an increase in mammographic density was significantly greater than in controls: 67 of 210 HRT recipients (31.9%; 95% CI 25.7%, 38.6%) and one of 30 controls (3.3%; 95% CI 0%, 17.2%) showed increases in mammographic density.

Increased density was reported in all treatment groups receiving estradiol or CEE (fig. 1). There was a trend for more increases with the estradiol-containing regimens than with the comparable CEE regimen (fig. 1). It was notable that unopposed regimens led to more increases than the comparable MPA-containing treatments.

There were no cases of increased mammographic density in patients treated with either tibolone or estriol ($p < 0.05$ compared with other HRT treatment groups in each case) [fig. 1]. Indeed, breast density decreased in eight (27%), six (20%) and four (13%) patients in the tibolone, estriol and control groups, respectively, whereas

Table I. Baseline characteristics of participants. Values are means, with range in parentheses

Variable	HRT recipients (n = 210)	Control group (n = 30)
Age (y)	52 (45-65)	51 (45-65)
Parity	3.7 (0-7)	3.5 (0-7)
Weight (kg)	69.9 (49-90)	68.8 (47-81)
Height (m)	1.64 (1.52-1.79)	1.63 (1.52-1.70)
Age at menopause (y)	50 (48-54)	51 (50-52)

HRT = hormone replacement therapy.

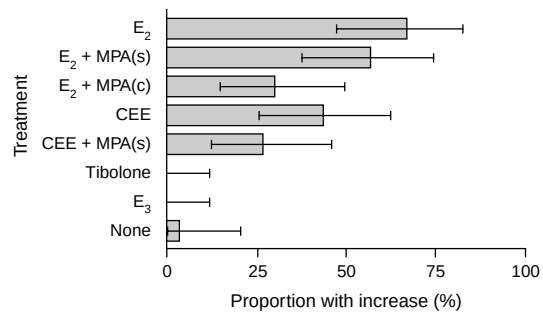

Fig. 1. Proportion of patients (with 95% confidence intervals) experiencing increased breast density after hormone replacement therapy for 1 year. Dosages are specified in the text. **(c)** = continuous; **CEE** = combined equine estrogens; **E_2** = estradiol; **E_3** = estriol; **MPA** = medroxyprogesterone acetate; **(s)** = sequential.

Table II. Intensity of change in Wolfe[18] classification of mammographic parenchymal pattern after 1 year. The table indicates the number of participants with a change in classification from baseline after 1 year following treatment with the indicated regimen or with no hormone replacement (control)

Regimen	Change in Wolfe classification (grades)					
	–1	0	+1	+2	+3	total
Estradiol 2mg daily	0	10	12	6	2	30
Estradiol 2mg daily + MPA 5mg sequentially	1	12	12	4	1	30
Estradiol 2mg daily + MPA 2.5mg daily	3	18	4	5	0	30
CEE 0.625mg daily	1	16	9	4	0	30
CEE 0.625mg daily + MPA 5mg sequentially	2	20	7	1	0	30
Tibolone 2.5mg daily	8	22	0	0	0	30
Estriol 2mg daily	6	24	0	0	0	30
Total HRT	**21**	**122**	**44**	**20**	**3**	**210**
Control	4	25	1	0	0	30

CEE = combined equine estrogens; **HRT** = hormone replacement therapy; **MPA** = medroxyprogesterone acetate.

Table III. Mammographic parenchymal patterns at baseline and after 1 year of follow-up, classified by Wolfe[18] category (see text for definitions)

Wolfe category	No. (proportion) of all patients at baseline	No. (proportion) of group with increased density at follow-up
N1	111 (46%)	44 (65%)
P1	84 (35%)	19 (28%)
P2	38 (16%)	5 (7%)
Dy	7 (3%)	0 (0%)[a]
Total	240 (100%)	68 (100%)

a By definition, patients classified Dy at baseline cannot increase to a denser Wolfe classification.

density reductions in the other groups were experienced by only 3 to 10% of patients (table II).

Overall, increases in breast density were more frequent in patients who had the involutional pattern N1 at baseline (table III).[18]

Discussion

Our study examined the effect of seven different HRT regimens on mammographic density, each regimen administered for 12 months. Overall, 32% of all HRT recipients (67 of 210 women) showed an increase in breast density during this period, compared with only 3% of non-HRT recipients. All conventional HRT regimens, i.e. those containing either estradiol or CEE, were associated with a markedly greater rate of density increase relative to untreated controls, ranging from 27 to 67%. No increases were reported in recipients of tibolone or estriol.

A number of previous studies have also reported increases in mammographic density associated with conventional HRT. In a non-longitudinal study of 599 women, high-density Wolfe patterns were significantly more frequent in HRT users relative to non-users.[4] In a similar study of 306 women aged >54 years, 37% of HRT users had high breast density (based on a local scoring system), compared with only 11% of non-users ($p < 0.001$).[3] In a smaller prospective study of postmenopausal women who received HRT for a mean of 11 months, breast density increased in nine of 33 patients (27%), but in none of 31 controls ($p = 0.002$).[10] Treatment with estradiol was associated with increased density in 28% and 10% of women who received continuous or sequential progestin, respectively, compared with 3% of non-HRT recipients.[19] However, although a total of 1108 women were followed up, 45% were not postmenopausal, and the interval between mammograms was variable.

Observations from 307 postmenopausal women in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial demonstrated density

increases after 12 months of HRT in 3.5% of patients receiving CEE 0.625 mg/day alone, 23.5% receiving CEE plus sequential MPA (10 mg/day for 12 days/month) and 19.4% receiving CEE plus continuous MPA (2.5 mg/day), but no increases in placebo-treated women.[11] These proportions differ from the current study, possibly because of the prospective design and different mammographic assessment method of the PEPI study. The study design may also explain our observations that adding a progestogen to estradiol or CEE may reduce the risk of increased density.

Overall, therefore, despite some interstudy variability, there is considerable evidence that conventional HRT is associated with increased breast density in postmenopausal women.

In the current study, it is notable that the incidence of density increases was significantly lower with tibolone than with CEE or estradiol therapy. Our results support those from a previous uncontrolled study that noted increased breast density in only two of 25 women after 2 years of treatment with tibolone.[9] Indeed, tibolone treatment has been associated with a decrease in mammographic density after stopping conventional HRT (fig. 2). Preclinical data suggest that tibolone lacks estrogenic stimulation on the breast. In preventative and therapeutic rat models it has been shown to prevent the development of induced mammary tumours.[17] Tibolone inhibits the local conversion of estrone sulfate to estradiol.[16] This may therefore explain the absence of detectable effects on breast density, compared with the marked increases observed with opposed or unopposed estradiol or CEE-containing regimens.

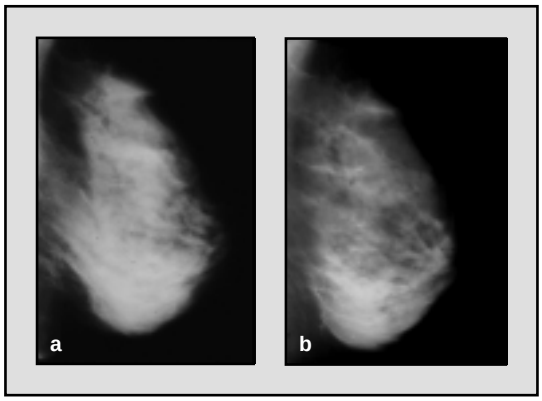

Fig. 2. (**a**) Mammogram of a woman taking combined equine estrogens/medroxyprogesterone acetate (CEE/MPA). (**b**) Mammogram in the same woman 1 year after replacing CEE/MPA with tibolone 2.5mg daily.[20]

There was also less density increase with estriol, which is known to be a mild, short-acting estrogen with minimal systemic effects. However, estriol is primarily used to treat local urogenital symptoms, rather than all postmenopausal symptoms.[21] Others have also found that estriol, administered intravaginally, has a lesser effect on mammographic density than estradiol-containing regimens.[19] The lack of increase in density with this agent similarly supports the hypothesis that increased breast density is an estrogenic effect.

It is notable that mammographic density decreased in some women, particularly in 27 and 20% of the tibolone and estradiol groups, respectively. It would be interesting to follow up these observations in a larger study to further characterise the effect of these less estrogenic therapies.

The design of our study ensured that the radiologists grading the mammograms were unaware of the patient characteristics, and so all grades of baseline mammographic pattern were included. Although women with baseline density of Dy could be assessed for decreased breast density, no increase in density could be recorded for these women. However, this would not have markedly affected our interpretation, as these women comprised only 3% of the total sample. Although Wolfe's classification has been widely used as a measure of breast density,[18] it should be noted that parenchymal patterns are closely related to, but not identical with, breast density. It has proven difficult to identify a truly objective measure of breast density.

Increased breast density may obscure potentially malignant lesions during screening and hamper mammographic interpretation. Diffuse, dense histology in particular can obscure known

cancerous regions.[22] Data from three large screening programmes have demonstrated that both sensitivity (i.e. the false-negative rate) and specificity (the false-positive rate) are significantly reduced in current HRT users relative to women who have never used any HRT ($p < 0.001$).[23-25] These effects are reversed once HRT is stopped.[23]

In addition, direct associations have been noted between mammographic parenchymal patterns and the risk of breast cancer. Case-control studies have found a three-fold greater relative risk of breast cancer in women with either P2 or Dy patterns, relative to women with a mammographic density of N1 or (N1 + P1).[5,6,26] Increased breast density may therefore partly contribute to the clear correlation between the use of estrogen- or estradiol-containing regimens and the increased risk of having breast cancer diagnosed.[1,2]

In users of conventional HRT, high breast density has also been significantly associated with moderate or severe breast pain.[10] Breast pain occurs significantly less frequently with tibolone than with estradiol plus continuous progestogen,[13] further supporting the suggestion that tibolone and conventional HRT have differential effects on the breast. Studies to further characterise these observations are currently in progress.

Conclusion

In summary, our study demonstrated marked increases in mammographic parenchymal patterns and breast density following treatment with HRT regimens containing estradiol or CEE. In contrast, there were no increases with the tissue-specific HRT tibolone or the locally acting estrogen estriol. HRT with tibolone is less likely to impair interpretation of mammograms than conventional HRT.

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