

# Long-term effects of continuous oral and transdermal estrogen replacement therapy on sex hormone binding globulin and free testosterone levels

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## Abstract

**Objective:** To determine the long-term effects of estrogen replacement therapy on sex hormone binding globulin (SHBG) and free testosterone (fT) levels in surgical postmenopausal women. **Study Design:** Forty patients with surgical menopause were enrolled in this prospective study. The women were randomly divided into two groups. The first group received oral therapy (continuous conjugated equine estrogens (CEE) — 0.625 mg per day) and the second group received transdermal therapy (patches delivering continuous 17 $\beta$ -estradiol (E2) — 0.05 mg per day). Serum SHBG and fT levels were determined at baseline and after first and second years of treatment. Two-way repeated measures analysis of variance with Bonferroni adjusted post-hoc test and unpaired-*t*-test were performed for statistical analysis with SPSS program. **Results:** Serum SHBG levels increased significantly with oral CEE after first year of treatment ( $P < 0.05$ ) and remained at this level for the next year. Transdermal therapy did not affect SHBG levels after first and second years ( $P < 0.05$ ). Serum fT levels did not change significantly in either group at the end of the first or second years ( $P < 0.05$ ) although there was a significant difference between the groups after 2 years ( $P < 0.05$ ). **Conclusion:** Oral conjugated estrogens increased SHBG levels during therapy. This effect may balance the increased estrogen and androgen stimulation on breast tissue and may be more beneficial to the cardiovascular system in postmenopausal women. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Estrogen replacement therapy (ERT); Free testosterone (fT); Sex hormone binding globulin (SHBG)

## 1. Introduction

Postmenopausal estrogen replacement therapy (ERT) decreases the risk of cardiovascular disease (CVD) and osteoporosis [1,2]. However, recently, circumstantial evidence has indicated a causal relationship between ERT and breast cancer development in long-term users [3,4].

Monitoring some biologic markers which are known to be associated with some risk factors of breast cancer and CVD may be beneficial in women receiving ERT. Sex hormone binding globulin (SHBG) is a plasma glycoprotein with a high binding affinity to free sex steroids particularly free testosterone (fT) and a lower affinity to estradiol [5]. SHBG has shown to be associated with some risk factors of CVD. A protective effect on breast tissue has been found by increasing levels

of SHBG and it has also been shown that high levels of biologically active testosterone, free testosterone, is associated with the increased risk of breast cancer and CVD [6–8]. We think that it will be useful to determine these markers which have been found to be related with breast cancer and CVD. It has been shown that ERT increases the estradiol levels [1,2]. However, the long-term effects of ERT on fT and SHBG are as yet unproven. We are unaware of any published study which compares the long-term effects of continuous transdermal and oral ERT on SHBG and fT levels.

This study was designed to assess the effects of transdermal and oral ERT on SHBG and fT levels in surgical menopausal women in a 2-year period.

## 2. Materials and methods

This study was performed at the Menopause Clinic of Erciyes University Hospital between January 1998 and July

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Table 1  
Sex hormone binding globuline (SHBG) levels (nmol/l) of groups

Groups	N	Baseline	First year	Second year
Oral therapy	20	38.6 ± 29.0	74.4 ± 56.2*	89.3 ± 57.3**
Transdermal therapy	20	42.1 ± 23.4	41.1 ± 22.4	44.1 ± 28.1

\* Significantly different from baseline (column 4) and transdermal therapy group (columns 4 and 5) ( $P < 0.05$ ).

\*\* Significantly different from baseline ( $P < 0.01$ ).

2000. Our study was approved by the Institutional Review Board of Erciyes University Hospital. Fifty premenopausal patients aged 40–48 (mean  $45.0 \pm 2.07$ ) undergoing hysterectomy and bilateral salpingo-oophorectomy for benign conditions were enrolled in this prospective study. Each patient was free from any other disorder including hypertension, liver disease, diabetes mellitus, thromboembolism, or history of alcohol abuse or smoking. At the beginning of this study, the patients were randomly assigned into two groups, each consisting of 25 patients. The first group received transdermal estradiol 0.05 mg per day continuously (CIBA Pharmaceutical Co., Summit, NJ), and the second group received continuous oral conjugated estrogen 0.625 mg per day (Premarin; Ayerst Laboratories, New York, NY). ERT was started 1 month after surgery. Seven patients who did not turn up for follow-up visits, and three patients with skin reactions were excluded from the study. A total of 40 patients, 20 in each group completed the study. For ethical reasons, symptomatic women were not included as a control group in our long-term study.

Blood samples were taken at baseline before therapy and after first and second years. Blood samples for fT and SHBG assay were obtained by veinpuncture between 07.30 and 11.00 h after a compulsory 12 h fast, and the plasma was separated and frozen at  $-70^{\circ}\text{C}$  until assayed. SHBG (Orion Diagnostica, Espoo, Finland) levels were determined using immunoradiometric assay (IRMA) method and fT (Diagnostic system Laboratories, TX, USA) levels were determined using radioimmunoassay (RIA). The sensitivity and the intra- and inter-assay coefficients of the variation of the assays used were, respectively, as follows: SHBG, 0.5 nmol/l, 4–5.5 and 3.3–6.9%, and free testosterone, 0.18 pg/ml, 3.7–6.2 and 7.3–9.7%.

Two-way repeated measures analysis of variance with Bonferroni adjusted post-hoc test and unpaired-*t*-test were performed for statistical analyses with SPSS program. The values are expressed as mean ± S.D.  $P < 0.05$  was defined as statistically significant.

### 3. Results

The mean ages were  $45.0 \pm 2.0$  and  $44.9 \pm 2.1$  years, BMI values were  $24.8 \pm 3.9$  and  $24.3 \pm 3.3 \text{ kg/m}^2$  in the transdermal and oral therapy groups, respectively. There was no significant difference between the two groups in terms of mean age or BMI before therapy ( $P < 0.05$ ).

Table 2  
Free testosterone (fT) levels (pg/ml) of groups

Groups	N	Baseline	First year	Second year
Oral therapy	20	1.6 ± 0.8	1.0 ± 0.6	1.0 ± 0.3
Transdermal therapy	20	1.4 ± 0.7	1.1 ± 0.6	1.4 ± 0.6*

\* Significantly different from oral therapy group ( $P < 0.05$ ).

The serum SHBG levels of the two groups are shown in Table 1. There was no significant difference in SHBG levels between the groups at the onset of trial ( $P < 0.05$ ), whereas we found a significant difference after the first and second years of treatment ( $P < 0.05$ ). The SHBG levels increased significantly with oral estrogens ( $P < 0.05$ ) after the first year, although no significant difference was found between the first and second year values of SHBG in oral therapy group ( $P < 0.05$ ). Transdermal therapy did not affect SHBG levels in the 2 years ( $P < 0.05$ ).

The fT levels are given in Table 2. While there was no significant difference between the groups before treatment and after the first year of trial ( $P < 0.05$ ), a significant difference was found at the end of the second year of therapy ( $P < 0.05$ ). Changes in fT levels within the groups were not significant after first or second years ( $P < 0.05$ ).

### 4. Discussion

While use of hormone replacement therapy effectively alleviates menopausal symptoms and prevents osteoporosis and cardiovascular disease, there is concern that it has a detrimental impact on breast cancer risk. Some epidemiologic studies indicate that long-term therapy is associated with a slightly increased risk of developing breast cancer [3,4]. It has also been found that the current use of hormone replacement therapy lowers the efficacy of screening for breast cancer [9]. Recently, The Heart and Estrogen/Progestin Study (HERS) group found no overall effect of 4.1 years of therapy with estrogen plus progestin on secondary prevention of coronary heart disease in postmenopausal women [10]. Because of these different effects, it seems necessary to evaluate the risk/benefit ratio of ERT for each patient individually. The cardioprotective effects of ERT has been shown in several studies, but the long-term effects of ERT on risk factors such as SHBG and fT in cardiovascular system and breast tissue are not well established.

The association of breast cancer and cardiovascular disease with several risk factors such as androgen levels and android obesity has been discussed in several studies [11,12]. Androgens have been hypothesized to increase breast cancer risk, either directly by increasing the growth and proliferation of breast cancer cells, or indirectly by their conversion to estrogens [13–15]. It has also been shown that androgen excess may be a signal of increased risk of coronary artery disease [16].

Android obesity is associated with an increased aromatization of androgens and decreased levels of SHBG, resulting in an increase in free, biologically active, sex steroid concentrations [12,17]. We think that the similar BMI values of patients in both groups at the beginning of our study has eliminated the difference in androgenic aromatization. SHBG has been shown to be associated with some risk factors of cardiovascular disease. It is usually positively correlated to high density lipoprotein cholesterol (HDL-C) levels, and negatively to insulin and triglyceride (TG) levels in postmenopausal women [18,19]. SHBG is an index of androgenism in women and of insulin resistance in both sexes, and might be useful in prediction of cardiovascular risk [20].

Different routes of ERT administration and their effects on cardiovascular system and breast tissue remain to be the subject of investigations. The hepatic metabolism of oral and transdermal compounds is different — oral estrogens produce marked hepatocellular effects, such as increased serum levels of sex hormone binding globulin which could partially counterbalance the unfavorable effects of estrogen stimulation on breast tissue [21]. Although higher estrogen levels may have both beneficial and adverse effects, reducing the levels of endogenous estrogens may be a promising means in the prevention of breast cancer. Increasing levels of SHBG with oral ERT may also have beneficial effects on the cardiovascular system by reducing free testosterone levels. On the other hand, low circulating bioavailable testosterone, androgen deficiency, may cause low libido. Testosterone replacement therapy results in significant improvement in symptomatology and hence the quality of life for majority of women [22].

Transdermal estrogens have only been used for a few years and it is unknown whether this route of administration may produce different effects on breast cancer risk when compared to oral estrogens. However, it is well established that transdermal therapy has cardioprotective effects by lowering triglycerides, and total and LDL cholesterol levels [23,24]. Crook and Stevenson [25] concluded that transdermal monotherapy neither increased nor decreased HDL-C levels. Nieto et al. [26] reported a significant increase in HDL-C levels with continuous transdermal estradiol 0.05 mg per day and dydrogesterone 10 mg per day (days 15–28) after 6 months. It seems that oral dydrogesterone affects the hepatic metabolism which causes favorable changes in HDL-C levels. We were not able to find any study which evaluates the long-term effects of transdermal estradiol on hepatic proteins, especially SHBG levels.

In this study, our aim was to assess the long-term effects of ERT on SHBG and fT levels which were found to be risk factors of breast cancer and CVD in surgical menopausal women. In a study carried out at our institution, Başbuğ et al. [27] reported that oral conjugated estrogens increased SHBG levels in 22 weeks, whereas transdermal estrogen had no effect. Obel et al. [28] determined a significant increase in SHBG levels with oral 2 mg oestradiol and 1 mg norethisterone acetate (NETA) in combined and sequential therapy. In the study of Pedersen and Jensen [29], SHBG and lipid levels were shown not to change with transdermal 0.05 mg per day twice a week plus 10 mg oral medroxyprogesterone acetate (days 12–25) after 1 year.

In our study, SHBG levels increased with oral therapy at the first year which confirms other studies and these levels remained the same after second year of treatment. Transdermal therapy had no effect on SHBG levels after first or second years. It seems that duration of transdermal therapy does not affect hepatic metabolism. While fT levels did not change significantly within the groups, there was a significant difference in fT levels between the groups after 2 years. We think that it may be possible to describe this difference between oral and transdermal therapy with long-term studies. Further studies are needed to determine the relationship between ERT and risk factors of breast cancer and CVD.

In conclusion, increasing levels of SHBG with oral therapy may have a balancing effect on breast tissue and this treatment may also be more beneficial to the cardiovascular system.

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