

## Effects of Four Different Hormone Replacement Therapy Regimens on Certain Cardiovascular Risk Factors

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**Abstract:** This study was performed to compare the effects of 4 different hormone replacement therapy (HRT) protocols on certain cardiovascular risk factors. Eighty-nine postmenopausal women were treated with oral conjugated estrogens, transdermal 17 beta-E2, cyclic oral E2-17-valerate+cyproterone acetate (E2-17-V+CA) or tibolone. Blood pressure (BP) measurements, fasting blood glucose (FBG), serum total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and triglyceride levels at the 12th month were compared with the pretreatment values in each treatment group. There were no

significant changes in the systolic BP, FBG, serum total and LDL-cholesterol levels in any group. Diastolic BP measurements were lower in the E2-17-V+CA group; HDL-cholesterol levels increased in the conjugated E and E2-17-V+CA groups; and triglyceride levels decreased in the tibolone group significantly ( $p < 0.05$ ). However, the differences between the initial and post-treatment values of those parameters were not significant among the treatment groups ( $p > 0.05$ ). Therefore, these HRT protocols were not significantly different from one another in eliminating certain cardiovascular risk factors.

**Key Words:** Menopause, cardiovascular disease, estrogen, progesterone, tibolone

### Introduction

Cardiovascular disease, especially coronary heart disease, is the leading cause of death among women in developed countries (1,2). The incidence increases sharply after menopause, and 1 in 4 women dies of coronary heart disease after the age of 60 (3). Menopause is associated with increased cardiovascular risk factors such as android obesity, hyperinsulinemia, disturbed glucose tolerance, increased insulin resistance, increased serum low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and triglyceride levels, and hypertension (2,4,5).

In postmenopausal women, hormone replacement therapy (HRT) reduces the incidence of coronary heart disease by almost 50% (6,7). One of the mechanisms is that estrogens induce several changes in cholesterol metabolism, thus decreasing the LDL and increasing the high-density lipoprotein (HDL) levels (2). Other possible mechanisms by which estrogens favorably affect the cardiovascular system include improved insulin resistance and carbohydrate metabolism, enhanced fibrinolysis

rather than coagulation, decreased vascular resistance and improved blood flow through endothelium-dependent and calcium-dependent processes (6). Progestins, on the other hand, if included in the HRT, seem to have some deleterious effects on plasma LDL and HDL concentrations, although they lower the triglyceride levels increased by estrogens (2,8). In general, these effects are less pronounced with the progestins having less androgenic properties, such as 17-hydroxyprogesterone derivatives including medroxyprogesterone acetate and cyproterone acetate (8).

It is obvious that the effects of HRT on cardiovascular risk factors will be influenced by the type of estrogen or progestin used as well as by the route of administration. Our aim was to determine the effects of 4 different HRT protocols on several cardiovascular risk factors. The protocols investigated in this study are oral conjugated equine estrogens (conj-E), transdermal 17-beta estradiol (17 $\beta$ E2), cyclic oral estradiol 17-valerate combined with cyproterone acetate (E2-17-valerate+CA), and oral tibolone which is a synthetic steroid with estrogenic, androgenic, and progestogenic properties (9).

**Materials and Methods**

This study included 89 postmenopausal patients who regularly attended the outpatient clinic of Ondokuz Mayıs University - Obstetrics and Gynecology Department for a 1-year period, since January 1997. Sixty-nine of these had surgical menopause due to previous hysterectomy and bilateral salpingo-oophorectomy performed for benign disorders. The rest had natural menopause and were amenorrheic for at least 12 months with serum FSH more than 30 IU/L and estradiol less than 20 pg/ml. None of the patients had previously used hormone preparations or any other drug which may influence the plasma lipid profile. None of them had diabetes mellitus or any contraindication for hormone replacement therapy.

Before the treatment, all patients were evaluated with general physical and pelvic examination as well as mammography, transvaginal ultrasonography and cervicovaginal or cuff smears. Blood pressures (BP) were recorded in the sitting position with a standard mercury sphygmomanometer after 10 minutes of rest. All patients underwent routine laboratory work-up including fasting blood glucose, serum total cholesterol, LDL, HDL and triglyceride levels which were measured by enzymatic calorimetric tests.

The 4 HRT protocols used in this study are listed in Table 1. These protocols were not randomly chosen, but decided on by both the doctor and his/her patient after the doctor had given the necessary information. In patients with natural menopause, the 3<sup>rd</sup> or 4<sup>th</sup> protocols

were used in order to protect the endometrium, and the 3<sup>rd</sup> protocol was chosen rather than the 4<sup>th</sup> if they wanted to have regular menses. The control examinations were performed at 3-month intervals and the ones who did not attend these examinations were not included in the study. The patients were also told not to change their life-styles or eating habits and to try to maintain their body weights during the study period.

All patients served as their own controls, and the systolic and diastolic BP measurements, fasting blood glucose, serum total cholesterol, LDL, HDL and triglyceride levels at the 12<sup>th</sup> month of therapy were compared with the pretreatment values. The paired-samples T test, Wilcoxon matched-pairs signed-ranks test, Kruskal-Wallis variance analysis and Mann-Whitney U test were used for the statistical analyses where appropriate. All data is expressed as the mean±standard error of the mean. The results were considered significant if the p value was less than 0.05.

**Results**

The ages of the 89 patients ranged between 35 and 62 years. The mean ages were 42.2±2.2, 45.6±1.2, 46.3±1.4, and 43.1±1.7 years in groups I, II, III, and IV respectively. These figures were not significantly different from each other (p > 0.05).

Pretreatment BP measurements ranged between 90 and 180 mmHg systolic and 50 and 120 mmHg diastolic.

GROUPS	HRT* Protocols	n	%
G I	Conjugated equine estrogens (0.625 mg/d continuous protocol p.o**.)	32	35.9
G II	Transdermal 17-beta estradiol (50 mg/d continuous protocol)	22	24.7
G III	E2 17-valerate (2 mg/d p.o. 1 <sup>st</sup> -11 <sup>th</sup> day) E2 17-valerate (1 mg/d p.o. 12 <sup>th</sup> -21 <sup>st</sup> day) +cyproterone acetate (1 mg/d p.o. 12 <sup>th</sup> -21 <sup>st</sup> day) No treatment between 22 <sup>nd</sup> -28 <sup>th</sup> day (cyclic protocol)	19	21.4
G IV	Tibolone (2.5 mg/d continuous protocol p.o.)	16	18.0
TOTAL		89	100.0

Table 1. The HRT protocols used in the study.

\* HRT: Hormone replacement therapy  
\*\* p.o: Per oral

These values tended to decrease in all the treatment groups at the end of 12 months, ranging between again 90 and 180 mmHg systolic and 50 and 110 mmHg diastolic. A significant difference between the initial and post-treatment values, was only observed in the diastolic BP measurements of the group treated with E2-17-valerate+CA ( $p < 0.05$ ) (Table 2). There was not any significant difference among the 4 groups when the amounts of decrease in either systolic or diastolic BP measurements were evaluated ( $p > 0.05$ ).

Fasting blood glucose at the end of the 1-year therapy were similar to the pretreatment values in all groups (Table 3). This was also true for the total cholesterol levels of groups I, III and IV. In the 2nd group (transdermal  $17\beta E_2$  group), mean total cholesterol levels decreased after the treatment but this decrease was not significant ( $p > 0.05$ ) (Table 3).

HRT decreased the serum LDL levels of the patients in groups I, II and IV, but in the 3rd group (E2-17-valerate+CA group) LDL levels tended to increase. However, these changes were not significant in any group ( $p > 0.05$ ) (Table 3). Furthermore, mean serum HDL levels were higher in groups I, II and III at the end of the 1-year therapy, and this increase was significant in the 1st and 3rd groups (conj-E and E2-17-valerate+CA groups respectively) ( $p < 0.05$ ). In the 4th group (tibolone group) HDL levels decreased with the treatment, but not significantly ( $p > 0.05$ ). (Table 3)

Serum triglyceride measurements were increased in the 1st group (conj-E group) but decreased in the others.

A significant difference between the initial and posttreatment values was only present in the 4th group (tibolone group).

When the differences between the initial and post-treatment levels of all those metabolic parameters were evaluated, there was no significant difference between the treatment groups ( $p > 0.05$ ).

## Discussion

Today, there are various types of postmenopausal hormone replacement therapy protocols and these are increasing in number every day. As one of the primary purposes of HRT is to decrease the morbidity and mortality secondary to cardiovascular diseases, the effects of these therapeutic agents on the cardiovascular system should be known.

The changes in lipid profile induced by estrogens, account for approximately 25-30% of the cardiovascular benefit of the HRT (2,10). LDL levels decrease and HDL levels increase with estrogen treatment. However, a paradoxical increase in serum triglyceride levels due to increased VLDL production is also observed (1,11). The proposed mechanism for these changes in the lipid profile was the hepatic first-pass effect of oral estrogens (11). But later on it was reported that, although non-oral systemic estrogens (transdermal or percutaneous) did not induce such effects with short-term use, longer than 4 to 6 months of treatment might yield similar results (11,12). In this 1-year study, we also observed that oral

Blood Pressure (mmHg)	Group I Oral Conj-E	Group II Transdermal 17 $\beta$ E2	Group III Oral <i>cyclic</i> E2- 17-valerate+CA	Group VI Oral Tibolone
SBP-BT	129.8 $\pm$ 3.6	132.3 $\pm$ 4.9	126.1 $\pm$ 4.5	134.4 $\pm$ 4.2
SBP-AT	128.3 $\pm$ 3.5	130.5 $\pm$ 3.5	120.0 $\pm$ 3.9	129.7 $\pm$ 2.8
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
DBP-BT	81.6 $\pm$ 2.3	85.0 $\pm$ 3.5	75.8 $\pm$ 2.8	82.8 $\pm$ 1.4
DBP-AT	79.7 $\pm$ 2.4	79.6 $\pm$ 2.6	70.5 $\pm$ 2.9	81.9 $\pm$ 2.5
	$p > 0.05$	$p > 0.05$	$p < 0.05$	$p > 0.05$

Table 2. Systolic and diastolic blood pressure values of the treatment groups before and after 12 months of HRT treatment.

Values are mean  $\pm$  SEM  
HRT: Hormone replacement therapy  
CA: Cyproterone acetate  
SBP: Systolic blood pressure  
DBP: Diastolic blood pressure  
BT: Before HRT treatment  
AT: After HRT treatment

Metabolic parameters (mg/dl)	Group I Oral Conj-E	Group II Transdermal 17βE2	Group III Oral cyclic E2-17-valerate+CA	Group VI Oral Tibolone
FBG-BT	94.7±2.0	92.9±2.7	94.4±3.4	94.1±4.0
FBG-AT	93.3±2.3	94.5±2.2	95.7±3.0	95.3±2.0
	p>0.05	p>0.05	p>0.05	p>0.05
TC-BT	217.4±1.0	212.3±7.6	228.2±6.9	226.4±11.0
TC-AT	218.1±8.9	198.2±6.5	229.2±9.0	224.1±8.7
	p>0.05	p>0.05	p>0.05	p>0.05
LDL-BT	153.6±7.5	142.8±8.8	149.7±7.1	162.5±9.3
LDL-AT	143.1±5.4	135.3±8.5	157.5±8.9	158.9±6.0
	p>0.05	p>0.05	p>0.05	p>0.05
HDL-BT	40.3±1.6	44.1±1.8	37.5±1.7	37.8±3.4
HDL-AT	46.3±2.2	47.0±2.5	45.3±3.3	33.3±2.7
	p<0.05	p>0.05	p<0.05	p>0.05
TG-BT	148.1±16.1	146.1±19.7	148.9±20.8	144.6±21.4
TG-AT	155.1±17.3	133.4±12.7	139.3±16.2	118.3±14.7
	p>0.05	p>0.05	p>0.05	p<0.05

Table 3: Fasting blood glucose, serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels of the treatment groups before treatment and after 12 months of HRT treatment.

Values are mean±SEM  
 CA: Cyproterone acetate  
 HRT: Hormone replacement therapy  
 FBG: Fasting blood glucose  
 TC: Total cholesterol  
 LDL: Low-density lipoprotein  
 HDL: High-density lipoprotein  
 BT: Before treatment  
 AT: After treatment

conjugated estrogens decreased LDL, significantly increased HDL (p<0.05), and increased triglyceride levels. Transdermal 17-beta estradiol decreased LDL, increased HDL, and decreased triglyceride levels but none of these changes was statistically significant (Table 3).

Estrogens have to be combined with progestins in order not to induce proliferative changes in the endometrium. There are several protocols of this type, either continuous or cyclic. Although progestins disturb the lipid profile and are atherogenic when used alone, in combined protocols, the beneficial effects of estrogens are still maintained. Furthermore, the plasma triglyceride levels are decreased with the effect of progestins (13). In our study, we observed an increase in serum LDL, a significant increase in HDL (p<0.05) and a decrease in triglyceride levels with the cyclic combined protocol, in which cyproterone acetate was present (Table 3).

Tibolone, which has estrogenic, progestagenic and androgenic properties, is reported not to affect the LDL levels even with long-term use, but to decrease the HDL

and triglyceride levels. The decrease in the serum HDL measurements may be due to its androgenic effects (9,14,15). In accordance with the literature, triglyceride levels were significantly decreased (p<0.05) in our tibolone group; LDL and HDL levels were decreased, but not significantly. However, we should repeat that when the differences between the initial and posttreatment values of total cholesterol, LDL, HDL and triglyceride were evaluated, there was no significant difference between our treatment groups (p>0.05).

It is suggested that oral estrogen preparations increase the synthesis of renin-substrate again via the hepatic first-pass effect and this might cause a rise in blood pressure (10). In fact, the clinical studies show a decrease in blood pressure measurements both with oral and non-oral HRT protocols, which is probably due to the direct vascular effects of estrogens. (10) In our study groups, BP measurements were lower at the end of the 1-year period than the initial values. This decrease was significant only in the diastolic blood pressures of the

group treated with cyclic E2-17-valerate+CA ( $p < 0.05$ ) (Table 2). There was no significant difference among the 4 groups, when the differences between the initial and posttreatment systolic and diastolic BP measurements were evaluated ( $p > 0.05$ ).

Hyperinsulinemia and glucose intolerance are associated with the development and progression of atherosclerosis. Estrogens, either oral or transdermal, improve insulin sensitivity and increase insulin secretion at usual doses (4,16). Progestins also augment pancreatic insulin secretion, but they may attenuate the beneficial effects of estrogens and increase the insulin resistance. However, fasting blood glucose levels are not altered with estrogen replacement and do not increase with the addition of

progestins (4,16,17). We also did not observe any change in the fasting blood glucose levels with any of the protocols.

In conclusion, we may say that the blood pressure and lipid profile changes observed with these 4 hormone replacement therapy protocols are not significantly different among the study groups. Until the cardiovascular protective effects of certain protocols are definitely proven to be better than the others, it will not be wise to choose any of them according to the theoretical presumptions. Of course, randomized studies performed on larger groups of postmenopausal women will give us more accurate results in this respect.

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