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Effects of conjugated estrogens alone and in combination with dydrogesterone on plasma lipoproteins

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ABSTRACT

Objectives: *The aim of this study, was to determine the effect of hormone replacement therapy on the lipoprotein parameters which are predictive markers of reduced cardiovascular risk.*

Methods: *Prospectively, for 6 months, to the women who never used hormone replacement therapy before, if they had surgical menopause, 0.625 mg/day Conjugated Equine Estrogen (CEE) and if they present with natural menopause 0.625 mg/day (CEE) and 10 mg/day dydrogesterone (DD) were given every day and alterations in the lipid profiles have been determined. The group of postmenopausal women who had not taken any kind of therapy was considered as control group. The lipid profiles are screened at the beginning and in the 3rd and 6th month post-therapy. The results are evaluated statistically using the Student Newman – Keuls (SNK) tests by one-way-ANOVA.*

Results: *Following 6 months of therapy in both CEE – DD and CEE administered postmenopausal women the High Density Lipoprotein (HDL-c) and Apolipoprotein A1 (Apo A_1) levels were increased significantly when compared with the baseline values ($p < 0.01$), Low Density Lipoprotein (LDL-c) levels were, however, decreased significantly relative to the beginning when compared with the control group.*

When both of the groups were compared with the controls it is observed that the Apo A_1/ Apo B ratio has increased ($p < 0.01$) and the cholesterol/HDL-c ratio (Atherogenic Index) has decreased dramatically at the end of the therapy. All of these changes in these two groups were observed till the 3rd month of the study. The only change was that an increase of the HDL-c levels was statistically significant ($p < 0.05$) from adding the progesterone to the estrogen therapy.

Conclusions: *As a result ERT and HRT are associated with an improved lipid profile in the postmenopausal period. These improved parameters are, increasing HDL-c, decreasing LDL-c, decreasing of the cholesterol/HDL-c ratio (Atherogenic index) and an elevation of the Apo A1/Apo B ratio in women receiving hormone replacement therapy. HRT is beneficial and could provide a cardioprotective effect to postmenopausal women.*

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INTRODUCTION

The effects of estrogens and progestogens on reproductive tissues and menopausal symptoms are unambiguous. There is considerable controversy regarding effects on other tissues, however, particularly in the cardiovascular system. Epidemiologic data suggest that premenopausal women are largely protected from coronary heart disease (CHD)

compared with aged-matched men[1]. This phenomenon, sometimes referred to as *female protection*, is more accurately characterized as a delay in disease onset, with CHD events in women lagging behind those of men by about 10 years[2]. Both natural and surgical menopause are associated with increased risk of CHD[3], further suggesting beneficial effects of ovarian hormones. In addition, estrogen replacement therapy (ERT) is associated with about a 30% to 50% decrease in CHD risk in postmenopausal women[4,5] and about a 50% decrease in atherosclerosis in animal models[6–9]. The foregoing findings suggest beneficial effects of estrogens on the cardiovascular system. Surprisingly, randomized trials in postmenopausal women with pre-existing CHD have found no benefits of combined hormone replacement therapy (HRT)[10].

Unopposed estrogen replacement therapy increases a woman's risk of the development of endometrial cancer by approximately 120% for each 5 years of use[11,12]. The addition of a progestogen protects the endometrium against hyperplasia and carcinoma[11–14], therefore, combined estrogen-progestogen therapy has become an essential feature of hormone replacement therapy (HRT) for women with an intact uterus. Protection of the endometrium is the primary reason for adding progestogen to HRT.

Combined estrogen-progestogen HRT is available in 2 different designs. In the traditional design, the progestogen is given sequentially or cycically on 7 to 15 days each month. This type of combination was designed to mimic the menstrual cycle and gives optimally a regular bleed every month when the endometrium is rejected. In a more recent design, the progestogen is given continuously to keep the endometrium atrophic throughout the month.

Not only the dose but also the length of progestogen intake seems to be important for the endometrial protection. In the cyclic combination, the progestogen should be given for at least 10 days per month to protect the endometrium from cancer[11–14]. The continuous-combined combinations seem to be protective[11].

Postmenopausal women have an increased risk of coronary heart disease, consistent with their typically adverse serum lipoprotein profile[15–18]. Hormone replacement therapy with estrogen counters this increased risk[19], but a progestin is usually added sequentially for 10–14 days each cycle to prevent endometrial neoplasia[20]. Progestins, especially those with androgenic properties, can oppose the beneficial effects of estrogen on serum lipoproteins[21], leading some authors to predict that estrogen-progestin therapy may not provide all the protection from coronary heart disease seen with estrogen alone[22].

Serum lipoproteins are frequently used as surrogates for coronary heart disease. A major limitation of this "rise-marker" approach is the cost and complexity of the necessary studies. For example, only six of 31 studies summarized in one review[23] were no longer than 1 year's duration. Some studies[24–26] have indicated that the metabolic effects of hormone replacement therapy may disappear after some years. If hormone replacement therapies do not induce long-term metabolic changes, then the current emphasis on short-term studies is misplaced.

The incidence of coronary heart disease rises after menopause consistent with the emergence of a more atherogenic lipid profile. Although few studies in women directly examine the possibility that variation in endogenous estrogen may contribute to atherosclerosis risk, several pieces of evidence are suggestive of such an association. Firstly, early menopause is associated with an increased risk of CHD, as is a history of menstrual irregularity[27]. Also, in comparison with normally cycling controls, irregularly menstruating women have elevated plasma fibrinogen concentrations (a risk factor for atherosclerosis) and a thickened arterial intima[28]. Finally, premenopausal women with angiographically confirmed coronary disease have significantly lower plasma estradiol concentrations than do controls[29]. We have in this study evaluated the effects of HRT on plasma lipoprotein risk factors for cardiovascular disease. We also examined the untreated group to continue for temporal changes in lipoprotein levels.

MATERIAL – METHODS

In a prospective randomised-controlled study of 110 women who attended hospital's menopause unit Estradiol (E_2), Follicle Stimulating Hormone (FSH) and luteinizing hormone (LH) levels in these menopausal women were investigated. FSH values were more than 30 mlu/ml and E_2 value was between 10–20 pg/ml. Their postmenopausal period was of at least 1 year duration.

The history and physical examinations of the patients were noted. Any patient who has uterine, breast or ovarian malignancy or uterine dysfuntion, patients who have allergies to the drugs used or with diabetes mellitus (or anormal GTT results), abnormal laboratory results or predisposed to migraine have been excluded. The selected patients have never been on estrogen and progestin therapy before. They were not taking any kind of medicine which adversely affects the cholesterol or lipoprotein levels. Alcohol and drug addicts and people smoking more than 20 cigarettes/day were also not accepted to this study.

Among the selected patients 40 of them had surgical menopause while 70 of them were in the natural menopause group. The control group comprised women who didn't want to use any form of hormone replacement therapy or wanted to delay the therapy voluntarily. The height and weight of the patients were recorded.

Their blood samples (10ml) were collected consistently between 8.00–10.00am on commencement of therapy and during 3rd and 6th months post-treatment from the naturally and surgically menopause patients. After centrifugation, the plasma was stored frozen at –20°C till analysis. Apolipoprotein A1 and B levels are analysed using the Hitachi 911 autoanalyzer and Boehringer Mannheim kits by the immunoturbidimetry technique.

All samples in the 3rd and the 6th months were analysed by the laboratory staff who had no knowledge of the patients special features or their chronological order. The patients on natural menopause used 0.625 mg/day conjugated equine estrogen (CEE) and 10 mg/day dydrogesterone (DD) perorally continuously every day while the surgically menopause patients used only 0.623 mg/day CEE orally. The control groups were devoid of any medication.

The study was completed by 37 women who had natural menopause, 38 surgically menopause women and 30 control group patients. The results were analysed by the one-way-ANOVA method using Student – Newman – Keuls (SNK) test.

The study has covered 105 postmenopausal patients admitted to our hospital's menopause unit. 37 surgically menopause CEE using and 30 naturally menopause patient as a control group are grouped randomly. The average age of the 30 postmenopausal control group patient was 49.03±3.34 (mean±SD), CEE-DD using 37 naturally menopause patient's average age was 49.27±2.64 and surgically menopause CEE using 38 postmenopausal patient's average age was 48.32±2.34.

When the age, the period of menopause and BMI are compared, there were not statistically different between these 3 groups examined.

RESULTS

The increase in HDL-c and Apo A_1 levels at the end of 3rd month is statistically significant ($p<0.05$). The positive increase in these two parameters had continued at the end of the 6th month ($p<0.01$). Meanwhile the increase in the triglyceride level at the end of the 3rd month was also significant ($p<0.05$) with the same increase being noticed till 6th month of treatment ($p<0.05$) (Table 1–2).

The increase in ApoA_1 / Apo B ratio was observed at the 3rd month although this increase is not statistically significant. This increase was noted even at the end of the 6th month of HRT being statistically significant ($p<0.01$) (Table 1–2).

TABLE 1
Changing lipid parameters during therapy of natural menopausal group taking continuously combined CEE-DD.

	Baseline (mg/dl) mean±SD	3 month (mg/dl) mean±SD	Between baseline to 3 month p-value	6 month (mg/dl) mean±SD	Between baseline to 6 month p-value
Cholesterol	204.02±39.35	198.35±30.70	N.S.	195.62±24.50	N.S.
HDL-C	41.05±10.89	42.27±12.08	P:0.02	48.29±11.04	P:0.006
LDL-C	133.16±35.33	126.51±31.25	N.S.	125.08±26.12	N.S.
Triglycerides	137.91±22.06	146.18±29.26	P:0.027	150.59±22.41	P:0.017
VLDL-C	29.81±16.95	24.62±18.20	N.S.	22.24±11.18	P:0.026
APO A1	141.78±29.50	155.54±26.53	P:0.016	159.16±26.88	p:0.004
Apo B	113.28±25.50	112.80±20.15	N.S.	108.20±23.36	N.S.
Apo A1 / Apo B	1.29±0.32	1.41±0.29	N.S.	1.52±0.35	P:0.002
Chol/HDL-C	5.15±1.15	4.42±1.20	P:0.005	4.22±0.98	P:0.000

CEE-DD, Conjugated equine estrogen dydrogesterone SD, standard deviation P<0.05

After 6 months of therapy women with natural menopause taking CEE-DD, when compared with the control group indicated a remarkable increase in the HDL-c and Apo A1 levels than the beginning in the CEE-DD using group ($p<0.01$). The LDL-c levels decreased significantly compared to onset of therapy ($p<0.01$). Apo A1 / Apo B ratio was elevated after 6 months of HRT ($p<0.01$).

Administration of CEE for 6 months in women with surgical menopause resulted in elevation in HDL-c, Apo A1 levels and Apo A1 / Apo B when compared with the baseline LDL levels while the atherogenic index (cholesterol / HDL-c) decreased over the same period ($p<0.01$).

Adding DD to the therapy effected only an increased in HDL-c levels negatively. The HDL-c levels had increased with respect to its baseline values DD was added ($p<0.05$), but this increase is not statistically different when compared with women using only CEE. The other parameters were not statistically different when DD was included in the therapeutic regimes (Table 3).

No statistical difference in lipid parameters were observed in the control group of women without medication over the 6 months period.

TABLE 2

Changing lipid parameters during therapy, of surgical menopause group taking CEE.

	Baseline (mg/dl)	**3.month (mg/dl) mean±SD**	**Between Baseline to 3.month p-value**	**6.month (mg/dl) mean±SD**	**Between Baseline to 6.month p-value**
Cholesterol	204.26±36.54	201.52±38.60	N.S.	201.63±31.14	N.S.
HDL-C	40.76±9.65	48.50±11.04	P:0.001	53.15±9.21	P:0.000
LDL-C	132.00±35.62	125.39±33.54	N.S.	119.26±27.05	N.S.
Triglycerides	139.21±20.06	144.02±24.04	N.S.	147.63±27.79	N.S.
VLDL-C	31.50±10.35	27.63±12.74	N.S.	29.21±11.54	N.S.
Apo A1	141.11±20.11	153.55±23.66	P:0.008	163.34±17.10	P:0.000
Apo B	110.22±18.71	109.54±17.74	N.S.	105.16±15.18	N.S.
Apo A1/Apo B	1.31±0.31	1.43±0.32	N.S.	1.59±0.33	P:0.000
Chol/HDL-C	5.22±1.33	4.32±1.08	P:0.001	3.88±0.80	P:0.000

CEE, Conjugated equine estrogen SD, standard deviation P<0.05

TABLE 3

Changes in all lipid parameters after 6 months of the CEE-DD and CEE treatment groups.

	CEE-DD (mg/dl) mean±SD	**CEE (mg/dl) mean±SD**	**Between treatment p-value**
Cholesterol	195.62±24.50	201.63±31.14	N.S.
HDL-C	48.29±11.04	53.15±9.21	P:0.035
LDL-C	125.08±26.12	119.26±27.05	N.S.
Triglycerides	150.59±22.41	147.63±27.79	N.S.
VLDL-C	22.24±11.18	29.21±11.54	P:0.016
Apo A1	159.16±26.88	163.34±17.10	N.S.
Apo B	108.20±23.36	105.16±15.18	N.S.
Apo A1/Apo B	1.52±0.35	1.59±0.33	N.S.
Chol/HDL-C	4.22±0.98	3.88±0.80	N.S.

CEE-DD, Conjugated equine estrogen dydrogesterone SD, standard deviation P<0.05

DISCUSSION

Menopause is associated with increased total serum cholesterol, triglycerides and a decrease in HDL-c levels. The major reason for these changes following menopause is believed to be a result of fluctuations in hormonal status, primarily a deficiency in estrogen.

Epidemiological data suggest that the use of ERT and HRT in healthy postmenopausal women is associated with a decrease risk of cardiovascular events[30]. In sharp contrast, the HERS study, a secondary prevention trial in postmenopausal women with established coronary heart disease, did not show a favourable effect, with a trend towards an increased risk of cardiovascular disease in the first year of treatment[31].

Our aim in this study that was carried out in the menopause department of our hospital was to show the effect of estrogen-progesterone therapy in patients with natural menopause and estrogen therapy in surgically menopause patients used often for relieving the vasomotor symptoms of menopause and their beneficial effects on serum lipoproteins and apolipoprotein A_1 and B. Estrogen reduces cardiovascular risk by decreasing LDL-c and simultaneously increasing HDL-c. The changes in the HDL-c/LDL-c ratio is directly related to the incidence of heart disease[32].

Based on our results adding DD to the CEE therapy effected only the increase in the HDL-c level negatively. When DD was added, the HDL-c levels increased but this increase is less significant than in women using ($p<0.05$). The other changes in the lipoprotein parameters were not statistically different from those receiving in addition the DD regime.

The beneficial effect of hormone replacement (HRT) on osteoporosis and menopausal symptoms has been well documented in randomised trials, but the impact of estrogen-mediated metabolic changes on the risk of ischaemic heart disease is still a matter of debate. Randomised studies have shown that HRT increases levels of high-density lipoprotein cholesterol while causing a reduction in the levels of low-density lipoprotein cholesterol, serum fibrinogen, plasminogen activator inhibitor and homocysteine[33].

The studies with estrogen replacement therapy showed that estrogen decreases LDL-c and increases HDL-c levels in plasma. Similar and significant decreases in low-density lipoprotein were observed in all groups, but high-density lipoprotein and triglycerides were increased only in the unopposed estrogen groups in the two-year, parallel-group double-blind study[34]. Increasing 1 mg/dl HDL-c in plasma; decreases coronary risk by 3%. Decreasing 1 mg/dl LDL-c in plasma; decreases this risk by 2%[35].

In one of the studies from Japan, in the normal cholesterol group with a total hysterectomy received CEE 0.625 mg/day; physiological menopause received CEE 0.625 mg/day plus MPA 2.5 mg/day fasting blood samples were monitored periodically for 3 years. Serum levels of HDL-c were increased in their study groups[36]. In our study we obtained a significant increase in HDL-c levels in both of the groups. However the decrease in LDL-c levels were not meaningful statistically.

In literature despite the MPA and the other progestins; the combined DD therapy regimens doesn't exists anymore. In 1997, in a study with a two group of naturally menopause patients, one group had given 0.625 mg/day CEE and 10 mg/day MPA for 14 days/cycle and the other group had given 0.625 mg/day CEE and 10 mg/day DD for 14 days/cycle for 12 months. The serum lipoproteins of the patients were compared. The percent changes from baseline to cycle 12 were statistically significantly larger for the DD group than the MPA group for LDL-c, HDL_2-c, HDL-c/LDL-c, apolipoprotein A_1 and apolipoprotein B, indicating greater improvement in the DD group. In addition, statistically significant increase(mean percent change) from baseline to cycle 12 were observed for HDL-c/LDL-c ratio, HDL_3-c, apolipoprotein A_1 and HDL-c in both treatment groups and also for HDL_2-c in the DD group[37].

At the end of our study, when the results were analysed statistically, either CEE-DD using naturally menopause group or only CEE using surgically menopause group showed evident increase is HDL-c and Apo A1 levels than beginning ($p<0.01$) when compared with the control group. Also LDL-c levels have decreased with respect to the beginning ($p<0.01$).

However, either of the two groups when compared with the control group showed an increase in Apo A1/Apo B ratio ($p<0.01$) and decrease in cholesterol/HDL-c ratio ($p<0.01$) at the end of the therapy. In a study from Colombia they found that both cyclic sequential preperations used in HRT showed a favorable effect on plasma lipids in healthy peri and postmenopausal women, with an increase in HDL-c and a decrease in LDL-c levels, as well as in the LDL-c/HDL-c and Total cholesterol/HDL-c ratios[38].

The changes, observed in both of the groups have obtained till the 3rd month of the therapy. Although the increase in Apo A1/Apo B ratio started in the 3 month, this increase is not valuable statistically. However the increase continued till the end of the

6th month and this is statistically valuable ($p<0.01$). The decrease in cholesterol and LDL-c levels in either of the groups observed at the end of 3rd and the 6th months but this is not statistically meaningful. Wolfe and his friends had found that the combined hormones significantly lowered plasma LDL Apo B by increasing the mean fractional catabolic rate of LDL Apo B by 20%. Plasma HDL-c rose significantly[39].

The final findings showed that addition of DD to the CEE therapy affected only the HDL-c increase minimally. Although the HDL-c levels have increased with respect to the beginning in the DD added group, this increase is significantly in women taking less than the only CEE ($p<0.05$). The other parameters were not affected by inclusion of the DD. As a result ERT and HRT regimes are associated with an improvement in lipid profiles.

The changes caused by progestogens are known to be short-lived and "carry-over" metabolic effects are therefore unlikely to affect the results of this study[40]. In addition progestogens are mainly added to HRT to protect the endometrium against hyperplasia and the resulting impending risk of carinoma. The added progestogen should not or as little as possible, counteract the beneficial effects of the estrogen component.

Postmenopausal hormone replacement therapy positively effects the plasma lipoproteins HDL-c, Apolipoprotein A1 may eliminate the risk factors of atherosclerosis.

Our study clearly indicates that the estrogen and progesterone replacement therapy given to the selected appropriate patient during the postmenopausal period, is of benefit to such postmenopausal women to decrease the impaired lipid profiles.

In terms of cardiovascular risk, the optimal lipoprotein profile for an estrogen-progestogen replacement therapy would combine elevated HDL with reduced LDL and reduced triglyceride levels. More studies are necessary to identify such regimes.

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