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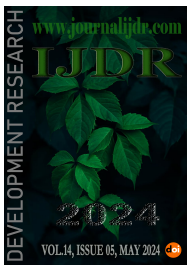

RESEARCH ARTICLE **OPEN ACCESS**

EFFECT OF ESTROGEN REPLACEMENT THERAPY ON BLOOD LIPID LEVELS IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Background*:* Menopause is the period of changing hormone status that unfavourable cardiovascular risk factors increase. Our aim was to examine the impact of ERT (estrogen replacement therapy), three specific procedures of oral conjugated estrogen, micronized estradiol and transdermally administered estrogen on serum lipids in postmenopausal Turkish women. ***Methods:*** Our study included 120 volunteer patients between the ages of 44 and 60. Lipid values were examined before and 6 months after ERT treatment. Patients selected in a random manner into three way: 40 were taken transdermally 17β-estradiol 0.05 mg/day (Climara weekly), 40 were taken conjugated estrogen 0.625 mg/dl (Premarin)and 40 were taken micronized estradiol 2 mg/dl (Estrofem). ***Results:*** Total cholesterol decreased in the CEE, E2 groups (−1,8%, −5.5% respectively), while transdermal group have a 0,9% total cholesterol increase. In general, a decrease in total cholesterol values was observed after 6 months of use of all three drugs. The level of mean HDL cholesterol was found high in both E2 and transdermal group (5,5% ,8,5% respectively). A slight increase in HDL cholesterol level was observed in all three groups. ***Conclusion:*** Every menauposal therapy had a various effect on lipoprotein and lipid levels. It has been observed that ERT had more effective on lowering of cholesterol in women who are hypercholesterolemic.ERT therapy should be choosen due to patients lipid profile, women needs and indications.

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INTRODUCTION

The risk of coronary heart diseases (CHD) are lower in women than at same age of men in premenopausal time. With the onset of menopause this risk turn on favor of men. While the CHD prevalence was 14.2% in between 45-64 age of women, the prevalence was found 33.3% in over 65 age. Estrogen deficiency is related with the progress of atherosclerosis which results as CHD. Normal ovarian estrogen production prevents this progression (Genazzani, 2000 and Mongraw-Chaffin et al., 2015). During the menopause, women have disadvantage about the cardiovascular risk factors due to variations at hormone levels. At this point, each of the hormone replacement treatments to be applied has different effects. It has been observed that HRT applied to healthy menopausal women is not related with an increased risk of myocardial infarction (Wild, 1996). As known oral estrogens decrease total cholesterol (TC) and low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL) cholesterol and triglycerides(TG). The risk of developing CHD is higher in women with high fasting serum triglyceride levels than in women with low or normal triglyceride levels (Speroff, 2000). The relationship of fasting triglycerides level and cardiovascular disease (CVD) was studied many times, a metaanalysis of data from 17 population based prospective studies achieved that this relationship was stronger in women after menopause (Hokanson, 1996).

For every 1 mmol/l increase in triglyceride level, CVD risk in men and women was found to increase by 14% and 37%, respectively (Hokanson et al., 1996). So although transdermal estradiol has a less pronounced effect on plasma lipids than oral estrogens, because of its reducing effect on triglycerides, transdermal way has to be chosen in patients (Stanczyk, 1998). Studies have shown that oral or transdermal estrogen use provides only 20-25% of the overall cardioprotective effect from favorable changes in the lipid. Estrogen dilates coronary arteries and brachial arteries in postmenopausal women and men. This effect is due to increased nitric oxide release. Estrogen causes rapid reendothelialization by acting on local vascular endothelial growth factors. Additionally, the bioavailability of nitric oxide in the vascular system increases with estrogen (Ertungealp, 1999). Although the positive effect of ERT on lipids and lipoproteins is known (Ossewaarde, 2001), it is necessary to add progestin to the treatment to protect the endometrium (Sitruk-Ware, 2002). Tibolone, a steroid generally used in Europe, reduces triglyceride levels and serum HDL cholesterol levels (Von Eckardstein, 2001). However, Tibolone effects on the endometrium and breast is lesser than ERT, making it preferred in long-term treatments (Mendoza, 2000). Our aim in the study is to examine the effect of ERT, which is three different treatments consisting of oral conjugated estrogen, micronized estrogen and transdermal estrogen, on serum lipid values in postmenopausal women.

MATERIALS AND METHODS

This study has done as a thesis for specialization. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with1964 Declaration Helsinki and its later amendments or comparable ethical standards. The study group was determined as a total of 120 postmenopausal female patients aged between 44-60. A random sample from the menopause outpatient clinic of a city hospital Gynecology and Obstetrics Clinic was included in the study. Patients who were at least 2 years past menopause were included in the study. Follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol tests were performed in patients with menopause less than 3 years to confirm the postmenopausal status (FSH level > 40 mIU/ml and estradiol level < 30 pg/ml). Before initiatng ERT treatment, all patients underwent bimanual examination, breast examination, PAP (Papanicolaou), smear test, transvaginal sonography and mammography. All liver, kidney, thyroid function tests and blood clotting tests were requested as biochemical tests. Patients were included in the study if they had an endometrial thickness ≤ 5 mm and no history of gynecological malignancy, ischemic heart disease, thromboembolism, diabetes, untreated thyroid dysfunction, and the absence of lipid-lowering or antihypertensive drug intake. The duration of our study was 6 months. Lipid tests were performed before and 6 months after ERT treatment. The weight and height of patients were measured and their body mass index (BMI) was calculated at each visit. For laboratory values blood samples were taken at 09.00 in the morning on an empty stomach. Lipids were evaluated by an auto analyzer AU 5800 (Beckman Coulter, Brea, CA, USA). Informed consent was obtained from each patient before registration. The 120 female patients included in the study were randomly divided into three groups: 40 with transdermal 17β-estradiol 0.05 mg/day (Climara weekly), 40 with conjugated estrogen 0.625 mg/dl (Premarin) and 40 with micronized estradiol 2 mg. /dl given. (Estrofem)

Statistical analysis: Analysis were performed with a statistical package software, PSS (version 23.0, IBM Corp. Armonk. NY). Baseline characteristics were compared between therapy groups by analysis of variance (ANOVA). Baseline and follow-up lipid mean levels were compared across the same therapy group by ANOVA for repeated measures. In comparisons between groups, "Independent Sample T Test" or "Mann Whitney U Test" was used for the two groups, and "Chi-square or Fisher's Exact Test" was used to evaluate categorical variables. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

All 120 patients completed the study. There were no significant differences in the evaluated characteristics (age, menopause duration and body mass index) and all other lipid values (HDL cholesterol, TC, triglycerides) between the three groups before treatment (Tables 1 and 2). In our study, when the results before and after treatment were compared, a decrease in TC ($p<0.005$) and an increase in TG and HDL cholesterol ($p>0.005$) were detected. (Table 2). Women in all three groups increased their TG levels by 6,1%. Total cholesterol decreased in the CEE, E2 groups (−1,8%, −5.5% respectively), while 0,9% total cholesterol increase was observed in the transdermal estradiol group. In general, a decrease in total cholesterol values was observed after 6 months of use of all three drugs. In both transdermal estradiol and E2 group HDL cholesterol level was increased (5,5% ,8,5% respectively). Although there was no significant change in HDL cholesterol levels after the use of all three drugs, a slight increase was observed in all three groups. In terms of cardiovascular protection, HDL increase indicates a positive result. All estrogen treatments demonstrated more LDL cholesterol reductions in hypercholesterolemic women than normocholesterolemic women.

DISCUSSION

Although CVD protection is provided by high levels of female hormones in the premenopausal period, the risk of CVD increases rapidly with changes in sex steroid metabolism during menopause (Kojima, 2001). There are many studies showing that total cholesterol, triglyceride and LDL cholesterol levels increase with age (Chamberlain, 2007). There is also significant evidence associated with the increase in TC, LDL cholesterol and TG levels during menopause (Price, 2021 and Campos, 1988). LDL cholesterol level, which increased faster in women than in men after menopause, paralleled the increase in TC level (Wang, 2016). Our study findings were consistent with previous results. While HDL cholesterol levels are lower after menopause than before, total and LDL cholesterol levels increase significantly, indicating a shift towards more atherogenic lipid profiles after menopause. Increases in LDL cholesterol and decreases in HDL cholesterol during menopause have been confirmed by longitudinal follow-up, showing that they are not simply related to aging. The increase in the frequency of CVD after menopause is also an indicator of this (Nathan, 1997). Premenopausal and postmenopausal lipid values are examined by Wang et al. and they determined significantly higher dyslipidemia prevalence in postmenoposal group (%69.7) (Wang et al., 2016).

Table 1. The mean and standard error values of age, duration of the menopause and body mass index (BMI) of the patients receiving CEE, micronized estradiol or transdermal estradiol

	Age(years)	Duration of menopause (years)	BMI(kg/m^2)
CEE	50,58±5,6	6,38±4,81	28,75±3,85
E2	48±5,88	48±5,88	28,38±5,08
TDE2	50,05±4,40	5,05±4,65	29,8±3,95
* *P- value*	0.084	0.154	0.308

CEE, conjugated equine estrogens; TDE, transdermal estradiol; E2, estradiol;
*Comparison between groups by ANOVA for continuous variables or by Pearson χ2 for nominal variables; † p < 0.001 compared to never users, if overall effect between groups significant

Table 2. Baseline and follow-up profile of 120 women receiving various therapy regimens

	Months	CEE (n=40)	E2 (n=40)	TDE (n=40)	pValue
T.Chol.(mg/dl)	0 6	212,73±40.25 208.7±30.19	216.30±42,92 204,08±36 P=0,023	219,83±39,21 221,18±38,61	<0.005
TG (mg/dl)	0 6	146,5±62,22 154,43±63,56	153.4±70,2 162,2±77,8	192,6±123,01 201±323,5	>0.005
High Density Chol.(mg/dl)	0 6	56.8±16.28 55.48±13,99	47,95±12,27 51,7±15,21	54,33±35,24 57,63±31,79	>0.005
Glucose (mg/dl)	0 6	106,78±43,83 106,18±48,63	104,88±22,06 104,98±24,48	109,05±28,71 103,7±20,35	>0.005

CEE: conjugated equine estrogens; E2: estradiol; TDE: transdermal estradiol; T. Chol: total cholesterol, TG Triglycerides

In a metaanalysis study from Godsland investigated effects of 42 different HRT treatments in two hundred forty-eight studies. It has been concluded that with estrogen therapy alone, total cholesterol and LDL decrease, while triglycerides and HDL increase. Also while 17-beta triglycerides were lowered by transdermal estradiol lowered, estrogen-induced reductions in LDL and total cholesterol had been little effected by progestogens (Godsland et al., 2001). Although extensive data from observational and experimental studies suggest that replacement therapy may be cardioprotective when applied to healthy postmenopausal women, some controlled studies (such as HERS-I, HERS-II, WHI) mentioned by Christodoulakos et al. question the effectiveness of ERT in reducing the incidence of CVD. (Wang et al., 2016).

Different mechanisms may be included in the cardiac protection of ERT treatment, such as the effect on the vascular wall and endothelium (Mijatovic, 1999) as well as positive changes in the lipid-lipoprotein profile. As Hodis et al. determined that when estradiol treatment was initiated at early years after menaupose, subclinical atherosclerosis progression would be seen less than placebo by measuringcarotid-artery intima-media thickness (CIMT) (Hodis et al., 2016). We see in our study that the majority of healthy postmenopausal women participating the study have serum cholesterol levels above normal values. When smoking and diastolic blood pressure have increased and physical activity has been decreased, serum cholesterol levels have increased in Turkey (Wang et al., 2016). The type, dose and route of administration of estrogen influence the levels of TG (Godsland, 2001). TG level is increased with CEE and it has been shown that its effect was greater with higher doses in Godsland metanalysis.He determined CEE (1.25 or 0.625 mg/d) reduced LDL and total cholesterol as it also increased HDL cholesterol and triglycerides significantly.The effect of CEE on LDL and total cholesterol did not differ depending on the dose given (Godsland et al., 2001).

When a progestin included to the treatment, it opposes CEE. Also according to the dose and type of progestin, its effect changes (Ylikorkala, 2000). CEE increased TG levels by 5.4% in our study. Christado et al. confirmed that TG levels increased by 23.7% and 21.8% in the CEE and CEE/MPA groups, respectively (Christodoulakos, 2004). Also Walch et al. stated that the CEE at doses of 0.625 mg/day and 1.25 mg p/ day increased triglyceride level 42 % due to increased productıon of large TG rich –VLDL (Walsh, 1991). Our TG levels increased lesser than preceding studies. This variation may be due to difference in dose, duration of follow up and regimen. CVD risk is inversely related to HDL cholesterol level; High levels of HDL have been found to be effective in cardioprotection (Assmann, 1992). In our group, HDL levels increased by 5.5% and 8.5% in E2 and transdermal E2, respectively. HDL increases significantly with ERT, and the amount of HDL increase may vary depending on the type, dose, and route of administration of estrogen used (Godsland, 2001). While higher doses of estrogen caused a greater increase in HDL, oral E2 administration also increased HDL more than transdermal, but not without exception (Erenus, 2001). When we use transdermal estradiol in postmenopausal women with different triglyceride levels, there didn't any change in the increase of HDL cholesterol and the decrease of the triglyceride level.

We have to add a progesterone in postmenopausal woman with a uterus. HRT preparations contains progesterone such as medroxyprogesterone acetate and norethisterone acetate reduced the increase of HDL cholesterol which was activated by transdermally estradiol but triglycerides level had been little effected. Many studies demonstrated the decreasing effect of progesterone on HDL cholesterol (Anagnostis, 2017). In women who have natural menopause were effected weaker by the elevating effect of transdermal estradiol with progesterone on HDL cholesterol than in women with a surgical menopause (Anagnostis, 2017). Limitations in our study are the duration of it and the low number of the patients. More clinical trials may be necessary to explain ERTtreatment effects on lipid levels.

CONCLUSION

According to all these data, estrogen replacement therapy/HRT is effective in postmenopausal hypercholesterolemic women if a specific regimen is selected according to the patient's indication and lipid profile. Changes in treatment modality, estrogen dose, and progesterone addition have been shown to have different effects on the lipoprotein-lipid level. Unlike orally administered estrogens, transdermal estradiol has been found to significantly reduce serum triglycerides and increase HDL levels.

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