Lipid Profile Changes During Different Hormone Replacement Therapy Regimens in Postmenopausal Women

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Abstract

Objective: To compare the effects of hormone therapy on serum lipids in postmenopausal women.

Materials and Methods: A retrospective study in 173 healthy postmenopausal women enrolled for this study. Participants had received 2 mg 17β-estradiol (E2) and 1 mg norethisterone acetate (E2/NETA) (n=21), 0.625 mg conjugated equine estrogen (CEE) and 2.5 mg medroxyprogesterone acetate (MPA) (n=38), 0.625 mg conjugated equine estrogen and 5 mg medroxyprogesterone acetate (n=39) and 2.5 mg tibolone (n=75). From the medical records, fasting serum lipid samples were evaluated before and after 6 months of treatment.

Results: Total cholesterol decreased significantly only in E2/NETA group ($p<0.05$). Mean levels of LDL decreased significantly in E2/NETA ($p<0.05$) and CEE/2.5 mg MPA ($p<0.05$). There was a significant increase of HDL within the CEE/5 mg MPA group ($p<0.01$), whereas in the other groups increase of HDL was not found to be significant. Triglycerides decreased in all groups although the differences were not significant. When percentage of lipid profile changes among four groups were compared, only percentage of changes in LDL was significant between E2/NETA and tibolone groups.

Discussion: Different hormone therapy regimes have different effects on lipid profile and none of them seem to be ideal. While many other factors are important for the cardiovascular system, changing of lipid profile may have an important role; so that when prescribing hormone therapy, lipid profile should be evaluated and monitored thereafter.

Keywords: hormone therapy, lipid profile, medroxyprogesterone acetate, norethisterone acetate, tibolone

Özet

Postmenopozal Kadınlarda Hormon Tedavileri Sırasında Lipid Profili Değişimi

Amaç: Postmenopozal kadınlarda hormon tedavisinin serum lipidleri üzerine olan etkilerini karşılaştırmak.

Materyal ve Metot: Yüz yetmiş üç sağlıklı postmenopozal kadın retrospektif çalışmaya dahil edildi. Katılımcılara 2 mg 17β–östradiol ve 1 mg noretisteron asetat (E2/NETA) (n=21), 0.625 mg konjüge östrojen (CEE) ve 2.5 mg medroksiprogesteron asetat (MPA) (n=38), 0.625 mg konjüge östrojen ve 5 mg medroksiprogesteron asetat (n=39) ve 2.5 mg tibolon (n=75) verilerek tedavi öncesi ve 6 ay sonra serum lipid örnekleri dosya kayıtlarından değerlendirildi.

Sonuçlar: Sadece E2/NETA alan grupta total kolesterolde anlamlı düşüş saptandı ($p<0.05$). Ortalama LDL değerleri E2/NETA ($p<0.05$) ve CEE/2.5 mg MPA ($p<0.05$) alan grupta anlamlı şekilde azaldı. CEE/5 mg MPA alan grupta anlamlı şekilde HDL artışı saptanırken ($p<0.001$), diğer gruplardaki HDL yükselişleri anlamsız bulundu. Trigliserid seviyeleri tüm gruplarda azalırken, bu değişim istatistiksel olarak anlamsız tespit edildi. Tüm gruplardaki lipid profillerinin yüzde değişimleri karşılaştırıldığında, sadece E2/NETA ve tibolon arasında LDL anlamlı değişim tespit edildi.

Tartışma: Değişik hormon tedavilerinin lipid profili üzerinde değişik etkileri olup, hiçbiri mükemmel görünmemektedir. Kardiyovasküler sisteme birçok faktörle beraber değişen lipid profilinin de etkisi olabileceğinden, hormon tedavisi sırasında lipid profili monitörizasyonu yapılmalıdır.

Anahtar sözcükler: hormon tedavisi, lipid profili, medroksiprogesteron asetat, noretisteron asetat, tibolon

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Introduction

Although cardiovascular disease is the most common cause of death, premenopausal women are at low risk of cardiovascular disease relative to men of the same age (1). The incidence of cardiovascular disease in women increases rapidly after menopause and reaches the same rates in male population. The changing of the lipid profile has an effect on the increased risk of coronary heart disease (2). Women with elevated fasting serum triglyceride levels are at a higher risk of developing coronary heart disease than those with normal triglyceride levels. This relationship is stronger than the association with LDL cholesterol but weaker than HDL cholesterol (3). Drugs which decrease HDL cholesterol are suspected to increase cardiovascular risk and drugs which increase HDL cholesterol have anti-atherogenic effect. Estrogens have been shown to increase HDL cholesterol and triglyceride and decrease LDL cholesterol and total cholesterol in many studies (1,2). Progesterone reduces the protective effects of estrogens on lipid profile by decreasing HDL cholesterol (4). Tibolone is a steroid, which has tissue specific estrogenic, progestogenic and androgenic properties. Its androgenic property has a role on the reduction of the HDL cholesterol (5,6).

The purpose of this study was to compare the effects of continuous treatment with 0.625 mg conjugated equine estrogen (CEE) and 2.5 mg medroxyprogesterone acetate (MPA), 0.625 mg CEE and 5 mg MPA, 2 mg 17β-estradiol and 1 mg norethisterone acetate(E2/NETA) and 2.5 mg tibolone on blood lipid profiles in postmenopausal women.

Materials and Methods

Medical records of 173 postmenopausal women, who had visited Eskişehir Osmangazi University School of Medicine, Department of Obstetrics and Gynecology division of Menopause Clinic, between January 2003 and February 2004 and been informed about beneficial effects and potential risk factors related to hormone replacement therapy were evaluated retrospectively and the study was approved by the Medical Ethical Board of University Hospital. All subjects had had 12 months of amenorrheic period, plasma levels of FSH were

>40 mIU/ml and were complaining about vasomotor symptoms. Patients who had endocrinological or metabolic diseases, cardiovascular and active hepatic diseases, uncontrolled hypertension were excluded from the study. It was understood that none of the patients had received any hormonal therapy or lipid lowering drug prior to the study.

The recorded data included the results of physical and pelvic examinations, cervical smear evaluation, mammography, transvaginal ultrasonography and complete blood count, serum glucose, urea, creatine, liver function tests (AST, ALT), lipid profile including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol of all study participants before and after 6 months of treatment.

Subjects were further classified into four different groups in terms of hormone therapy as follows: Group 1 (n=21) continuous treatment with E2/NETA, Group 2 (n=38) CEE/2.5 mg MPA, Group 3 (n=39) CEE/5 mg MPA and Group 4 (n=75) 2.5 mg tibolone regimes.

Statistical analyses were performed using Statistically Package Programme for Social Sciences (SPSS 12.0, Chicago, IL, USA). Paired samples t test was used for analysis of lipid profile changes within each group. Descriptive patient characteristics and mean percentage changes in lipid profile between groups were assessed by using ANOVA and *post-hoc* Tukey test was applied to determine the groups from which the difference arises. Data were expressed as mean±standard deviation (SD) and *p*-value <0.05 was considered statistically significant.

Results

A total of 173 women were included in this study. As presented in Table I, mean ages, parity, number of pregnancies, abortion, living children, body mass index, systolic and diastolic blood pressures of patients were similar in all groups (*p*>0.05).

Baseline lipid levels and control lipid levels after 6 months of treatment are shown in Table II. Total cholesterol

Table 1. Demographic characteristics of all enrolled cases allocated to four hormone treatment arms (Group 1-4)

Variables	Group 1 (E2/NETA)	Group 2 (CEE/2.5 mg MPA)	Group 3 (CEE/5 mg MPA)	Group 4 (Tibolone)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p* value
Age (age)	49.51±2.84	50.28±3.51	48.72±5.24	50.77±3.81	NS
Gravidy (n)	4.20±1.23	4.09±2.21	4.10±3.06	4.02±1.64	NS
Parity (n)	2.33±0.45	2.39±0.67	2.51±0.87	2.58±0.95	NS
Abortion (n)	1.87±1.00	1.51±1.60	1.64±1.31	1.32±1.44	NS
Living children (n)	2.18±0.36	2.21±0.02	2.20±0.37	2.26±0.86	NS
BMI (kg/m^2)	27.48±3.25	27.83±3.14	26.63±3.18	26.77±3.03	NS
Systolic BP	120.21±15.76	124.59±19.72	122.32±10.80	123.91±16.54	NS
Diastolic BP	78.26±6.96	81.79±9.18	79.15±6.68	79.89±6.75	NS

SD: standard deviation; BMI: body mass index; BP: blood pressure, mmHg;
NS: non significant.

Table 2. Baseline and final lipid levels following six months of hormone treatment

Variables		Group 1 (E2/NETA) Mean±SD	Group 2 (CEE/2.5 mg MPA) Mean±SD	Group 3 (CEE/5 mg MPA) Mean±SD	Group 4 (Tibolone) Mean±SD
	Visit	Mean±SD	Mean±SD	Mean±SD	Mean±SD
TC (mg/dl)	Baseline	223.09±34.09	216.65±37.66	204.28±38.59	216.40±38.45
	Final	201.47±27.03	213.86±29.52	205.97±37.96	215.66±35.59
LDL (mg/dl)	Baseline	146.40±32.39	139.89±37.47	123.88±34.97	135.39±31.09
	Final	123.77±30.61	127.90±28.17	126.67±42.59	141.11±35.24
HDL(mg/dl)	Baseline	49.00±9.07	55.22±14.60	50.63±11.11	48.97±11.69
	Final	54.15±13.10	58.05±12.57	55.73±10.42	49.45±14.46
TG (mg/dl)	Baseline	142.14±54.21	132.80±51.47	142.26±78.06	129.80±66.77
	Final	124.61±68.00	131.52±42.71	132.71±54.76	119.58±55.68

SD: standard deviation;

TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides.

decreased significantly in E2/NETA group ($p<0.05$). Total cholesterol levels also decreased in CEE/2.5 mg MPA and tibolone groups, and increased in CEE/5 mg MPA group; but these changes were found to be statistically insignificant.

Mean levels of LDL decreased significantly in E2/NETA and CEE/2.5 mg MPA groups ($p<0.05$), whereas no significant changes were seen in CEE/5 mg MPA and tibolone groups. There was a significant increase of HDL within the CEE/5 mg MPA group ($p<0.01$), whereas in the other groups increase of HDL was found to be insignificant.

Triglyceride decreased in all groups, although the difference of change was not significant. The changes of lipid profile and mean percent changes in four groups after 6 months of treatment were shown in Table 3 and Figure 1 respectively.

When percent lipid profile changes among four groups were compared, only percent changes in LDL was significant between E2/NETA and tibolone group ($p<0.05$). Total cholesterol, triglyceride and HDL percent changes were not significant among four groups. For the comparison of percent

change from baseline in lipid profiles of the treatment groups p values are shown in Table 4.

Discussion

Different hormone therapy regimes may have different effect on serum lipids. Optimal hormone therapy should increase HDL cholesterol, reduce LDL cholesterol and triglyceride levels. A meta-analysis about hormone replacement therapy on lipid, lipoprotein and apolipoprotein (a) concentrations by Godsland [7] reported that, oral conjugated equine estrogens (CEE) significantly increases HDL and triglyceride, decreases LDL and total cholesterol. Orally administered 17β-estradiol also increases HDL and triglyceride, decreases LDL and total cholesterol but with different percentages. Addition of MPA to CEE regimes diminished the estrogen induced increase in HDL, triglyceride and has a little effect on LDL. Orally administered 17β-estradiol and progesterone is associated with reductions in HDL, triglyceride and LDL. Reduction of LDL is greater than estradiol alone therapy. Estrogen induced increases in HDL and triglyceride were opposed according to the type of progesterone [7].
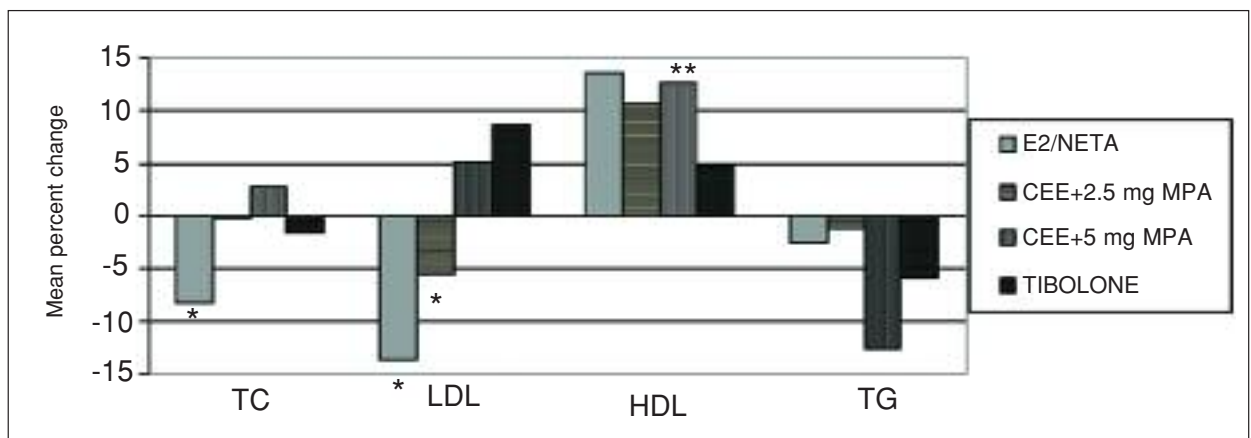
Figure 1. Mean percent changes of lipid profile after 6 months of treatment in the study groups. TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides.
* $p<0.05$
** $p<0.01$

Table 3. Changes of lipid profile following six months of hormone treatment (paired sample t test)

Dependent variable	Study groups	Coeff±SD	*p*
Δ TC	Group 1 (E2/NETA)	-21.61±39.27	0.020*
	Group 2 (CEE/2.5 mg MPA)	-2.78±28.66	NS
	Group 3 (CEE/5 mg MPA)	+1.69±6.38	NS
	Group 4 (Tibolone)	-0.73±4.57	NS
Δ LDL	Group 1 (E2/NETA)	-22.62±35.88	0.010*
	Group 2 (CEE/2.5 mg MPA)	-11.98±32.91	0.032*
	Group 3 (CEE/5 mg MPA)	+2.78±6.19	NS
	Group 4 (Tibolone)	+5.72±4.46	NS
Δ HDL	Group 1 (E2/NETA)	+5.15±14.93	NS
	Group 2 (CEE/2.5 mg MPA)	+2.82±13.86	NS
	Group 3 (CEE/5 mg MPA)	+5.10±1.45	0.001**
	Group 4 (Tibolone)	+0.48±1.79	NS
Δ TG	Group 1 (E2/NETA)	-17.52±80.28	NS
	Group 2 (CEE/2.5 mg MPA)	-10.91±49.37	NS
	Group 3 (CEE/5 mg MPA)	-9.55±12.76	NS
	Group 4 (Tibolone)	-10.21±8.36	NS

Delta (Δ) values are computed as final value minus baseline value. TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; SD: standard deviation; NS: non-significant.

* $p<0.05$

** $p<0.01$

Epidemiological data suggest that hormone therapy is associated with a reduction of coronary heart disease risk (8). HERS study is a double blind study against placebo control RCT. There were 2763 postmenopausal women between 50-79-years of age (mean 66.7) with a history of coronary heart disease. During the follow up of 4.1 years treatment with oral 0.625 CEE and 2.5 mg MPA, thromboembolic events increased and overall rate of coronary heart disease events did not reduce (9). An observational study, HERS II, showed long term use of hormone therapy, an average of 5.2 years follow-up, among healthy postmenopausal women indicated that, hormone therapy should not be continued for primary prevention of coronary heart disease (10). WHI study was the first randomized primary prevention of trial of postmenopausal hormones. The part of study that compared 0.625 mg CEE and 2.5 mg MPA with placebo was terminated early because women receiving the active drug were found to have an increased risk of developing breast cancer. However, other outcomes including an increased incidence of coronary heart disease, stroke and pulmonary embolism also suggested harm (11).

Although in the light of these clinical trials, results cannot be extrapolated to young postmenopausal women, since the mean age of women in the WHI study was relatively higher (63.3-years old) and one third of this population was on antihypertensive medication, it would be reasonable not to advice hormone therapy for primary or secondary prevention of coronary heart disease. These studies (HERS, WHI) showed a decrease in total cholesterol and LDL; an increase in triglyceride and HDL after 1 year of treatment. Different estrogens may have different effects on lipid metabolism and adding a progestin may modulate estrogens action. A high level of triglyceride is independent risk factor for coronary

artery disease (12). Triglyceride metabolism is associated with atherogenesis. Increased levels of triglyceride and total cholesterol cause arteriosclerosis and result in an increase in coronary heart disease (13).

Orally administered estrogens have an elevating effect on triglycerides. In the review by Godsland (7), orally administered CEE/MPA and E2/NETA preparations increased while tibolone decreased triglyceride levels (7). Contrary to reported data (13-15) in this study, triglyceride levels were not increased not only in CEE/2.5 mg MPA and CEE/5 mg MPA but also in E2/NETA and tibolone groups. Many studies observed a significant reduction in triglyceride levels in tibolone users (15-17). Although the decrease in triglyceride levels were not significant in all groups, CEE/5 mg MPA, tibolone, E2/NETA, CEE/2.5 mg MPA groups all decreased triglyceride from most to least respectively. Reduction in total cholesterol and LDL has been reported in many studies (14,15,18). Our finding is LDL and total cholesterol decreased in CEE/2.5 mg MPA group whereas increased in CEE/5 mg MPA group.

Increases in HDL cholesterol levels are important for cardio-protective effect of estrogen in hormone therapy although androgenic progestins are known to decrease HDL cholesterol. It has shown that 1% increase in total cholesterol or LDL increases the risk of ischemic heart disease by 2% and 1% reduction in HDL increases this risk by 2-4.7% (19). Androgenic progestins like NETA may abolish the estrogen induced increase in HDL (7,20). In our study, although the increase in HDL was seen in E2/NETA group, it was not found to be significant. HDL levels were both increased in CEE/2.5 mg MPA and CEE/5 mg MPA groups but interestingly signifi-

Table 4. For the comparison of percent changes in lipid profiles of the treatment groups p values from the baseline

Groups	Group 2 (CEE/2.5 mg MPA)	Group 3 (CEE/5 mg MPA)	Group 4 (Tibolone)
Group 1 (E2/NETA)			
TC	NS	NS	NS
LDL	NS	NS	p=0.02
HDL	NS	NS	NS
Group 2 (CEE/2.5 mg MPA)			
TC		NS	NS
LDL		NS	NS
HDL		NS	NS
TG		NS	NS
Group 3 (CEE/5 mg MPA)			
TC			NS
LDL			NS
HDL			NS
TG			NS

NS: non-significant;

TC: total cholesterol; LDL: low density lipoprotein;

HDL: high density lipoprotein; TG: triglycerides.

cant increase in HDL was only found in higher progesterone dosage, namely in CEE/5 mg MPA group.

Many studies pointed out that, compared with placebo, tibolone reduced HDL (5,15,16,21). The reduction in HDL by tibolone may be due to an androgenic effect of the compound. This negative effect on HDL has been reported as ranging between 9.3% and 34% (5,16). Kloosterboer and co-workers (22) demonstrated that, after treatment with tibolone for 3 years, HDL returned to pretreatment levels (22). Another long-term study pointed out that HDL was decreased by 11.3% at the second year and 15.5% at the fifth year of tibolone administration (15). However, from experimental studies, tibolone may have non-lipid mechanisms of cardioprotection and may cause qualitative alterations on HDL that do not attenuate ability of HDL to protect LDL from oxidation (23). In the present study, tibolone increased HDL by 4.7% after the six months of treatment, but it was not found to be statistically significant.

As a result, different hormone therapy regimes have different effect on lipid profile and none of them seem to be ideal. While many other factors are important for the cardiovascular system, changing of lipid profile may have an important role; so that when prescribing hormone therapy, lipid profile should be evaluated and monitored thereafter.

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