Serum lipids and apolipoproteins in Greek postmenopausal women: Association with estrogen, estrogen-progestin, tibolone and raloxifene therapy

G. Creatsas[1], G. Christodoulakos[1], I. Lambrinoudaki[1], C. Panoulis[1], C. Chondros[2] and P. Patramanis[1]

[1]2nd Department of Obstetrics and Gynecology; [2]Biochemical Laboratory, University of Athens, Aretaieion Hospital, Athens

ABSTRACT. The aim of this study was to assess lipid and apolipoprotein levels in postmenopausal women taking various regimens of replacement therapy or no therapy. Seven hundred forty-eight postmenopausal women followed in the Menopause Clinic of the 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital, were studied in a cross-sectional design. Women were either non-users of replacement therapy (no.=511) or users of one of the following regimens: conjugated equine estrogen 0.625 mg (CEE, no.=34), CEE 0.625 mg plus medroxyprogesterone acetate 5 mg (CEE/MPA, no.=60), 17β-estradiol 2 mg plus norethisterone acetate 1 mg (E_2/NETA, no.=44), tibolone 2.5 mg (no.=84), raloxifene HCl 60 mg (no.=51). Total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C), triglycerides (TG), apolipoprotein A_1 ($ApoA_1$) and apolipoprotein B (ApoB) levels were assessed. Women were grouped according to replacement regimen and mean levels of lipid and apolipoproteins were compared between groups. Women in the raloxifene group were older and longer menopaused. After adjustment for age and duration of menopause, TG levels were significantly lower in the tibolone and E_2/NETA groups (75 and 89.9 mg/dl, respectively) compared to non-users. TC was lower in all therapy groups, but the difference acquired significance only in the E_2/NETA (207.8 mg/dl), compared to non-users (231.5 mg/dl). LDL-C levels were significantly lower in the CEE (133.8 mg/dl), CEE/MPA (130.4 mg/dl) and raloxifene group (129.9 mg/dl) compared to non-users (151.9 mg/dl). There was no difference in HDL-C levels between users and non-users (58.9 mg/dl) except for the tibolone group where HDL-C was significantly lower (48.6 mg/dl). $ApoA_1$ levels were significantly higher in the CEE/MPA group (194.4 mg/dl) and significantly lower in the tibolone group (141.6 mg/dl) compared to non-users (170.4 mg/dl). No difference was detected between groups concerning ApoB levels. In conclusion, tibolone therapy is associated with lower TG levels as well as lower HDL and $ApoA_1$ levels. ERT, continuous combined estrogen-progestin therapy (HRT) and raloxifene are associated with lower LDL-C levels. Among continuous combined HRT users, CEE/MPA is associated with higher $ApoA_1$ levels, while E_2/NETA with lower TG levels. Large prospective randomized studies are required to validate these results.

(J. Endocrinol. Invest. *26:* 545-551, 2003)

INTRODUCTION

The incidence of cardiovascular disease (CVD) rises after menopause and this eventually becomes the principal cause of morbidity-mortality among postmenopausal women (1-3). Observational studies suggest that estrogen (ERT) or combined estrogen-progestin therapy (HRT) administered to healthy postmenopausal women may have a cardioprotective effect (4, 5). Meta-analyses have indicated a relative risk (RR)=0.5 in CVD among replacement therapy users as compared to non-users (3, 6, 7). Although the mechanisms involved have not been completely elucidated, evidence suggests that HRT is associated with a more favorable lipid-lipoprotein profile with respect to CVD (1, 4, 8). Moreover, HRT may have a direct beneficial effect on the vas-

Key-words: ERT, HRT, tibolone, raloxifene, lipids, apolipoproteins.

Correspondence: Ass. Prof. G. Christodoulakos, 3, Neofytou Douka Street, Athens GR-10674, Greece.

E-mail: ilambrinoudaki@hotmail.com

Accepted February 14, 2003.

cular wall and endothelium and on the regulation of the synthesis and release of vasodilatory and vasoconstricting agents (1, 9-11). Furthermore, other non-lipid mechanisms such as an estrogen-related decrease in insulin resistance, serum fibrinogen, factor VII and plasminogen activator inhibitor-1 may also contribute to cardioprotection (1, 3).

The Heart and Estrogen/Progestin Replacement Study (HERS) I and II, and the Women's Health Imitiative (WHI) study have raised a veil of uncertainty as to the efficacy of HRT in preventing CVD. Although the HERS I showed that after prolonged administration (4 yr) HRT was associated with a decreasing trend in the risk for a second cardiovascular event, the HERS II, extended for an additional 2.7 yr, failed to be associated with secondary prevention (12, 13). The WHI study, investigating the same regimen as in HERS, showed that postmenopausal women after prolonged exposure to HRT had an increased risk of developing CVD compared to placebo (14). These results, however, cannot be extrapolated to young postmenopausal women, since the mean age of women in the WHI study was relatively high (63.3 yr) and one third of this population was on antihypertensive medication.

Evaluation of the effect of ERT-HRT on lipid-lipoprotein metabolism continues to hold the interest of investigators. Different types of estrogen and different doses and routes of administration may have a varied effect on the lipid profile of the women (15). Furthermore, the co-administration of a progestin in naturally menopaused women complicates the matter further, since the androgenicity of the progestin, the dose and the mode (sequential vs continuous) of administration may modulate the estrogen-related effect (3, 16).

In Greece different replacement therapy formulations have been administered orally. Postmenopausal women are treated with conjugated equine estrogens (CEE) and 17β-estradiol (E_2) and these are combined with medroxyprogesterone acetate (MPA) and norethisterone acetate (NETA), respectively. These combinations may have different effects on serum lipids, depending mainly on the progestin employed in each regimen (4, 15). In addition, tibolone has been extensively prescribed and recently the selective estrogen receptor modulator raloxifene. Tibolone is a synthetic gonadomimetic steroid; it converts to 3 major active metabolites (3αOH, 3βOH, Δ_4), which bind with variable affinity and activate the estrogen, progesterone and androgen receptor differently (17-19). Tibolone is equally effective to ERT-HRT in treating climacteric symptoms and bone loss but has a different effect on lipid-lipoprotein metabolism compared to "classical" HRT (18, 19).

Raloxifene is an antiosteoporotic drug given to non-symptomatic postmenopausal women. The drug is reported to have an estrogen-agonist effect on lipids-lipoproteins, which, however, does not seem to extend to HDL-cholesterol (HDL-C) (20-22).

Since each regimen employed in postmenopausal women in Greece is different with respect to the effects on lipid-lipoprotein profile, we undertook this study in order to evaluate differences on lipid-lipoprotein levels among non-users and users of ERT, HRT, tibolone and raloxifene.

METHODS

Between January 1998 and October 2001, 1344 women visited the Menopause Clinic of the 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital, to be informed on issues concerning the menopause and its associated morbidities. These women had a complete physical examination, height and weight assessment. The battery of tests we routinely perform include: transvaginal ultrasonography, pap smear, mammography, bone mineral density assessment, lipid and apolipoprotein profile, thyroid, liver and renal function tests and gonadotrophin and estradiol levels. The above women were evaluated for the presence of climacteric symptoms and risk factors for osteoporosis and CVD and were accordingly assigned to a treatment regimen. The lipid-lipoprotein profile was re-evaluated every 6 months for the first 18 months and annually thereafter.

The design of this study was cross-sectional and the analysis was performed on the data recorded in our database until October 2001. Out of the 1344 women registered in our Clinic, 560 were excluded from further analysis on the basis of the following exclusion criteria: menopausal age <2 yr, endometrial thickness >5mm, recent use of ERT, HRT, tibolone or raloxifene (the last 9 months), liver or renal dysfunction, untreated hyper- or hypothyroidism, diabetes mellitus, ischemic heart disease, history of thromboembolism and the intake of antihypertensive or lipid-lowering medication.

Out of the remaining 784 women, 273 were current users of ERT, HRT, tibolone or raloxifene for 6 months or more. Hysterectomized women with climacteric complaints as the presenting complaint were randomly allocated to CEE 0.625 mg users or tibolone 2.5 mg. Women with an intact uterus and climacteric complaints were randomly allocated to CEE 0.625 mg plus MPA acetate 5 mg (CEE/MPA), or E_2 2 mg plus NETA 1 mg (E_2/NETA) or tibolone 2.5 mg. Hysterectomized women with osteopenia or osteoporosis were randomly allocated to CEE 0.625 mg or tibolone 2.5 mg or raloxifene 60 mg. Women with an intact uterus and osteopenia or osteoporosis were randomly allocated to CEE 0.625 mg plus MPA 5 mg (CEE/MPA), or E_2 2 mg plus NETA 1 mg (E_2/NETA) or tibolone 2.5 mg or raloxifene 60 mg. Randomization was performed by the use of a random number table.

The remaining 511 women had either never used the above-mentioned medications or had completed a wash-out period of 9 months or more. These women had normal bone mineral density and were devoid of climacteric complaints. The final 6 groups according to the replacement therapy status were: non-users (No HRT, no.=511), CEE users (no.=34, mean

duration of use:10.4 months, SD 5.2), CEE/MPA users (no.=60, mean duration of use:9.6 months, SD 4.9), E_2/NETA users (no.=44, mean duration of use: 8.4 months, SD 5.7), tibolone 2.5 mg (no.=84, mean duration of use: 12.3 months, SD 6.1), raloxifene HCl 60 mg (no.=51, mean duration of use: 14.8 months, SD 5.7). Informed consent was obtained from each subject and the study was approved by the Ethics Committee of Aretaieion Hospital.

In every woman a fasting blood sample was drawn in the morning and was immediately centrifuged. Serum was stored at –80 C until assayed. The following parameters, assessed in fasting serum, were compared between non-user and therapy groups: total cholesterol (TC), HDL-C, LDL-cholesterol (LDL-C), triglycerides (TG), apolipoprotein A_1 ($ApoA_1$) and apolipoprotein B (ApoB). If more than one lipid-lipoprotein profile was recorded in a subject, the most recent assessment was included in statistical analysis.

Serum TC, HDL-C and TG were assessed enzymatically by an autoanalyzer (COBAS-MIRA, Roche Diagnostics Limited, Lewes, East Sussex, UK). Coefficients of variations were: TC: 0.86%, HDL-C: 1%, TG: 1.87%. LDL-C was estimated as described by Friedewald (LDL-C=TC-TG/5-HDL-C). $ApoA_1$ and ApoB were determined by an immunoturbimetric assay (ABX Diagnostics BP7290-34187 Monpellier, France). Coefficients of variation were 2.31% and 2.45%, respectively.

Statistical analysis was performed by SPSS Version 8.0 (Statistical Package for the Social Sciences, Chicago, Illinois). The study had 80% power to detect the following differences in mean levels of lipid-lipoproteins with a statistical significance levels of 0.05 in groups of 40 subjects minimum: TC 22.7 mg/dl, LDL-C 22.7 mg/dl, TG: 26 mg/dl, HDL-C 8.4 mg/dl, $ApoA_1$: 19.5 mg/dl, ApoB 19.5 mg/dl.

Means of continuous variables were compared between groups by Analysis of Variance (ANOVA). Nominal variables were compared between groups by Pearson X^2. Adjustments for possible confounding factors were performed by Analysis of Covariance (ANCOVA). Bonferroni test was used for adjustment for multiple comparisons. Statistical significance was set at 0.05 level.

RESULTS

Demographic characteristics of the 784 postmenopausal women included in the study are presented in Table 1. Significant differences between groups were observed in mean age and years since menopause. Women in the raloxifene group were older and had longer menopausal age compared to the other therapy groups. Women in the CEE group had longer menopausal age compared to the other groups. Current smoking, alcohol consumption, physical exercise and family history of CVD were evenly distributed between groups. Mean estradiol levels reflected the therapy regimen in each group.

Mean unadjusted levels of lipids and apolipoproteins in non-user and therapy groups are presented in Table 2. TC was significantly lower in the combined HRT and tibolone groups, and marginally lower in the CEE and raloxifene groups compared to non-users. LDL-C was significantly lower in the CEE, CEE/MPA and raloxifene groups compared to non-users. HDL and triglycerides were significantly lower in the tibolone group compared to non-users. $ApoA_1$ was significantly higher in the CEE/MPA group and significantly lower in the tibolone group compared to non-users. No difference between groups was observed concerning the ApoB levels.

Mean levels of lipids and apolipoproteins in non-user and therapy groups, adjusted for age and years since menopause are presented in Table 3. TC remained significantly lower only in E_2/NETA group, while LDL-C was significantly lower in the CEE, CEE/MPA, and raloxifene groups, compared to non-

Table 1 - *Demographic characteristics of 784 postmenopausal women according to replacement therapy status.*

	No HRT (no.=511)	CEE (no.=34)	CEE/MPA (no.=60)	E_2/NETA (no.=44)	Tibolone (no.=84)	Raloxifene (no.=51)	*p**
			Continuous variables (mean, SD)				
Age	52.4 (5.9)	50.9 (8.5)	51.3 (4.2)	52.0 (3.3)	51.9 (4.3)	57.7[b] (5.9)	0.001
Years since menopause	5.3 (5.7)	7.2 (8.1)	4.1 (3.8)	4.8 (3.0)	4.2 (3.6)	9.3[b] (6.4)	0.001
BMI (kg/m^2)	25.4 (3.7)	25.2 (3.1)	25.2 (3.0)	25.0 (3.2)	25.1 (3.2)	25.4 (2.4)	0.99
Estradiol (pg/ml)	23.6 (15.6)	58.6 (40.1)[a]	64.6 (45.5)[b]	57.4 (40.8)[a]	33.4 (20.1)	19.1 (11.0)	0.001
			Nominal variables (%)				
Current smoking	29.4%	45.5%	40.4%	43.1%	29%	30.8%	0.21
Family history of cardiovascular disease	32.4%	40.9%	31.9%	30.8%	33.9%	33.3%	0.97
Alcohol (daily)	1.2%	0.8%	0.9%	0.7%	1.0%	0.9%	0.92
Physical exercise (>3 h/week)	30.6%	40.9%	44.7%	29.7%	24.2%	25.6%	0.42

*p: comparison between groups by ANOVA for continuous variables or by Pearson X^2 for nominal variables.
[a]p<0.01 compared to never users, if overall effect between groups significant; [b]p<0.001 compared to never users, if overall effect between groups significant.
BMI: body mass index; HRT: combined estrogen-progestin therapy; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; E_2: 17β-estradiol; NETA: norethisterone acetate.

Table 2 - *Lipid-apolipoprotein levels (mean, SD) of 784 postmenopausal women according to replacement therapy status.*

	No HRT (no.=511)	CEE (no.=34)	CEE/MPA (no.=60)	E_2/NETA (no.=44)	Tibolone (no.=84)	Raloxifene (no.=51)	*p**
Total cholesterol (mg/dl)	229.4 (39.3)	212.6 (32.6)	214.9 (40.2)[a]	214.6 (45.5)[a]	216.5 (39.9)[a]	215.1 (42.7)	0.0003
Triglycerides (mg/dl)	102.2 (55.2)	107.7 (49.3)	106.3 (52.8)	88.7 (32.1)	74.9 (31.1)[c]	108.5 (56.3)	0.0001
LDL-C (mg/dl)	149.5 (37.5)	128.7 (29.6)[a]	125.4 (35.0)[c]	142.3 (40.5)	152.9 (46.8)	134.9 (43)[a]	0.0001
HDL-C (mg/dl)	58.4 (14.2)	59.9 (12.0)	62.8 (13.1)	54.1 (12.7)	47.6 (11.5)[c]	57.2 (14.4)	0.0001
$ApoA_1$ (mg/dl)	169.5 (33.7)	185.2 (32.3)	193.3 (31.4)[c]	163.7 (29.8)	147.1 (32.3)[c]	178.4 (46.3)	0.0001
ApoB (mg/dl)	111.2 (31.8)	101.5 (26.8)	105.9 (31.6)	108.3 (30.3)	116.8 (34.7)	106.2 (27.6)	0.29

**p*: Univariate Analysis of Variances (ANOVA), Bonferroni test.
[a]$p<0.05$ compared to non-users; [b]$p<0.01$ compared to non-users; [c]$p<0.001$ compared to non-users; [d]$p=0.06$ compared to non-users.
LDL-C: LDL-cholesterol; HDL-C: HDL-cholesterol; $ApoA_1$: apolipoprotein A_1; apolipoprotein b; HRT: combined estrogen-progestin therapy; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; E_2: 17β-estradial; NETA: norethisterone acetate.

Table 3 - *Adjusted means of lipid-apolipoprotein levels of 784 postmenopausal women according to replacement therapy status.*

	No HRT (no=511)	CEE (no=34)	CEE/MPA (no=60)	E_2/NETA (no=44)	Tibolone (no=84)	Raloxifene (no=51)	*p**
Total cholesterol (mg/dl)	231.5	221.6	222.0	207.8[b]	216.3	211.7	0.001
Triglycerides (mg/dl)	103.4	108.9	111.4	89.9[a]	75.0b	100.1	0.001
LDL-C (mg/dl)	151.9	133.8[a]	130.4[a]	135.7	152.3	129.9[a]	0.003
HDL-C (mg/dl)	58.9	58.4	62.3	55.9	48.6[c]	59.3	0.001
$ApoA_1$ (mg/dl)	170.4	178.8	194.4[a]	166.1	141.6[b]	181.3	0.0001
ApoB (mg/dl)	109.6	100.0	110.7	103.2	118.5	102.3	0.21

**p*: Analysis of covariance (ANCOVA), Bonferroni test. Covariates: age, years since menopause.
[a]$p<0.05$ compared to non-users; [b]$p<0.01$ compared to non-uses; [c]$p<0.001$ compared to non-users; [d]$p=0.06$ compared to non-users.
LDL-C: LDL-cholesterol; HDL-C: HDL-cholesterol; $ApoA_1$: apolipoprotein A_1; ApoB: apolipoprotein B; HRT: combined estrogen-progestin therapy; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; E_2: 17β-estradiol; NETA: norethisterone acetate.

users. HDL-C remained significantly lower in the tibolone group, compared to non-users. TG levels were significantly lower in the tibolone and the E_2/NETA groups, compared to non-users. $ApoA_1$ levels were significantly lower in the tibolone group and significantly higher in the CEE/MPA group compared to non-users. No difference was observed between groups concerning the ApoB levels.

DISCUSSION

Favorable lipid-lipoprotein changes resulting from ERT-HRT administration may be responsible for a part of the cardioprotective effect observed among treated postmenopausal women in observational studies (2).

The high mean levels of TC and LDL-C seen in our study were unexpected, as the Mediterranean diet consumed in Greece does not favor the increase of cholesterol. A possible explanation for this finding may be the recent "westernization" of diet in our country, especially in the urban population, where the majority of the women included in the study come from. On the contrary, postmenopausal women receiving replacement therapy had in general more favorable lipid-lipoprotein profile. However, this did not hold for all parameters: levels of ApoB remained unchanged in all treatment groups, while tibolone decreased significantly HDL-C.

ERT may influence lipid-lipoprotein concentrations differently from HRT. Different estrogens may differ in their effect and adding a progestin may modulate estrogen's action. The dose, mode and route of administration may further influence lipid-lipoprotein concentrations. Finally, tibolone and raloxifene may behave differently from "classical" replacement therapy.

In this study CEE favorable action was seen in the decreased levels of LDL-C. Reductions in TC and LDL-C have been repeatedly reported (15, 23, 24). Our finding that TG levels were not increased in the CEE treated women is contrary to reported data (2, 23, 24), which further suggests that, compared to E_2 (15) and estriol (7) CEE induces the greatest increase in TG levels. In a recently published review (15) CEE appears not only to increase HDL but also to have the strongest effect compared to E_2 and estradiol valerate. Furthermore, oral administration and higher doses are associate with a greater increase (15, 23). It is interesting that in our study we found no significant difference in HDL-C levels. $ApoA_1$ is an important antiatherogenic marker which

up-regulates HDL-C production (5). In agreement with previous reports (8), we found that women on CEE had higher $ApoA_1$ levels compared to non-users. However, after adjustment for age and duration of menopause this difference lost statistical significance. Since our group of hysterectomized women receiving CEE was relatively small, our study might not have adequate power to detect small changes in the above-mentioned lipid parameters. Combined estrogen-progestin regimens appeared to have varied effects on the lipid profile. While CEE/MPA acts more favorably on LDL-C, the combination of E_2/NETA appears to have a more androgenic profile, lowering TG levels. Our observations are consistent with the data suggesting that androgenic progestins like NETA may abolish the estrogen-induced increase in HDL and $ApoA_1$ (4, 15, 25, 26). HDL-C and TG levels observed in this study are contrary to data reporting significant increases under CEE/MPA (7, 24, 27, 28). Although HDL-C levels were initially significantly higher, adjustment for age and menopause duration rendered the difference non-significant. The lack of an effect of CEE/MPA on these parameters may be due to the cross-sectional design of the study, which may not have been able to control for various inaccessible parameters, which confer uncertainty in the result assessment.

Tibolone's mode of action on lipids-lipoproteins is contradictory. Compared to non-users, tibolone lowers TC, but this is mainly attributed to the significant decrease on HDL-C (17, 18, 26). We found no change in LDL-C among tibolone-treated women and this is consistent with previous reports (6, 17). Nevertheless, it has been suggested that tibolone may render LDL particles less atherogenic and may protect LDL from oxidation (29). In lowering TG levels significantly, tibolone may express a favorable action with respect to CVD. With the exception of one study reporting no significant change (17), all other studies also observed a significant reduction in TG levels (6, 18, 28, 26, 30, 31). Tibolone users were found to have significantly lower concentrations of HDL and $ApoA_1$. This negative effect on HDL has already been reported, the decrease ranging between 20 and 30% (17, 18, 26, 31). However, this action may not necessarily translate clinically in an increase in CVD risk (6, 30). Experimental studies have indicated that tibolone may have non-lipid mechanisms of cardioprotection (19, 32) and, furthermore, that tibolone may cause such qualitative alterations on HDL that do not compromise the ability of the plasma to remove cellular cholesterol and do not attenuate the ability of HDL to protect LDL from oxidation (17, 33). Regarding tibolone effect on $ApoA_1$ levels, our findings are consistent with those of other studies indicating a statistically significant reduction (17, 26).

In our study, women receiving raloxifene have significantly lower levels of LDL-C. This estrogen-agonist action has already been commented upon (34, 35) and four studies have reported a decrease in LDL-C ranging from 3.8 to 12% (20, 21, 34, 36). We observed that this favorable action on LDL-C did not extend to HDL-C, whose concentrations were unchanged compared to those of untreated women. With respect to $ApoA_1$ levels, we noticed a trend towards higher levels, which, however, was not significant. The absence of an effect on HDL-C has also been reported in the Multiple Outcomes of Raloxifeme Evaluation (MORE) study (34), the work of Walsh et al (20) and Delmas et al (22). However, in the Euralox study (21), raloxifene was found to increase HDL-C levels significantly. In the literature there is no consensus as to the effect of raloxifene on TG levels. In this study raloxifene was not associated with any change in TG levels and, although similar findings were reported by Walsh et al. (20) and Delmas (22), others have found a moderate decrease (21), or even an increase (34).

Recently, the meaning of the effect of HRT on lipid-lipoprotein profile with respect to the risk of CVD has been challenged. In the WHI study (14), 5 yr of continuous combined HRT (CEE 0.625 mg / MPA 2.5 mg) were not able to confer cardioprotection to healthy postmenopausal women. In fact, a small increase in the incidence of cardiovascular events was observed in this study (7 more cases per 10,000 person-yr). Women employed in this study, however, were relatively old (mean age 63.3 yr) and many of them had diseases which affect the CVD risk; namely, 35% were treated for hypertension and 4.4% for diabetes mellitus. Furthermore, the study did not control for statin use, which has a proven effect on cardiovascular outcome. It may be possible that late intervention in already long-menopaused women cannot protect from a disease already in evolution. As shown in experimental studies in cynomolgus monkeys, institution of ERT immediately after ovariectomy prevents atherosclerotic plaque formation, while the same therapy started 2 yr after ovariectomy (equivalent to approximately 6 yr in humans) has no effect on plaque evolution (37).

Our study bears certain limitations. The study being cross-sectional in design, no causative inference on the effect of replacement therapy on lipids-apolipoproteins can be drawn. Furthermore, although groups were homogeneous with respect to all recorded demographic and life-style parameters, possible state of health differences be-

tween users and non-users cannot be overlooked. In conclusion, different therapy regimens have a different effect of the lipid profile of postmenopausal women and none are associated with an ideal mode of action. Furthermore, decreasing or increasing a lipid factor may not be enough to provide cardioprotection and qualitative as well as quantitative alterations in these factors may be equally important. This study suggests that the therapy regimens evaluated may all have an overall beneficial effect on lipid profile among Greek postmenopausal women. However, prescribing a particular regimen should not be based only on its effect on the lipid profile, and clinicians should also consider the side effects on other tissues and the overall effect of the quality of life.

REFERENCES

1. Nazr A, Breckwoldt M. Estrogen replacement therapy and cardiovascular protection: lipid mechanisms are the tip of the iceberg. Gynecol Endocrinol 1998, 12: 43-59.
2. Chen FP, Lee N, Wang CH, Cherng WJ, Soong YK. Effects of hormone replacement therapy on cardiovascular risk factors in postmenopausal women. Fertil Steril 1998, 69: 267-73.
3. Sitruk-Ware R. Progestins and cardiovascular risk markers. Steroids 2000, 65: 651-8.
4. Ylikorkala O, Lim P, Caubel P. Effects on serum lipid profiles of continuous 17β-estradial, intermittent norgestimate regimens versus continuous combined 17β-estradiol/norethisterone acetate hormone replacement therapy. Clin Ther 2000, 22: 622-6.
5. Kojima K, Abe-Dohmae S, Arakawa R, Murakami I, Suzumori K, Yokoyama S. Progesterone inhibits apolipoprotein-mediated cellular lipid release: a putative mechanism for the decrease of high-density lipoprotein. Biochim Biophys Acta 2001, 1532: 173-84.
6. Crook D. Lipid predictors of coronary heart disease and tibolone users. Eur Heart J 2001, 3 (Suppl M): M22-6.
7. Itoi H, Minakami H, Iwasaki R, Sato I. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen on serum lipid profile in early postmenopausal women. Maturitas 2000, 36: 217-22.
8. Stevenson JC. Are changes in lipoproteins during HRT important? Br J Obstet Gynecol 1996, 103 (Suppl 13): 39-44.
9. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med 1999, 340: 1801-11.
10. Mijatovic V, van der Mooren MJ, Stehouer CD, Netelenbos JC, Kenemans P. Postmenopausal hormone replacement, risk estimators for coronary artery disease and cardiovascular protection. Gynecol Endocrinol 1999, 13: 130-44.
11. Creatsas GC, Malamitsi-Puchner AB, Hassan EA, Economou EB, Aravantinos DI. Endothelin plasma levels in primary amenorrheic adolescents before and after estrogen treatment. J Soc Gynecol Investing 1996, 3: 350-3.
12. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. JAMA 1998, 280: 605-13.
13. Petitti DB. Editorial: Hormone replacement therapy for prevention. More evidence, more pessimism. JAMA 2002, 288: 1.
14. The Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002, 288: 321-33.
15. Godsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and alipoprotein (a) concentrations: analysis of studies published from 1974-2000. Fertil Steril 2001, 75: 898-915.
16. Sitruk-Ware R. Progestogens in hormonal replacement therapy: new molecules, risks and benefits. Menopause 2002, 9: 6-15.
17. Von Eckardstein A, Schmiddem K, Hovels A, et al. Lowering of HDL cholesterol in postmenopausal women by tibolone is not associated with changes in cholesterol efflux capacity or paraoxonase activity. Atherosclerosis 2001, 159: 433-9.
18. Mendoza N, Suarez AM, Alamo F, Bartual E, Vergara F, Herruzo A. Lipid effects, effectiveness and acceptability of tibolone versus transdermic 17β-estradiol for hormonal replacement therapy in women with surgical menopause. Maturitas 2000, 37: 37-43.
19. Williams JK, Hall J, Anthony MS, Register TC, Reis SE, Clarkson TB. A comparison of tibolone and hormone replacement therapy on coronary artery and myocardial function in ovariectomized atherosclerotic monkeys. Menopause 2002, 9: 41-51.
20. Walsh BW, Kuller LH, Wild RA, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 1998, 279: 1445-51.
21. Nickelsen T, Creatsas G, Rechberger T, et al. Differential effects of raloxifene and continuous combined hormone replacement therapy on biochemical markers of cardiovascular risk: results from the Euralox 1 study. Climacteric 2001, 4: 320-31.
22. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations and uterine endometrium in postmenopausal women. N Engl J Med 1997, 337: 1641-7.
23. Prelevic GM, Kwong P, Byrne DJ, Jagroop JA, Ginsburg J, Mikhailidis DP. A cross-sectional study of the effects of hormone replacement therapy on the cardiovascular disease risk profile in healthy postmenopausal women. Fertil Steril 2002, 77: 945-51.
24. Sanada M, Nakagawa H, Kodama I, Sakasita T, Ohama K. Three-year study of estrogen alone versus combined with progestin in postmenopausal women with or without hypercholesterolemia. Metabolism 2000, 49: 784-9.

25. Ossewaarde ME, Bots ML, Bak AA, et al. Effect of hormone replacement therapy on lipids in perimenopausal and early postmenopausal women. Maturitas 2001, 39: 209-16.
26. Castelo-Branco C, Casals E, Figueras F, et al. Two-year prospective and comparative study on the effects of tibolone on lipid pattern, behavior of apolipoproteins A_1 and B. Menopause 1999, 6: 92-7.
27. Erenus M, Karakoc B, Gurler A. Comparison of effects of continuous combined transdermal with oral estrogen and oral progestogen replacement therapies on serum lipoproteins and compliance. Climacteric 2001, 4: 228-34.
28. Baracat EC, Barbosa IC, Giordano MG, et al. A randomised, open-label study of conjugated equine estrogens plus medroxyprogesterone acetate versus tibolone: effects of symptom control, bleeding pattern, lipid profile and tolerability. Climacteric 2002, 5: 60-9.
29. Barnes JF, Farish E, Rankin M, Hart DM. A comparison of the effects of 2 continuous HRT regimens on cardiovascular risk factors. Atherosclerosis 2002, 160: 185-93.
30. Jackson G. Tibolone and the cardiovascular system. Eur Heart J 2001, 3 (Suppl M): M17-21.
31. Bjarnason NH, Bjarnason K, Haarbo J, Bennink HJ, Christiansen C. Tibolone: influence on markers of cardiovascular disease. J Clin Endocrinol Metab 1997, 82: 1752-6.
32. Zandberg P, Peters JLM, Demacker PN, de Reeder EG, Smit MJ, Meuleman DG. Comparison of the antiatherosclerotic effect of tibolone with that of estradiol and ethinyl estradiol in cholesterol-fed, ovariectomized rabbits. Menopause 2001, 8: 96-105.
33. Von Eckardstein A, Crook D, Elbers J, et al. Tibolone lowers high density lipoprotein cholesterol by increasing hepatic lipase activity but does not impair cholesterol efflux. Clin Endocrinol (Oxf) 2003, 58: 49-58.
34. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women. Four year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002, 287: 847-57.
35. Blum A, Cannon RO 3rd. Selective estrogen receptor modulator effects on serum lipoproteins and vascular function in postmenopausal women and hypercholesterolemic men. Ann NY Acad Sci 2001,949: 168-74.
36. Johnston CC, Bjarnason NH, Cohen FJ, et al. Long-term effects of raloxifene on bone mineral density, bone turnover and serum lipid levels in early postmenopausal women: three-year data from 2 double blind randomized placebo-controlled trials. Arch Int Med 2000,160: 3444-50.
37. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis and vascular function. Cardiovasc Res. 2002, 53: 605-19.