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Effects of simvastatin only or in combination with continuous combined hormone replacement therapy on serum lipid levels in hypercholesterolaemic post-menopausal women

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Aims To evaluate the effects of simvastatin only or combined with continuous hormone replacement therapy on the serum lipid profile in hypercholesterolaemic post-menopausal women.

Methods and Results One hundred hypercholesterolaemic post-menopausal women were given either simvastatin 10 mg daily together with oestrogen 0·625 mg and medroxyprogesterone 2·5 mg daily (HRT+simvastatin group) (n:50) or simvastatin 10 mg daily (simvastatin only group) (n:50) in a prospective manner. Serum total, low density lipoprotein, and high density lipoprotein cholesterol and triglyceride levels were measured at baseline, at 3 and 6 months. The initial mean (± SD) cholesterol values were as follows for the HRT+simvastatin group and the simvastatin only group, respectively: total cholesterol 240·0 ± 28·0 and 248·9 ± 28·2 mg . dl^{-1}; low density lipoprotein cholesterol 174·7 ± 25·6 and 175·1 ± 25·9 mg . dl^{-1}; high density lipoprotein cholesterol 37·2 ± 5·0 and 39·9 ± 7·3 mg . dl^{-1}. Compared with the baseline, total and low density lipoprotein cholesterol levels decreased; and high density lipoprotein cholesterol levels increased significantly at 3 and 6 months in both groups. However, the mean percent reduction in total cholesterol and low density lipoprotein cholesterol was significantly greater in the HRT+simvastatin group compared with the simvastatin only group both at 3 months (12·3 ± 7·0% vs 8·9 ± 6·2%; P<0·01; and 19·0 ± 10·6% vs 13·2 ± 10·4%; P<0·005, respectively) and at 6 months (14·6 ± 7·7% vs 11·3 ± 7·4%; P<0·05 and 23·3 ± 9·7% vs 15·8 ± 12·3%; P<0·005, respectively). The mean percent increase in serum high density lipoprotein cholesterol concentrations was also significantly greater in the HRT+simvastatin group compared with the simvastatin only group at both times (14·6 ± 11·8% vs 9·8 ± 11·8%; P<0·005, at 3 months, and 21·3 ± 15·2% vs 11·1 ± 12·5; P<0·005, at 6 months, respectively). Furthermore, significantly more patients in the HRT+simvastatin group than in the simvastatin only group attained their target treatment goals dictated by the National Cholesterol Education Program Adult Treatment Panel II Guidelines. Although the mean percent decrease in triglyceride levels was significantly greater in the HRT+simvastatin group at 3 months, the significance disappeared at 6 months.

Conclusion The combination of simvastatin and continuous combined hormone replacement therapy seems to be more effective than simvastatin only in the treatment of hypercholesterolaemia in post-menopausal women.
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Key Words: Simvastatin, hormone replacement therapy, oestrogen, progesterone, hypercholesterolaemia.

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Introduction

Hormone replacement therapy (HRT) is claimed to reduce cardiovascular mortality by about 50% in post-menopausal women[1,2]. This improvement is caused by favourable changes in serum lipid concentrations due to these hormones and there exist several reports on the

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effects of HRT on serum lipid levels both in healthy and hypercholesterolaemic post-menopausal women[3–5].

About 30 to 35% of women older than 55 years are potential candidates for drug therapy for hypercholesterolaemia according to the USA National Cholesterol Education Program (NCEP) guidelines[6,7]. The same guidelines also recommend considering HRT for post-menopausal women with elevated low density lipoprotein (LDL) cholesterol levels. Potentially, this strategy may obviate the need for specific antilipidaemic medication or may allow the dosage of the lipid lowering drug in post-menopausal women to be reduced.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are effective and safe in lowering LDL cholesterol and in the prevention of coronary heart disease in hypercholesterolaemic patients[8,9]. The issue whether HRT given concomitantly with HMG-CoA reductase inhibitors could exert any significant additional favourable effect on the serum lipid profile has not yet been settled. Therefore, the aim of this study was to compare the lipid lowering effects of simvastatin only or in combination with continuous combined HRT in hypercholesterolaemic post-menopausal women.

Methods

Study design

The study was designed in a prospective, non-randomized, open, parallel and comparative fashion. Post-menopausal women were initially assessed at the Menopause Outpatient Clinic of the Marmara University Hospital. The women screened did not necessarily have perimenopausal symptoms as the Menopause Clinic also serves as a counselling centre. The women who matched the criteria for continuous combined HRT and who had hypercholesterolaemia according to NCEP treatment guidelines[7] were referred to the Cardiology Outpatient Clinic. Eligible patients were then recruited to one of the two treatment protocols on the basis of their own preference, having been given detailed information on the potential benefits of HRT. The HRT+simvastatin group consisted of patients receiving the combination of continuous combined HRT and simvastatin, whereas patients who were unwilling or who had any contraindications to HRT only received simvastatin and constituted the simvastatin only group. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all patients. The study was conducted between April 1995 and September 1997.

Lipid lowering therapy

Exclusion criteria

The presence of acute myocardial infarction during the preceding 3 months, current smoking status, and secondary forms of hypercholesterolaemia, diabetes mellitus, tendon xanthoma, impaired hepatic function, history of partial ileal bypass, history of drug or alcohol abuse and history of hypersensitivity to simvastatin were defined as exclusion criteria.

Inclusion into the study and primary work-up

Total cholesterol and triglyceride concentrations were measured by an Abbott Biochromatic Analyser (Irving, TX, U.S.A.), with the use of enzymatic and spectrophotometric methods. High density lipoprotein (HDL) cholesterol was quantitated spectrophotometrically by an Abbott Spectrum System following dextrane sulphate-magnesium chloride precipitation and centrifugation. LDL cholesterol was calculated when the serum triglyceride level was less than 400 mg . dl^{-1}, as described by Friedewald *et al.*[10].

Serum cholesterol and triglyceride levels were determined after 9 to 12 h of fasting on two occasions 1 week apart. The average of the two measurements was taken into account during the study. If a more than 30 mg . dl^{-1} difference in LDL cholesterol levels existed between the two measurements, a third analysis was done and the average of all three measurements was accepted as the baseline level. The initiation and maintenance of the lipid lowering therapy was decided according to the LDL cholesterol levels, the presence of atherosclerotic risk factors and the presence of documented atherosclerotic vascular disease for each patient as stated and formulated in the NCEP ATP II guidelines[7]. Dietary instruction was given by the institute's registered dietician and supervized by a cardiologist in accordance with the NCEP ATP II recommendations.

Initiation of the lipid lowering drug and follow-up:

Routine haematological and blood chemistry tests (haemoglobin, haematocrit, white blood cell count, platelet count, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine phosphokinase and serum creatinine) were performed at screening and at each subsequent visit. Additional blood chemistry tests (fasting glucose, T4, thyroid stimulating hormone and urinalysis) were also performed at the screening visit.

Patients in whom 12 week dietary therapy (Step II diet) alone proved to be inadequate were put on simvastatin, and continuous combined HRT was started no more than a week later. Serum lipid concentrations and body weight at the end of Step II diet therapy were taken as the baseline values. Simvastatin (Zocor, Merck Sharp & Dohme) was given at a fixed dose of 10 mg . day^{-1}. The drug was to be taken in the evening. Patients were encouraged to adhere to the strict dietary regimen, and to maintain their body weight. Regular physical activity was encouraged in all patients. After the initiation of the lipid lowering drug treatment, the patients were seen monthly, during which their compliance to simvastatin was questioned (interview and pill count) and dietary advice was reinforced. Serum lipid concentrations were

Table 1 Baseline clinical characteristics of the study population

	HRT+simvastatin group (n=50)	Simvastatin only group (n=50)
Age (years)	56 ± 8	58 ± 8
Duration of menopause (months)	66 ± 44	67 ± 42
BMI	35·6 ± 3·1	37·8 ± 4·9
Patients with AVD (−) and <2 CHD risk factors (n)	15	15
Patients with AVD (−) and ≥2 CHD risk factors (n)	16	19
Patients with AVD (+) (n)	19	16

No significant difference has been detected between two groups.
BMI=body mass index; AVD=atherosclerotic vascular disease; CHD=coronary heart disease; HRT=hormone replacement therapy.

measured 3 and 6 months after the initiation of simvastatin treatment.

Post-menopausal hormone replacement therapy

Inclusion criteria
Post-menopausal women who had had amenorrhea for at least 1 year, and in whom the serum follicle-stimulating hormone level was above 45 IU . l^{-1}, were candidates for HRT. Women who had undergone a hysterectomy were excluded and patients with a history of breast cancer were asked to participate in the simvastatin only group.

Initiation of continuous combined HRT and follow-up
Continuous combined HRT was recommended according to the Guidelines for Counselling Post-menopausal Women About Preventive Hormone Therapy[11]. Conjugated oestrogen (Premarin, Wyeth-Ayerst) at a dose of 0·625 mg, together with medroxyprogesterone acetate (Farlutal, Farmitalia) 2·5 mg daily, were given by the oral route. An elemental calcium supplement of 1000 mg . day^{-1} was also recommended. Patients were seen monthly at the Menopause Outpatient Clinic during the course of the study and were questioned as regards compliance (interview and pill count) and the probable adverse effects (e.g. breast tenderness and vaginal bleeding) related to continuous combined HRT. Serum transaminase levels were measured 3 months after the initiation of continuous combined HRT.

Discharge criteria

Poor compliance with either treatment (defined as not taking >25% of the tablets, ascertained on two consecutive visits), any adverse effect(s) of either treatment, or with any new onset contraindication to HRT were accepted as discharge criteria.

Statistical analysis

Changes in serum lipid concentrations compared to the baseline levels and between the HRT+simvastatin group and the simvastatin only group were tested after 3 and 6 months of treatment for differences by the unpaired Student's t-test or Chi-square where appropriate. The number of patients who achieved the treatment goal in each group were also compared with the Chi-square test. A P value <0·05 was considered to be the level of statistical significance. Data were expressed as mean ± standard deviation (SD).

Results

Four hundred and forty-eight women were screened initially and of these 28 were found to have diabetes mellitus; one was found to have hypothyroidism and these patients were excluded. Of the remaining 419 patients, 204 were eligible for the study regarding their initial serum lipid profiles. After Step II dietary therapy of 12 weeks, 108 women were candidates for the study. Of these women, two were excluded because of moderately elevated hepatic enzymes at baseline and six withdrew consent. The remaining 100 patients were recruited into either the HRT+simvastatin group (n:50) or the simvastatin only group (n:50). No patient was excluded because of simvastatin intolerance. All patients but one, with a history of breast cancer, in the simvastatin only group, chose to be recruited to this group. The two groups did not differ significantly with regard to age, menopause duration, body mass index and severity of atherosclerotic risk factors at entry (Table 1). As one patient in the HRT+simvastatin group had uterine bleeding and was discharged from the study at the fourth month, lipid profile assessment at the sixth month was performed in 49 patients in the HRT+simvastatin group and 50 in the simvastatin only group. No patient was discharged because of non-compliance. Body mass index remained virtually unchanged in both groups

Table 2 Serum lipid concentrations in hypercholesterolaemic post-menopausal women treated by simvastatin and continuous combined HRT combination (HRT+simvastatin group) and simvastatin alone (simvastatin only group)

	HRT+simvastatin group	Simvastatin only group
Total cholesterol (mg . dl^{-1})		
Baseline	240·0 ± 28·0 (186–319)	248·9 ± 28·2 (200–299)
3 months	208·2 ± 20·6 (171–264) P<0·0001	225·6 ± 31 (177–288) P<0·0005
6 months	201·5 ± 17·0 (175–254) P<0·0001	218·6 ± 25·3 (178–278) P<0·0001
LDL cholesterol (mg . dl^{-1})		
Baseline	174·7 ± 25·6 (130–238)	175·1 ± 25·9 (122–230)
3 months	138·8 ± 21·5 (96–190) P<0·0001	145·3 ± 24·7 (95–203) P<0·0001
6 months	129·6 ± 18·4 (95–174) P<0·0001	150·8 ± 28·4 (104–213) P<0·0001
HDL cholesterol (mg . dl^{-1})		
Baseline	37·2 ± 5·0 (30–54)	39·9 ± 7·3 (30–63)
3 months	42·2 ± 6·2 (33–56) P<0·0001	43·5 ± 6·1 (33–61) P<0·01
6 months	45 ± 6·9 (36–63) P<0·0001	44·1 ± 5·6 (35–59) P<0·005
Triglycerides (mg . dl^{-1})		
Baseline	154·4 ± 37·7 (113–335)	163·1 ± 31·0 (98–230)
3 months	137 ± 24·9 (110–260) P<0·01	158·2 ± 26·1 (110–209)
6 months	135·6 ± 21·8 (107–238) P<0·005	149·3 ± 21·8 (100–197) P<0·01

Data are presented as mean ± SD. Numbers in the parenthesis represent ranges. P values represent significant changes compared to baseline levels.
LDL cholesterol=low density lipoprotein cholesterol; HDL cholesterol=high density lipoprotein cholesterol.

during the study (35·6 ± 3·1 and 37·8 ± 4·9 initially vs 34·9 ± 3·6 and 36·1 ± 5·1 at the end of the study in the HRT+simvastatin group and the simvastatin only group, respectively).

Effects of simvastatin only or in combination with continuous combined HRT on serum lipids

HRT+simvastatin group

The initial mean serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were 240·0 ± 28·0, 174·7 ± 25·6, 37·2 ± 5·0 and 154·4 ± 37·7 mg . dl^{-1}, respectively (Table 2). Total cholesterol, LDL cholesterol and triglyceride concentrations were significantly reduced by the simvastatin+continuous combined HRT combination after 3 months of treatment and this reduction was maintained at 6 months. The reduction in total cholesterol from the baseline levels was 12·3 ± 7·0 and 14·6 ± 7·7%, in LDL cholesterol was 19·0 ± 10·6 and 23·3 ± 9·7%, and in triglyceride was 9·6 ± 10·1 and 9·8 ± 15·3% at 3 and 6 months, respectively. On the other hand, HDL cholesterol levels were significantly increased, by 14·6 ± 11·8% at 3 months and 21·3 ± 15·2% at 6 months (Table 3).

Simvastatin only group

The initial serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were 248·9 ± 28·2, 175·1 ± 25·9, 39·9 ± 7·3 and 163·1 ± 31·0 mg . dl^{-1}, respectively (Table 2). Simvastatin only was also effective in reducing total cholesterol (3 months: 8·9 ± 6·2%; 6 months: 11·3 ± 7·4%), LDL cholesterol (3 months: 13·2 ± 10·4%; 6 months:

Table 3 Changes in serum lipid profiles by simvastatin together with continuous combined HRT (HRT+simvastatin group) and simvastatin alone (simvastatin only group)

	% Changes in serum concentrations			
	HRT+simvastatin group		Simvastatin only group	
	3 months	6 months	3 months	6 months
Total cholesterol	− 12·3 ± 7·0 *P*<0·01	− 14·6 ± 7·7 *P*<0·05	− 8·9 ± 6·2	− 11·3 ± 7·4
LDL cholesterol	− 19·0 ± 10·6 *P*<0·005	− 23·3 ± 9·7 *P*<0·005	− 13·2 ± 10·4	− 15·8 ± 12·3
HDL cholesterol	14·6 ± 11·8 *P*<0·005	21·3 ± 15·2 *P*<0·005	9·8 ± 11·8	11·1 ± 12·5
Triglyceride	− 9·6 ± 10·1 *P*<0·005	− 9·8 ± 15·3	− 2·1 ± 6·7	− 7·3 ± 9·0

P values are for the difference between the treatment groups.
LDL cholesterol=low density lipoprotein cholesterol; HDL cholesterol=high density lipoprotein cholesterol.

15·8 ± 12·3%) and in increasing HDL cholesterol (3 months: 9·8 ± 11·8%, 6 months: 11·1 ± 12·5%). Triglyceride levels remained unchanged both at 3 and 6 (Table 3).

Significant differences were evident when mean percent changes from baseline in the two treatment arms were compared, patients in the HRT+simvastatin group having more favourable changes compared with patients in the simvastatin only group. The mean reduction in total cholesterol and LDL cholesterol, and the mean increase in HDL cholesterol levels were significantly greater both at 3 and 6 months in patients in the HRT+simvastatin group (Table 3, Fig. 1(a) and (b)).

Magnitude of LDL cholesterol reduction and attainment of target treatment goals

There was also a significant difference between the two groups in favour of the HRT+simvastatin group in terms of distribution of patients by the magnitude of LDL cholesterol reduction. After 6 months of treatment, 70% of patients in the HRT+simvastatin group had a 20% or greater reduction in LDL cholesterol as compared to 40% in the simvastatin only group (Fig. 2). Furthermore, more patients in the HRT+simvastatin group than in the simvastatin only group attained the target treatment goals dictated by the NCEP ATP II guidelines[7] both at 3 and 6 months, as seen in Fig. 3.

Adverse effects

One patient in the HRT+simvastatin group had uterine bleeding at the fourth month and was discharged from the study. The aspartate aminotransferase and alanine aminotransferase levels did not increase three times the upper limit of normal in any of the patients during the study period.

Discussion

Elevated levels of total cholesterol and reduced levels of HDL cholesterol have clearly been linked to coronary heart disease in both women and men[12,13] while serum cholesterol in women has been shown to increase in relation to menopause[14]. On the other hand, epidemiological observations suggest that post-menopausal women using HRT have less coronary heart disease[2,15] and even lower mortality[16]. Although greatest attention has been focused on the impact of oestrogen and progesteron on the lipid profile as the underlying mechanism in risk reduction, the mechanism by which hormone replacement may prevent cardiovascular disease after menopause is most likely multifactorial given the wide spectrum of effects of these hormones on the cardiovascular system[17]. In the present study, two treatment modalities were compared; and hypercholesterolaemic post-menopausal women receiving simvastatin together with continuous combined HRT were found to benefit more in regard of the percent change in their serum lipids levels, compared with the women receiving simvastatin only.

Effects of HRT on serum lipid concentrations in post-menopausal women

There exist a significant number of studies on the effects of hormone replacement on lipid levels in post-menopausal women, and oestrogen alone increases serum HDL cholesterol levels, especially HDL_2, by up to

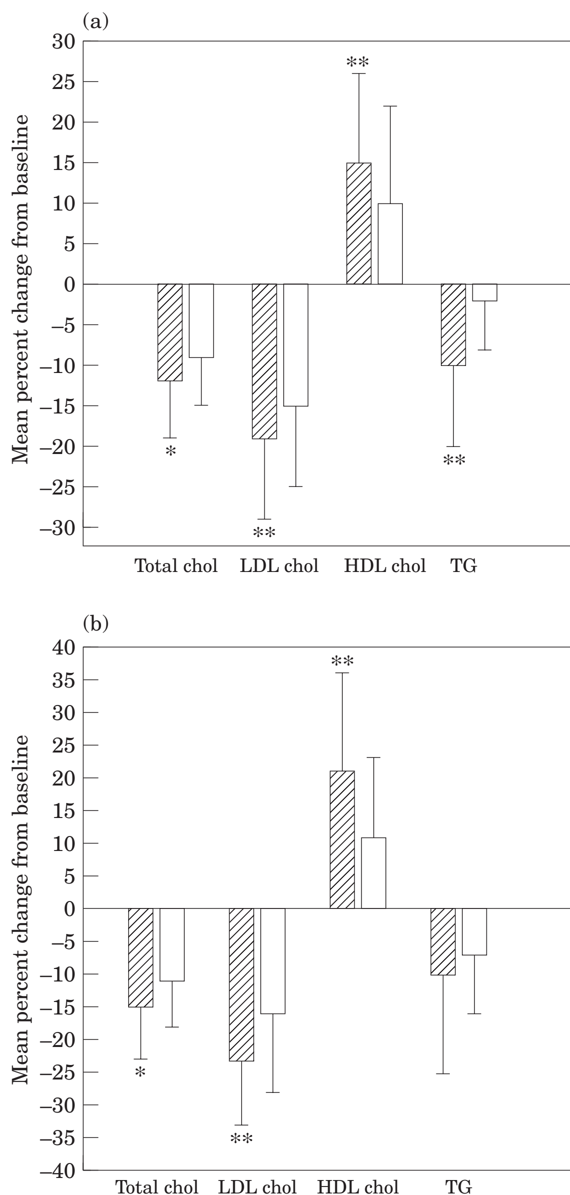

Figure 1 **(a) Mean change (%) from baseline in serum lipid levels after 3 months in both treatment groups. (b) Mean change (%) from baseline in serum lipid levels after 6 months in both treatment groups. HRT+simvastatin group (▨); simvastatin only group (□); total chol=total cholesterol; LDL chol=low density lipoprotein cholesterol; HDL chol=high density lipoprotein cholesterol; TG=triglycerides. ****P*<0·05; ******P*<0·005 compared with simvastatin only group.**

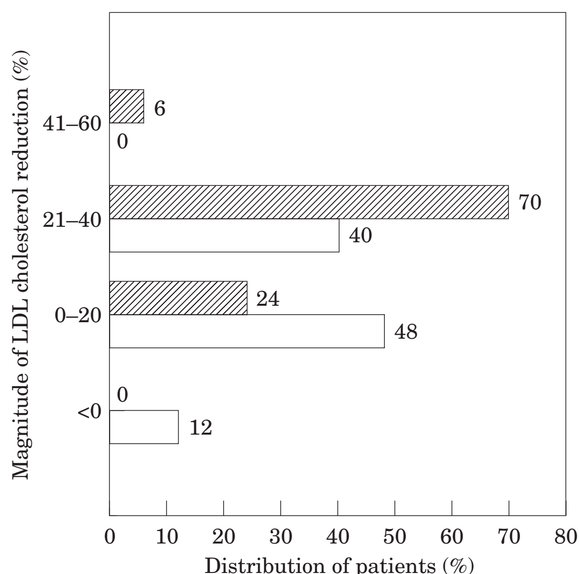

Figure 2 **Distribution of patients by magnitude of LDL cholesterol reduction. HRT+simvastatin group (▨); simvastatin only group (□). Between treatment comparison was significant.**

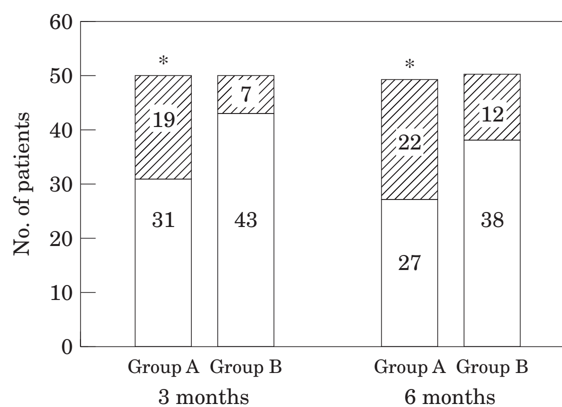

Figure 3 **Number of patients achieving treatment goals for LDL cholesterol according to the USA National Cholesterol Education Program Adult Treatment Panel II Guidelines. Between treatment comparison was significant. □=treatment goal not achieved; ▨=treatment goal achieved. Group A=HRT+simvastatin group; Group B=simvastatin only group. ****P*<0·05 compared with simvastatin only group.**

20% and decreases LDL cholesterol levels by up to 19%[17]. The effect of various HRT regimens have recently been evaluated in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial[18] in a prospective and controlled manner. Significant elevations in HDL cholesterol were found with all regimens, although progestins (either micronized or medroxyprogesteron) were reported to attenuate only mildly the increase in HDL cholesterol levels. On the other hand, similar reductions in all treatment groups were observed in LDL cholesterol levels. Several studies have compared the effects of HRT and lipid lowering drugs. Davidson *et al.*[19], in a randomized study have compared the effects of 0·625 mg of conjugated oestrogen, 20 mg pravastatin, oestrogen plus pravastatin and placebo in hypercholesterolaemic post-menopausal women. They found that while oestrogen was as effective as pravastatin in increasing HDL cholesterol levels, it was more effective than placebo but was less effective than pravastatin in reducing LDL levels in hypercholesterolaemic women. In a recent trial, simvastatin was compared with oestrogen plus

medroxyprogesteron treatment in a cross-over design[20]. Both hormone therapy and simvastatin caused significant reductions in total cholesterol and LDL cholesterol, but simvastatin was more effective than hormone therapy. On the other hand, both treatment regimens caused significant increases in HDL cholesterol, with no significant difference between the two.

Effects of the concomitant use of HRT and lipid lowering drugs on serum lipid concentrations in hypercholesterolaemic post-menopausal women and the present study

There are only a few studies on the effects of HRT and concomitant use of lipid lowering drugs. The effects of concomitant oestrogen use were investigated in a study originally designed for the efficacy and tolerability of lovastatin in women with hypercholesterolaemia[9]. Approximately 23% of the patients had been using oestrogen, and after adjusting for baseline lipid levels, concomitant oestrogen use was reported to have had no effect on either the efficacy or the safety of lovastatin. However, the above mentioned study, comparing oestrogen replacement alone with oestrogen plus pravastatin, demonstrated the beneficial effects of hormone therapy[19]. Oestrogen and pravastatin were both found to be effective compared with placebo, whereas oestrogen was more effective in increasing HDL cholesterol compared with pravastatin. The combination of pravastatin and oestrogen was found to alter plasma lipid concentrations more favourably than was the case when either agent was used alone.

Denke *et al.*[21] in a prospective and controlled study reported that continuous combined HRT could increase HDL cholesterol levels by 6% and decrease LDL cholesterol levels by 13%. Although HRT alone was not tested in our study it is possible that the combination of HRT and a statin has led to more favourable effects on serum lipid levels in regard to the data of the above mentioned study[21]. This could be attributed to the independent action of oestrogen and simvastatin on cholesterol metabolism; oestrogen appears to lower the level of LDL cholesterol by increasing its rate of clearance from plasma[22], whereas statins inhibit cholesterol synthesis[23]. The changes from baseline with simvastatin alone could be compatible with previous reports with 10 mg . day^{-1} of simvastatin, keeping in mind that only half of the study population in these trials were women[24,25]. However, when the mean changes from baseline were assessed, patients receiving simvastatin together with continuous combined HRT had significantly greater reductions in total cholesterol and LDL cholesterol and a greater increase in HDL cholesterol levels. A similar study recently reported by Sbarouni *et al.*[26] has also shown that the combination therapy, with HRT and simvastatin, could have more favourable effects on serum lipid levels. In this controlled study of only 16 patients with coronary artery disease, HRT with or without simvastatin was seen to decrease lipoprotein(a) and increase apolipoprotein A-I levels significantly compared to placebo or simvastatin only. However, none of the active treatment groups had any change in their HDL levels.

The effect of oestrogen in increasing HDL cholesterol levels is well known from previous studies, and is reported to be greater than traditional LDL-lowering drug therapy of bile acid binding resins, HMG-CoA reductase inhibitors and the fibric acids, and equal to that of nicotinic acid[27]. Denke *et al.*[21] in the above mentioned study have reported that HRT could increase HDL cholesterol levels by 6%. The 21% increase in HDL levels in our study might indicate an additive effect of HRT and simvastatin when used together. As an interesting point, a recent pilot study revealed that Turkish men are very sensitive to 10 mg . day^{-1} simvastatin with an increase in HDL cholesterol of 23%[28]. Progestins have been reported to increase the catabolism of HDL_2 and lower the levels of HDL cholesterol[29]; however, this was not the case in the present study, similar to the study of Darling *et al.*[20], although the dose of oestrogen was 1·25 mg in the latter study. The finding that simvastatin with continuous combined HRT could increase HDL cholesterol levels to a greater extent might have clinical importance, since the secondary prevention studies have suggested that the HDL cholesterol level is a more powerful predictor than the total or LDL cholesterol levels[12,30].

The present study has limitations: the study was not randomized and the treatment was not given in a blinded manner. The implications of the present study, when supported with large scale studies, could influence the management strategy of hypercholesterolaemia in post-menopausal women. The possible additive effect of HRT on lipid lowering drugs could help in achieving the target serum lipid levels in more patients or could lead to the opportunity of using smaller doses of the hypolipidaemic drug. The price of oestrogen replacement medication is lower than that of an HMG-CoA reductase inhibitor[31]. Moreover, oestrogen may have cardioprotective effects independent of its influence on lipid levels[17]. Therefore, when balanced against other costs (e.g. the additive price of medroxyprogesterone, screening tests, possibly increased risk of breast cancer, etc.) hormone replacement therapy could be a substantial component aiding the management of hypercholesterolaemia in post-menopausal women.

In conclusion, simvastatin together with continuous combined HRT, seems to be more effective compared with simvastatin only in the treatment of hypercholesterolaemia in post-menopausal women.

Simvastatin tablets used in this study were kindly supplied by Merck Sharp & Dohme Inc., Istanbul, Turkey.

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