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EFFECT OF STATINS ON ESTROGEN AND ANDROGEN LEVELS IN POSTMENOPAUSAL WOMEN TREATED WITH ESTRADIOL

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Abstract

Objective—A considerable number of postmenopausal women who receive estrogen therapy (ET) are also treated for hypercholesterolemia with cholesterol-lowering statins. Statins and steroid hormones can compete for the same steroid-metabolizing enzymes. We investigated whether long-term administration of statins had an effect on serum estrogen and androgen levels in postmenopausal women receiving and not receiving oral ET.

Methods—A subgroup analysis from the Estrogen in the Prevention of Atherosclerosis Trial, a randomized, double-blind, placebo-controlled trial, was performed. A total of 222 women were randomized to receive either placebo or 1 mg of oral micronized E_2 daily for 2 years. In both the placebo and treatment groups, participants with LDL-cholesterol levels >160 mg/dL were treated with statins. Blood samples were obtained at baseline and every 6 months during the trial. Serum levels of DHEA, androstenedione, testosterone, estrone and E_2 were measured by RIA.

Results—Among 86 placebo- and 90 estradiol-treated subjects with baseline and on-trial hormone measurements, no significant differences were observed between the statin-free and statin-treated groups in mean changes from baseline to on-trial levels in any of the androgens or estrogens, whether or not the postmenopausal women were treated with estrogen.

Conclusion—The results suggest that ET and statins can be used simultaneously with no deleterious effects on circulating hormone levels.

Keywords

statins; estrogen therapy; estrogens; androgens; postmenopausal women

INTRODUCTION

The levels of serum lipids and the incidence of cardiovascular disease have been found to increase in women at menopause.[1–3] A considerable number of postmenopausal women who

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receive estrogen therapy (ET) are also treated for hypercholesterolemia with cholesterol-lowering statins to reduce the risk of cardiovascular disease. During statin therapy there is reduction of low density lipoprotein (LDL), that is primarily due to hepatic inhibition of cholesterol synthesis, leading to an upregulation of LDL receptors, and clearance of LDL from the circulation.[4]

It is presumable that statin therapy could also have an effect on gonadal and adrenal steroidogenesis because steroid hormone synthesis requires a sufficient intracellular pool of free cholesterol. Lipoproteins, rather than de novo synthesis from acetate, contribute the majority of cholesterol used for steroid production.[5] The lipoproteins are imported into the steroidogenic cells via LDL-receptor-mediated endocytosis.[6] It has been shown that LDL cholesterol is used preferentially as a precursor for ovarian steroid biosynthesis.[5] Yet in a recent study, while pravastatin led to a significant reduction of total cholesterol and LDL cholesterol, there was no significant change in 17β-estradiol (E_2) in females and males with hypercholesterolemia.[7] In another study, total cholesterol and LDL cholesterol levels were significantly reduced during pravastatin treatment in women near or at menopause, but levels of endogenous estrogens were not significantly affected by pravastatin treatment.[8] Atorvastatin was also found to have no clinically significant effect on steroid hormone levels in hypercholesterolemic patients with type II diabetes.[9]

Steroid hormones are subject to extensive hepatic metabolism prior to elimination from the body. During the hepatic first pass of orally administered micronized E_2, there is extensive metabolism of E_2 to estrone (E_1). Both estrogens undergo extensive hepatic metabolism by the cytochrome P450 system to a variety of hydroxylated metabolites. E_1, E_2 and the hydroxylated metabolites are then conjugated to sulfated and glucuronidated metabolites that are excreted primarily in the urine.

Of the six hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) that have been used therapeutically, five (lovastatin, simvastatin, atorvastatin, cerivastatin and fluvastatin) are lipophilic and metabolized by the cytochrome P450 system in the liver, while pravastatin is hydrophilic and is not extensively metabolized by the liver.[10] Pravastatin does, however, contain hydroxyl groups, and therefore may compete with steroids for glucuronidation enzymes as it is converted to its glucuronide metabolite prior to elimination. In fact, glucuronidation has recently been identified as a common metabolic pathway for the hydroxy acid forms of several of the statins.[11] The statins and steroid hormones can therefore compete for the same steroid-metabolizing enzymes, which could potentially lead to increased circulating steroid hormone levels. No study has investigated whether statins have an effect on circulating estrogen and androgen levels in estrogen-treated postmenopausal women or on androgens in non-estrogen treated postmenopausal women. In the present randomized controlled trial, we investigated whether long-term administration of statins has an effect on serum estrogen and androgen levels in postmenopausal women receiving and not receiving oral ET.

MATERIALS AND METHODS

Study design

We performed a subgroup analysis from the Estrogen in the Prevention of Atherosclerosis Trial (EPAT). The EPAT study design has been described previously.[12] In brief, EPAT was a randomized, double-blind, placebo-controlled clinical trial designed to determine whether unopposed E_2 therapy reduces the progression of subclinical atherosclerosis in healthy postmenopausal women. Women were eligible if they were postmenopausal (serum $E_2 < 25$ pg/mL), 45 years of age or older, and had LDL-cholesterol levels greater than or equal to 130 mg/dL. They were excluded if they had been diagnosed with breast and/or

gynecological cancer in the 5 years prior to or during the screening visit, had previous hormone therapy use of >10 years' duration and/or current use within 1 month of the screening visit, diastolic blood pressure > 110 mmHg, life threatening disease with a prognosis < 5 years, total triglycerides greater than or equal to 400 mg/dL, high density lipoprotein (HDL)-cholesterol < 30 mg/dL, or were current smokers. Women with diabetes mellitus were included, provided that their fasting blood glucose was <200 mg/dL. All participants gave written informed consent, and the University of Southern California Institutional Review Board approved the study protocol. A total of 222 women were randomized to either placebo (n=111) or 1 mg of oral micronized E_2 (n=111) daily for 2 years (treatment group). In both the placebo and E_2 groups, participants with LDL cholesterol levels > 160 mg/dL were treated with statins. The participants were advised to take the estrogen or placebo in the morning and the statin in the evening.

Assay Methods

Fasting blood samples were drawn at baseline and every 6 months during the trial, and after being processed the resulting serum was stored at −70°C. Serum levels of androstenedione (A), dehydroepiandrosterone (DHEA), testosterone (T), E_1 and E_2 were quantified by validated, previously described RIAs.[13,14] Prior to RIA, the steroids were extracted from serum with hexane:ethyl acetate (3:2). A, DHEA, and T were separated by Celite column partition chromatography using increasing concentrations of toluene in trimethylpentane, and E_1 and E_2 were separated in a similar fashion by use of ethyl acetate in trimethylpentane. SHBG was measured by direct chemiluminescent immunoassay using the Immulite analyzer (Siemens Medical Solutions Diagnostics, Malvern, Pennsylvania, U.S.A.). Free T was calculated using total T and SHBG concentrations and an assumed constant for albumin in a validated algorithm.[15–17] Free E_2 was calculated in a similar manner.

All the immunoassay methods were shown to be reliable. Specificity was achieved by use of highly specific antisera and/or use of organic solvent extraction and chromatographic steps prior to quantification of the analytes. Assay accuracy was established by demonstrating parallelism between measured concentrations of the appropriate serially diluted analyte in serum with the corresponding standard curve. Intraassay and interassay coefficients of variation ranged from 4 to 8% and 8 to 13%, respectively. The assay sensitivities for E_1, E_2, T, A, DHEA and SHBG, were 5 pg/ml, 3 pg/ml, 1.5 ng/dL, 0.03 ng/ml, 0.3 ng/ml and 1nM, respectively.

Statistical Analysis

For the present study, baseline and on-trial blood samples for hormone measurements were available from 179 of 222 randomized subjects (89 placebo- and 90 E_2-treated subjects). Three placebo subjects who received estrogens from their private physicians were excluded from this analysis. Of the remaining 86 placebo subjects (77% of those randomized), 48 (56%) received statins and 38 (44%) did not receive statins during the trial. Among the 90 E_2 subjects, 36 (40%) received statins and 54 (60%) did not receive statins during the trial.

We summarized baseline and on-trial levels of total E_2, free E_2, E_1, total T, free T, A, DHEA and SHBG in statin-free and statin-treated postmenopausal women for placebo and estradiol-treated groups separately. On-trial hormone levels were calculated using the average of all available follow-up data for subjects who had at least one follow-up hormone assay. For each subject, we computed the change from baseline in each hormone (on-trial average level minus baseline level). Within each treatment group, we used paired t-tests to test whether the on-trial hormone levels significantly differed from the baseline levels. Within each treatment group, we used independent t-tests to test whether the hormone

changes differed between subjects who were treated and not treated with statins. Data were summarized as mean and standard deviations of baseline, on-trial, and changes in each hormone. All hypothesis testing used 2-sided p-values, with a p-value<0.05 considered statistically significant. All statistical analyses were performed with SAS 9.0 (SAS Institute Inc., NC).

RESULTS

All subjects with LDL cholesterol > 160 mg/dL were provided pravastatin as part of the trial design. Among these subjects given pravastatin, the average ± SD duration of pravastatin use was 15.8 ± 4.4 months among E_2-treated (n=37) and 14.9 ± 5.0 months among placebo-treated (n=52) subjects. Other statins that were used during the trial by these same subjects (through private physicians) included: lovastatin (n=3 E_2 subjects for an average 9.3 months; n=5 placebo subjects for an average 6.8 months), simvastatin (n=1 E_2 subject for 2 months), fluvastatin (n=3 E_2 subjects for 4 months) atorvastatin (n=2 E_2 subjects for 3 months; n=2 placebo subjects for 3 months) and pravastatin (through private physician, n=2 E_2 subjects for 8 months).

Serum levels (mean ± SD) of the measured estrogens, androgens, SHBG, as well as calculated free E_2 and free T in statin-free and statin-treated postmenopausal women in the placebo group are shown in Table 1. No significant changes were seen in any of the hormone levels or SHBG during the trial while on placebo treatment. Within each treatment group, the mean change between baseline and on-trial levels of the different compounds showed no significant difference between the statin-free and statin-treated groups.

Table 2 shows serum levels (mean ± SD) of the measured estrogens, androgens, SHBG as well as calculated free E_2 and free T in statin-free and statin-treated postmenopausal women in the estrogen-treated group. During E_2 therapy, serum total E_2, E_1 and SHBG levels rose significantly ($p<0.05$). While free T, A and DHEA levels fell and free E_2 and total T levels increased, the changes were not significant. Comparing the statin-free and statin-treated groups, no significant differences were observed in these changes between baseline and end of trial levels of the different compounds.

DISCUSSION

The clinical basis for administering ET to postmenopausal women has been to reduce menopausal symptoms, protect against bone loss, and until recently, to maintain the cardioprotective effects of estrogen. A lack of cardiovascular benefit in large trials of combined estrogen/progestogen therapy has led researchers to test unopposed ET in healthy postmenopausal women, and the EPAT trial indeed found a reduction in the progression of subclinical atherosclerosis in women receiving E_2.[12] However, unopposed ET is generally not recommended for women with a uterus because of the risk of uterine cancer, and it must therefore be used cautiously and at low doses, or combined with a progestogen. Because of the increasing number of postmenopausal women who are prescribed statin therapy to treat hypercholesterolemia, it is necessary to ensure that statins do not interfere with steroid hormone metabolism and cause increases in circulating hormone levels, especially in women receiving concomitant ET. An unintended rise in circulating E_2 could have implications for endometrial proliferation and uterine cancer risk.

In this randomized controlled trial, we sought to determine whether long-term administration of statins has an effect on serum E_2 levels in postmenopausal women without preexisting cardiovascular disease receiving oral ET. One limitation of our study is that pravastatin was the predominant statin that was used in the statin-treated postmenopausal

women, and only a very small number of the other statins were employed. Therefore, we were unable to compare the effects of pravastatin relative to other statin agents on circulating sex hormone levels. Since the chemical structures of statins differ and they are subject to metabolism by a substantial number of cytochrome P450, as well as glucuronyl and sulfuryl transferase isoenzymes, which also act on steroid hormones, their effects on circulating sex hormone levels may vary. Another limitation in our study is that we did not measure any conjugated metabolites of the principal estrogens and androgens that were measured. As mentioned earlier, glucuronidation has been identified as a common metabolic pathway for several statins. Also, we did not measure any sulfated conjugate such as estrone sulfate, which is quantitatively the major circulating estrogen in women.

In conclusion, postmenopausal women randomized to the E_2-treatment and placebo groups showed no significant difference in changes from baseline of estrogen or androgen levels in statin (predominantly pravastatin) and statin-free participants. Our data therefore suggest that ET and statins may be used simultaneously with no deleterious effects on circulating hormone levels.

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REFERENCES

1. Yamamoto A, Horibe H, Mabuchi H, et al. Analysis of serum lipid levels in Japanese men and women according to body mass index. Increase in risk of atherosclerosis in postmenopausal women. Research Group on Serum Lipid Survey 1990 in Japan. Atherosclerosis. 1999; 143:55–73. [PubMed: 10208480]
2. Trémollières FA, Pouilles JM, Cauneille C, Ribot C. Coronary heart disease risk factors and menopause: a study in 1684 French women. Atherosclerosis. 1999; 142:415–423. [PubMed: 10030394]
3. Azizi F, Ainy E. Coronary heart disease risk factors and menopause: a study in 1980 Tehranian women, the Tehran Lipid and Glucose Study. Climacteric. 2003; 6:330–336. [PubMed: 15006254]
4. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature. 1990; 343:425–430. [PubMed: 1967820]
5. Grummer RR, Carroll DJ. A review of lipoprotein cholesterol metabolism: Importance in ovarian function. J Anim Sci. 1988; 66:3160–3173. [PubMed: 3068221]
6. Gwynne JT, Strauss JF 3rd. The role of lipoproteins in steroidogenesis and cholesterol metabolism in steroidogenic glands. Endocr Rev. 1982; 3:299–329. [PubMed: 6288367]
7. Bohm M, Herrmann W, Wassmann S, Laufs U, Nickenig G. Does statin therapy influence steroid hormone synthesis? Zeitschrift fur Kardiologie. 2004; 93:43–48. [PubMed: 14740240]
8. Honjo H, Tanaka K, Urabe M, et al. Menopause and hyperlipidemia: pravastatin lowers lipid levels without decreasing endogenous estrogens. Clin Ther. 1992; 14:699–707. [PubMed: 1345259]
9. Santini SA, Carrozza C, Lulli P, Zuppi C, CarloTonolo G, Musumeci S. Atorvastatin treatment does not affect gonadal and adrenal hormones in type 2 diabetes patients with mild to moderate hypercholesterolemia. J Atheroscler Thromb. 2003; 10:160–164. [PubMed: 14564085]
10. Bottorff M, Hansten P. Long-term safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors: the role of metabolism-monograph for physicians. Arch Intern Med. 2000; 160:2273–2280. [PubMed: 10927723]
11. Prueksaritanont T, Subramanian R, Fang X, et al. Drug Metab Disposition. 2002; 30:505–512.
12. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001; 135:939–953. [PubMed: 11730394]
13. Goebelsmann, U.; Bernstein, GS.; Gale, JA., et al. Serum gonadotropin testosterone estradiol and estrone levels prior to and following bilateral vasectomy. In: Lepow, IH.; Crozier, R., editors.

Vasectomy: Immunologic and pathophysiologic effects in animals and man. New York: Academic Press; 1979. p. 165-175.

14. Goebelsmann U, Horton R, Mestman JH, et al. Male pseudohermaphroditism due to testicular 17-hydroxysteroid dehydrogenase deficiency. J Clin Endocrinol Metab. 1973; 36:867. [PubMed: 4349047]
15. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma protein at body temperature. J Steroid Biochem. 1982; 26:801–810. [PubMed: 7202083]
16. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999; 84:3666–3672. [PubMed: 10523012]
17. Rinaldi S, Geay A, Déchaud H, et al. Validity of free testosterone and free estradiol determinations in serum samples from postmenopausal women by theoretical calculations. Cancer Epidemiol Biomarkers Prev. 2002; 11:1065–1107. [PubMed: 12376508]

Table 1

Serum levels (mean ± SD) of estrogens, androgens and SHBG in the statin-free and statin-treated postmenopausal women in the placebo group.

	Statin-free (n=38)			Statin(n=48)			
	Baseline	**On-trial**	**Change**	**Baseline**	**On-trial**	**Change**	**p value***
Total estradiol (pg/mL)	19.3 ± 6.3	20.2 ± 8.2	0.9 ± 6.1	18.9 ± 4.7	21.5 ± 11.8	2.6 ± 11.3	0.38**
Free estradiol (pg/mL)	0.5 ± 0.2	0.6 ± 0.3	0.03 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.1 ± 0.2	0.58
Estrone (pg/mL)	39.1 ± 15.5	47.6 ± 43.6	8.5 ± 41.9	40.6 ± 11.8	47.3 ± 42.1	6.7 ± 43.1	0.85
Total testosterone (ng/dL)	20.2 ± 9.2	20.6 ± 7.9	0.3 ± 4.1	23.9 ± 8.9	24.1 ± 9.7	0.2 ± 3.3	0.89
Free testosterone (pg/mL)	3.5 ± 1.5	3.6 ± 1.1	0.1 ± 1.0	4.5 ± 1.8	4.6 ± 2.1	0.1 ± 1.0	0.97
Androstenedione (pg/mL)	490 ± 207	488 ± 124	−2.2 ± 175	570 ± 234	552 ± 226	−18.2 ± 163	0.66
DHEA (ng/mL)	2.2 ± 1.5	2.0 ± 1.1	−0.2 ± 1.2	2.6 ± 1.6	2.3 ± 1.5	−0.2 ± 0.7	0.87**
SHBG (nmol/L)	37.6 ± 15.9	36.8 ± 15.7	−0.8 ± 10.7	33.4 ± 13.2	35.2 ± 18.9	1.8 ± 13.3	0.34

* p-value from independent t-test, comparing mean change in hormone levels between statin-free and statin-treated women

** t-test for unequal variance used

Table 2

Serum levels (mean ± SD) of estrogens, androgens and SHBG in the statin-free and statin-treated postmenopausal women in the estradiol-treated group.

	Statin-free (n=54)			Statin (n=36)			
	Baseline	**On-trial**	**Change**	**Baseline**	**On-trial**	**Change**	**p value***
Total estradiol (pg/mL)	24.5 ± 24.9	70.4 ± 26.9	45.9 ± 28.5	17.1 ± 5.4	66.2 ± 28.6	49.0 ± 27.1	0.61
Free estradiol (pg/mL)	0.7 ± 0.6	1.6 ± 0.6	1.0 ± 0.7	0.5 ± 0.2	1.6 ± 0.7	1.1 ± 0.6	0.39
Estrone (pg/mL)	51.3 ± 37.9	312 ± 140	261 ± 141	40.9 ± 16.0	315 ± 200.	274 ± 196	0.72**
Total testosterone (ng/dL)	22.4 ± 11.8	23.9 ± 12.1	1.5 ± 7.2	19.9 ± 7.8	20.9 ± 8.4	1.0 ± 4.3	0.65**
Free testosterone (pg/mL)	4.3 ± 2.4	3.2 ± 1.7	−1.0 ± 1.4	3.6 ± 1.5	2.9 ± 1.3	−0.7 ± 1.5	0.37
Androstenedione (pg/mL)	571 ± 265	526 ± 192	−45.8 ± 198	511 ± 221	449 ± 150	−61.8 ± 136	0.65**
DHEA (ng/mL)	2.4 ± 1.7	1.9 ± 0.8	−0.5 ± 1.3	2.0 ± 1.0	1.6 ± 0.7	−0.4 ± 0.6	0.63**
SHBG (nmoles/L)	33.6 ± 16.1	57.7 ± 23.9	24.2 ± 17.7	37.7 ± 21.8	59.3 ± 23.6	22.0 ± 17.9	0.58

* p-value from independent t-test, comparing mean change in hormone levels between statin-free and statin-treated women

** t-test for unequal variance used