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NOTE

Effect of Estrogen Replacement Therapy on Hepatic Triglyceride Lipase, Lipoprotein Lipase and Lipids Including Apolipoprotein E in Climacteric and Elderly Women

MAMORU URABE, TAKARA YAMAMOTO, TOMOHIRO KASHIWAGI, TOMOHARU OKUBO, HIROSHI TSUCHIYA, KOICHI IWASA, NORIKO KIKUCHI, KAZUAKI YOKOTA, KENICHI HOSOKAWA, AND HIDEO HONJO

Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Kyoto 602, Japan

Abstract. Estrogen provides beneficial effects on hyperlipidemia in climacteric and elderly women. In this study of 68 women (37 to 67 years old), hepatic triglyceride lipase (HTGL), lipoprotein lipase (LpL) serum lipids and apolipoproteins were analyzed to investigate the effects of estrogen replacement therapy (ERT). After menopause, LpL, total choresterol, low-density lipoprotein (LDL)-cholesterol, and apolipoprotein B increased. But ERT suppressed total cholesterol, LDL-cholesterol, apolipoprotein B, and especially apolipoprotein E in menopausal women. The mechanism was thought that ERT significantly suppressed HTGL, but LpL was not affected. Estrogen also increases hepatic LDL receptors and accelerates transfer of serum LDL-C (and TC). It was said that HTGL accelerates conversion of intermediate-density lipoprotein (IDL) to LDL. The suppression of HTGL by the ERT may decrease conversion of IDL to LDL and lower LDL-C (and TC). These estrogen's beneficial effects on lipids, may prevent the atherosclerosis. In addition, apolipoprotein E increases senile plaques in senile dementia-Alzheimer's type. The decrease in apolipoprotein E with ERT may be related to cognitive functions of elderly women.

Key words: Hepatic triglyceride lipase, Lipoprotein lipase, lipids, Hormone replacement therapy, Apolipoprotein E

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HYPERLIPIDEMIA has become prominent in climacteric and elderly women [1]. Hypercholesterolemia (≧220 mg/dl) is seen in 46.2% of Japanese women in their 50s and 52.6% in their 60s, that is after menopause when endogenous estrogens decrease. In fact, the leading cause of death in women in 1993 was heart disease (25%), and the third most common was cerebrovascular disease (17%) [2]. Both conditions are closely associated with hyperlipidemia. Estrogen provides beneficial effects on hyperlipidemia after menopause [3]. Estrogen replacement therapy (ERT) has become common in Japanese women [4]. Recently, ε4 allele of apolipoprotein E (apo E) was reported to be a risk factor for late-onset senile dementia-Alzheimer's type (SDAT) [5]. Apo E accelerates precipitation of β-protein in senile plaques in SDAT [6, 7]. In this study, post heparin plasma lipases, namely hepatic triglyceride lipase (HTGL) and lipoprotein lipase (LpL), various lipids including apo E, and estrogen were analyzed to clarify the roles of these lipases under ERT. The effects of ERT on apolipoproteins were also investigated.

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Correspondence to: Dr. Mamoru URABE, Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Kawaramachi, Hirokoji, Kamigyo-ku, Kyoto 602, Japan

Method

Sixty-eight climacteric and elderly women (37 to 67 years old) without complications were recruited from among our outpatients. The aim of this study was explained and informed consent was obtained from these women. They were divided into 11 groups, (a)-(k), as shown in Table 1. ERT was performed as follows: day 0 to 21, 0.625 to 1.25 mg/day conjugated estrogen (CE); day 22 to 28, no hormone treatment. This cycle was repeated. In ERT (with P), 2.5 mg/day medroxyprogesterone acetate (MPA) was also given on days 11 to 21 of ERT. ERT(+) means that at least one cycle or more of ERT was given. ERT(−) means that no ERT was given for at least 2 months. Just finished ERT means that it was within 6 days after finished ERT.

Serum samples were obtained between 0900 h and 1400 h at our outpatient department in the fasting state. These serum samples were used to determine plasma levels of total cholesterol (TC, mg/dl), high density lipoprotein-cholesterol (HDL-C, mg/dl), triglyceride (TG, mg/dl), apo A-1 (mg/dl), apo B (mg/dl), apo E (mg/dl), estradiol-17β (E_2, pg/ml), lipid peroxides (LP, nM/ml) and post heparin plasma lipases (HTGL, μM/ml/min and LpL, ng/ml). Into the antecubital vein on one side, heparin (30 U/Kg, in 10 ml saline) was administered. Ten min later a plasma sample was obtained from the other antecubital vein. This sample was used to measure HTGL and LpL. These data on HTGL and LpL were used after 10 min in this study.

The TC level was measured by an enzymatic method and HDL-C was measured by a phosphotungstate/Mg^{2+} precipitation procedure [8]. The TG level was measured by an enzymatic method. The LDL-C level was calculated with Friedewald's equation [9]. Levels of Apo A-1, B, and E were measured by immunoturbidimetry [10]. E_2 was measured by a radio immunoassay. Lipid peroxides were measured with a methylen blue derivative [11].

The HTGL level was measured by an immunochemical method [12], and LpL was measured by an enzyme immunoassay [13].

Statistical analysis of results was performed by Student's *t*-test, unpaired, and simple regression.

Results

Comparison of the (a) premenopausal and ERT(−) group with the (c) postmenopausal and ERT (−) group

In women who also did not receive ERT [(a) premenopausal group, 16 women and (c) postmenopausal group, 19 women], neither HTGL nor LpL changed with age. On the other hand, LpL ($P<0.05$), TC ($P=0.001$) and LDL-C ($P<0.005$) were higher in the (c) postmenopausal and ERT (−) group than in the (a) premenopausal and ERT (−) group (Table 2). The mean level of HTGL was relatively higher in the (c) postmenopausal and ERT (−) group than in the (a) premenopausal and ERT (−) group (without statistical difference). The mean level of Apo E was higher in the (c) postmenopausal and ERT (−) group than in the (a) premenopausal and ERT (−) group. Serum E_2 showed a very low level in the (c) postmenopausal and ERT (−) group ($P<0.0005$).

Table 1. Subjects

- Premenopausal women: 20
  - (a) ERT (−): 16
  - (b) ERT (+): 4
    - (f) ERT (without P): 1
    - (g) ERT (with P): 3
- Postmenopausal women: 48
  - (c) ERT (−): 19
  - (d) ERT (+): 29
    - (h) ERT (without P): 14
    - (i) ERT (with P): 15
  - (e) Just finished ERT: 12
    - (j) ERT (without P): 5
    - (k) ERT (with P): 7

ERT, estrogen replacement therapy, ERT (−) means no ERT within 2 months. Just finished ERT means that it was within 6 days after finished ERT. P, medroxyprogesterone acetate.

Table 2. Comparisons of postheparin plasma lipases and lipids etc

		a	c	e	a *vs.* c	c *vs.* e
Age	year	45.6 ± 4.79	54.8 ± 6.95	52.2 ± 3.90	=0.0001	ns
HTGL	μM/ml/min	0.182 ± 0.064	0.198 ± 0.064	0.145 ± 0.037	ns	<0.05
LpL	ng/ml	225 ± 53.5	267 ± 58.5	281 ± 29.0	<0.05	ns
TC	mg/dl	189 ± 30.6	232 ± 37.2	190 ± 24.6	=0.001	<0.005
LDL-C	mg/dl	110 ± 23.9	145 ± 38.2	97.1 ± 27.1	<0.005	<0.005
HDL-C	mg/dl	58.6 ± 13.4	63.1 ± 15.3	69.4 ± 12.5	ns	ns
TG	mg/dl	103 ± 67.0	125 ± 59.1	118 ± 35.3	ns	ns
Apo A-1	mg/dl	125 ± 20.9	131 ± 19.1	151 ± 25.8	ns	<0.05
Apo B	mg/dl	92.2 ± 26.7	114 ± 34.4	87.1 ± 12.0	<0.1	<0.05
Apo E	mg/dl	4.48 ± 1.43	4.87 ± 1.63	3.41 ± 0.748	ns	<0.01
LP	nM/ml	4.59 ± 1.14	4.18 ± 0.859	3.64 ± 1.26	ns	ns
Insulin	μU/ml	6.44 ± 2.87	9.09 ± 16.1	3.56 ± 1.68	ns	ns
E_2	pg/ml	168 ± 163	14.2 ± 9.42	86.3 ± 81.1	<0.0005	<0.001

a, premenopausal and ERT (−) group (16 women); c, postmenopausal and ERT (−) group (19 women); e, postmenopausal and just finished ERT group (12 women).

Comparison of the (c) postmenopausal and ERT (−) group with the (e) postmenopausal and recent ERT(+) group

The ages in the (c) postmenopausal and ERT(−) group (19 women) and the (e) postmenopausal and recent ERT (+) group (12 women) were not significantly different. The HTGL level was significantly suppressed in the (e) postmenopausal and recent ERT(+) group, compared with that in the (c) postmenopausal and ERT (−) group ($P<0.05$, Table 2). The LpL level showed no difference. Serum E_2 and HTGL levels showed a weak inverse correlation ($r=-0.354$, $P<0.1$). Serum E_2 and LpL levels showed no correlation.

The TC ($P<0.005$), LDL-C ($P<0.005$), Apo B ($P<0.05$), and especially Apo E ($P<0.01$, Table 2) levels were significantly suppressed in the (e) postmenopausal and recent ERT (+) group, compared with those in the (c) postmenopausal and ERT (−) group. In contrast, serum E_2 ($P<0.001$) and apo A-1 ($P<0.05$) levels were higher in the (e) postmenopausal and ERT (−) group. The LP and insulin levels were similar in the above groups.

The (e) postmenopausal and recent ERT (+) group (12 women) was composed of the (j) ERT (= −P) group (=without progestogen, 5 women) and (k) ERT (= +P) group (=combination with progestogen, MPA, 7 women). Between the (j) and (k) groups, all parameters, including HTGL, LpL, lipids and so on showed no effect on post heparin plasma lipases and lipid levels.

HTGL and lipids

In whole samples, HTGL showed direct correlations with TC ($r=0.436$, $P<0.0005$), LDL-C ($r=0.460$, $P<0.0005$, Fig. 1) and apo B ($r=0.446$, $P=0.0005$) levels.

The apo E level was 4.80 ± 1.49 mg/dl in cases with < 20 pg/ml of serum E_2 and higher ($P<0.005$) than that (3.75 ± 1.13 pg/ml) in cases with ≧ 20 pg/ml of serum E_2.

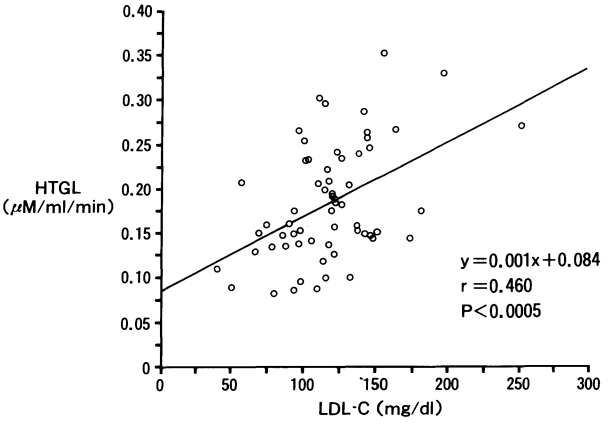

Fig. 1. HTGL and LDL-C in all samples.

Discussion

Applebaum-Bowden *et al.* [14] administered ethinylestradiol (1 μg/kg/day) to six postmenopausal women and produced a remarkable decrease in HTGL after just 4 days. Colvin *et al.* [15] administered E_2 in a stepwise manner (0.5 to 20 mg/day) to six postmenopausal women and showed that HTGL activity response was inversely correlated with the estrogen dose. Basdevant *et al.* [16] found a decrease in HTGL during oral E_2 treatment. In the present study, ERT suppressed HTGL but not LpL. Tikkanen *et al.* [17] administered estradiol valerate (2 mg/day for 3 months) to six postmenopausal women and produced suppression of HTGL but no suppression of LpL. Suppression of LpL could be seen only after high levels of estrogens, as during the third trimester of pregnancy [18], pancreatitis in pregnant women with hypertriglyceridemia [19], and hypertriglyceridemia with a high dose of estrogen to elderly women [20]. HTGL accelerates conversion of HDL2-C to HDL3-C and induces uptake of HDL by the liver [21]. ERT increases HDL-C levels in postmenopausal women [3]. The suppression of HTGL may increase serum HDL-C. Serum apo-A-1, which is the main component of HDL, tended to increase with serum E_2 [4]. In the present study, apo A-1 was higher in the ERT group. Intestinal and/or hepatic production of apo A-1 may be stimulated by estrogen, and, HDL and HDL-C may increase.

In our previous study [3], ERT strongly suppressed LDL-C after menopause. The present study also showed remarkable suppression of LDL-C and TC. Estrogen increases hepatic LDL receptors and accelerates transfer of serum LDL-C (and TC). On the other hand, HTGL accelerates conversion of intermediate-density lipoprotein (IDL) to LDL [22]. In the present study, HTGL decreased along with TC, LDL-C and apo B. The suppression of HTGL by the ERT may decrease conversion of IDL to LDL and lower LDL-C (and TC).

Estrogens have other beneficial effects on the vascular system [4]. Estrogens, especially, estradiol 17-sulfate (E_2–17-S) and its catecholized form, E_2–17-S (2-OH E_2–17-S, 4-OH E_2–17-S), strongly suppress lipid peroxidation [23]. These estrogens may protect human arterial endothelial cells from oxidative stress, and may inhibit oxidation (oxidizing degeneration) of LDL-C and suppress atherosclerosis of the vascular endothelium [24]. The third beneficial effect, ERT may become more widely applied. Today, combination with progestogen is recommended to protect against uterine endometrial cancer and other conditions [25]. On the other hand, the effect of the combination of progestogen with ERT on coronary heart disease is still unclear. In the present study, which was not conclusive because of the small number of cases, no difference was found in the post heparin plasma lipases and lipids with and without progestogens. Further large-scale studies on the effects of combined ERT on cardiovascular risk are necessary.

It is possible that estrogen has ameliorative effects on SDAT senile dementia-Alzheimer's type [26]. Senile plaques in SDAT are made of amyloid. The main component of amyloid is β-protein. Apo E accelerates precipitation of β-protein [6, 7]. The ε4 allele of apo E may be a risk factor for late-onset SDAT [5]. In the present study, Apo E was higher in cases with < 20 pg/m*l* of serum E_2. Apo E was noticeably suppressed by ERT in postmenopausal women. Our other conjugated estrogen therapy suppressed apo E significantly after 4 weeks (unpublished data). With ethinylestradiol administration [14] apo E decreased significantly.

Finally, the effect of ERT on lipid metabolism needs to be further investigated, but ERT may be useful in the management of postmenopausal women with hyperlipidemia, and also in the prevention of cardiovascular disease. ERT may improve the quality of life of postmenopausal women.

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