ORIGINAL

Differences in associations of follicle-stimulating hormone with lipid profiles according to oral and transdermal hormone replacement therapy in Japanese women during the menopausal transition

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Abstract : Background and aim : The associations between follicle-stimulating hormone (FSH) levels and lipid profiles have been controversial. The aim of this study was to examine the associations between FSH levels and lipid profiles before and during hormone replacement therapy (HRT) in Japanese women. Subjects and methods : We recruited 117 women who were receiving HRT and examined serum levels of FSH, LH, estradiol, triglycerides (TG), LDL-C and HDL-C. In addition, the associations of reduction rate of FSH and increase in estradiol level with changes in lipid parameters before and during HRT were examined. Results : FSH showed a significant negative correlation with TG and LDL-C and a significant positive correlation with LH and HDL-C. In women receiving oral estrogen, the rate of increase in HDL-C and TG was significantly greater in the group with a large decrease in FSH. In women receiving oral estrogen, LDL-C was significantly decreased and TG was significantly increased in the group with a large increase in estradiol. Conclusion : We demonstrated associations between FSH level and favorable lipid profiles in this study. During HRT, the action of reduction of FSH on lipid parameters did not exceed the direct action of estrogen. J. Med. Invest. 72 : 290-297, August, 2025

Keywords **:** *follicle-stimulating hormone, LDL-C, HDL-C, triglycerides, hormone replacement therapy*

INTRODUCTION

It has been demonstrated that postmenopausal women have higher levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) than those in premenopausal women (1, 2). Elevated plasma LDL-C has been found through a decrease in estrogen level in postmenopausal women and oophorectomized women (3). Plasma LDL-C level showed a significant negative correlation with plasma estradiol level (4). However, only estrogen deficiency cannot fully explain menopausal and postmenopausal dyslipidemia. It has been reported that unfavorable lipid profiles were found before estrogen levels decrease at the premenopausal stage (1, 5) and that some women can develop dyslipidemia despite using conventional doses of estrogen during HRT (6, 7).

Follicle-stimulating hormone (FSH) receptor is expressed in the liver (8), adipose tissue (9), osteoclasts (10) and renal juxtaglomerular cells (11) as well as in reproductive organs. Thus, FSH action beyond reproduction has been highlighted. Recently, it was reported that FSH was associated with the incidence of metabolic syndrome (12), risks of renal dysfunction (13) and rheumatoid arthritis (14), and pathogenesis of Alzheimer's disease in mice (15). It has been suggested that circulating FSH levels may be more highly associated than estrogen levels with bone loss in postmenopausal women (16). From the results of those previous studies, relationships between a high FSH level and occurrence of some diseases have been shown. The associations of FSH levels with adiposity and lipid metabolism have also been controversial. Although it has been reported that FSH was positively associated with HDL-C and was negatively associated with triglycerides (TG) (17, 18) and LDL-C (17), Song *et al*. reported that LDL-C was significantly higher in the higher FSH group (8). Serviente *et al*. reported that FSH showed a positive association with LDL-C (19). The reason for the different results regarding the associations between FSH and lipid profiles is not clear. To date, there has been no report in Japan.

On the other hand, among women who received HRT with a combination of estradiol valerate (1 mg) and dydrogesterone, postmenopausal women with a higher FSH level had higher serum levels of TC and LDL-C than those in women with a lower FSH level. In addition, women with a large decrease in FSH (decrease by ≧30%) had significantly improved serum levels of TC and LDL-C (8). The impact of lipid profiles in women with oral estrogen administration was greater than that in women with transdermal estrogen administration because of the presence of a first pass effect in the liver (20). The associations of FSH with lipid profiles may be different for oral administration and transdermal administration. To the best of our knowledge, there has been no report on associations of FSH with lipid profiles according to the administration route.

We previously reported that serum FSH level varied widely in Japanese postmenopausal women (21). The difference in FSH levels may be involved in metabolism in postmenopausal women in Japan. In addition, there have been few reports on the associations of luteinizing hormone (LH) with lipid parameters. The aim of this study was to determine the associations of levels of FSH and LH with lipid parameters in Japanese perimenopausal and postmenopausal women and the associations between changes in levels of FSH and LH and changes in lipid profiles

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before and during HRT with oral administration and transdermal administration.

MATERIALS AND METHODS

Subjects

One hundred and seventeen women (37 premenopausal women and 80 postmenopausal women) who underwent HRT for improvement of menopausal symptoms and who agreed to participate were included in this study. We did not include women who had undergone bilateral oophorectomy. The median age of the women was 50.0 (43.0-59.0) years and median body mass index (BMI) was 22.4 (18.1-26.1). Women with a history of any cardiovascular disease, hormone-dependent malignancy or breast cancer, venous thromboembolic disease, diabetes mellitus, renal dysfunction, liver disease, hypertension, and use of lipid-lowering drugs were excluded. As the HRT regimen, oral estrogen administration (conjugated equine estrogen : CEE and estradiol : E2) and transdermal estradiol administration were included. The proportion of women who received oral CEE was 67.1% and the proportion of women who received oral E2 was 32.9%.

Measurements

Fasting morning (9:00-12:00 h) blood samples were collected during the morning fasting period (9:00-12:00), centrifuged, and measured promptly. Serum levels of FSH and LH were examined before HRT and at 6 months and 1 year after the commencement of HRT. Serum levels of estradiol and lipids were examined before HRT and 1 year after the commencement of HRT. Lipids were analyzed by the cholesterol oxidase method for serum TC, by the enzymatic method using glycerol triphosphate oxidase for TG, and by the direct method for HDL-C levels using an automated chemical analyzer (Modular DPP ; Roche Diagnostics, Tokyo, Japan) with the use of Roche Diagnostics' Reagent kits for analysis. The intra-assay and inter-assay coefficients of variation were 0.40% and 0.80-1.00%, respectively, for TC, 0.50% and 0.80-0.90%, respectively, for HDL-C, and 0.30-0.60% and 1.60-1.70%, respectively, for TG. Estradiol was analyzed using an analyzer (cobas6000 ; Roche Diagnostics, Tokyo, Japan) with the electrochemiluminescence immunoassay. FSH and LH were analyzed by the chemiluminescent enzyme immunoassay (Alinity i system ; Abbott Japan, Tokyo, Japan). The intra-assay and inter-assay coefficients of variation were 1.18-2.82% and 1.42-2.04%, respectively, for estradiol, 1.31-2.00% and 2.19-2.39%, respectively, for FSH and 1.94-2.82% and 1.99-2.92%, respectively, for LH.

Statistical analysis

FSH and LH before and at 6 months and 1 year after the start of HRT were compared by using the Kruskal-Wallis rank test, and Bonferroni adjustment was used for a multiple comparison test. The relationships between gonadotropic hormones and circulating lipids were analyzed by using multivariate analysis. Spearman's rank correlation analysis was used for determining correlations of FSH and LH with lipid parameters. The rate of change in FSH during HRT was divided into two groups according to the median value, and changes in lipid parameters and basal lipid parameters, hormonal data, age and BMI were compared between the two groups by using the Mann–Whitney U test. SPSS version 20.0 for Windows was used for statistical analysis. $P<0.05$ was considered statistically significant.

Ethical consideration

This study was approved by the Tokushima University Hospital Research Ethics Committee for Life Sciences and Medicine (No. 4528), and permission for implementation was obtained from the respective institution's authorities. Informed consent was obtained from all participants in the study by checking the informed consent box in the questionnaire.

RESULTS

Associations of FSH and LH with lipid profiles in women before HRT

Multivariate analysis showed that FSH levels were not significantly associated with the confounding factors of lipids, age, and BMI, and LH levels were not significantly associated with lipids, age, or BMI. Therefore, we examined the correlation between gonadotropic hormones and lipid levels.

There were significant correlations between FSH and TG ($p<0.001$, $r=-0.312$) and between FSH and LDL-C ($p=0.049$, $r=-0.184$) but not between FSH and HDL-C (Figure 1A). There was a significant positive association between LH and HDL-C ($p=0.005$, $r=0.267$) (Figure 1B).

Levels of FSH and LH before HRT and at 6 months and 1 year after the commencement of HRT

Levels of FSH and LH before HRT and at 6 months and 1 year after the commencement of HRT are shown in Table 1. FSH level was decreased significantly ($p<0.001$) at 6 months and 1 year after the commencement of HRT. In both women with oral estrogen administration and women with transdermal estrogen administration, FSH levels were decreased significantly at 6 months and 1 year ($p<0.001$). There was no significant difference in the mean reduction rate of FSH between women with oral estrogen administration (-44.8%) and women with transdermal estrogen administration (-37.9%) ($p=0.162$). On the other hand, LH level was decreased significantly ($p=0.004$) at 1 year after the commencement of HRT. LH level in women with oral estrogen administration was decreased significantly at 1 year after the commencement of HRT ($p<0.001$), but there were no significant differences in LH levels in women with transdermal estrogen administration.

Associations of changes in FSH and LH with changes in lipid profiles before and during HRT

We used levels of FSH and LH at 1 year after the commencement of HRT and examined the associations of FSH and LH with lipid profiles. In women with oral estrogen administration, the mean rate of change in LDL-C was -7.0%, a decrease from 119.8 ± 29.0 (mean ± SD) mg/dl to 111.9 ± 29.9 mg/dl, the mean rate of change in TG was +2.4%, an increase from 96.6 ± 35.6 mg/dl to 99.0 ± 46.3 mg/dl, and the mean rate of change in HDL-C was +3.4%, an increase from 72.2 ± 26.9 mg/dl to 74.8 ± 17.5 mg/dl. In women with transdermal estrogen administration, the mean rate of change in LDL-C was -2.0%, a decrease from 138.2 ± 29.5 mg/dl to 135.5 ± 35.0 mg/dl, the mean rate of change in TG was -4.6%, a decrease from 104.9 ± 32.9 mg/dl to 100.2 ± 47.8 mg/dl, and the mean rate of change in HDL-C was +0.3%, an increase from 72.0 ± 39.8 mg/dl to 72.2 ± 17.8 mg/dl.

In addition, we divided the reduction rate of FSH by HRT into two groups according to the median reduction rate of FSH and compared various parameters in the two groups. As shown in Table 2, there was no significant difference in BMI. There was a significant difference between the two groups in the age of women with oral estrogen administration. There was no significant difference in baseline E2 levels between the two groups. However, estradiol levels during HRT in the group with a large reduction rate of FSH were significantly higher than those in

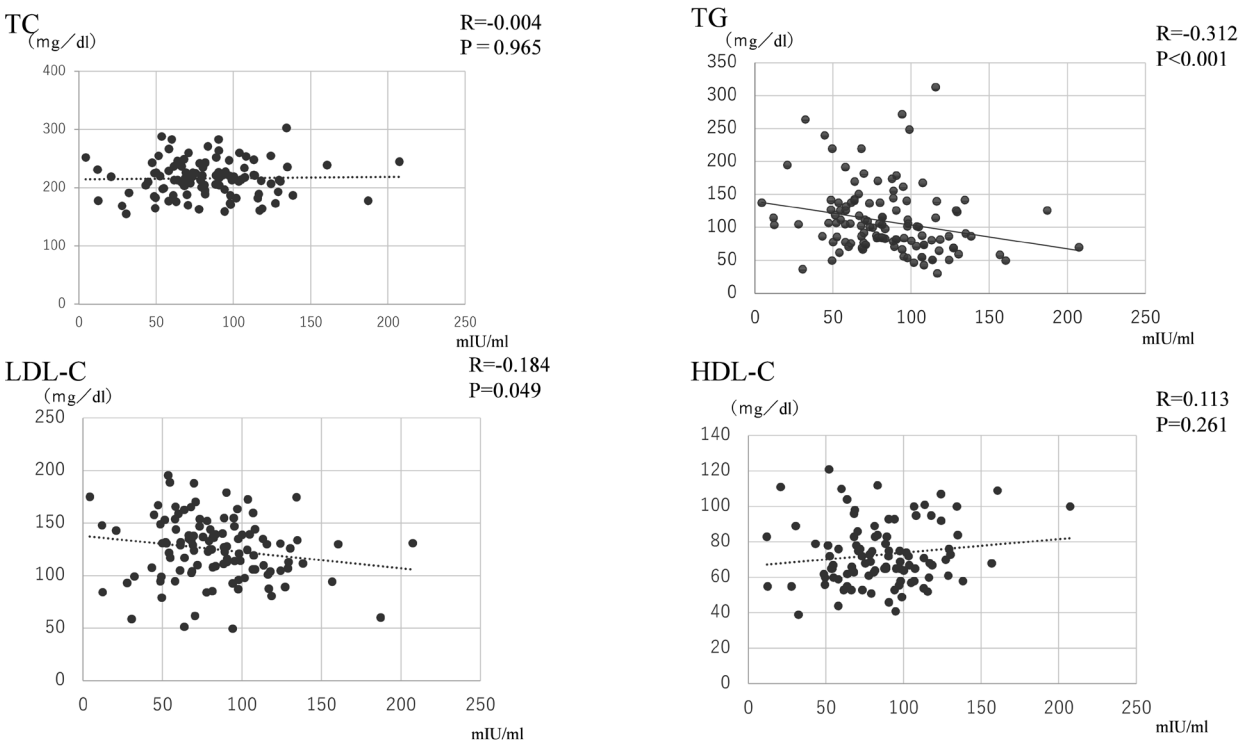

Figure 1A. Associations of FSH with lipid parameters before HRT.
The correlation between FSH and lipids before HRT administration was studied. Significant negative correlations were found in triglycerides and LDL cholesterol.

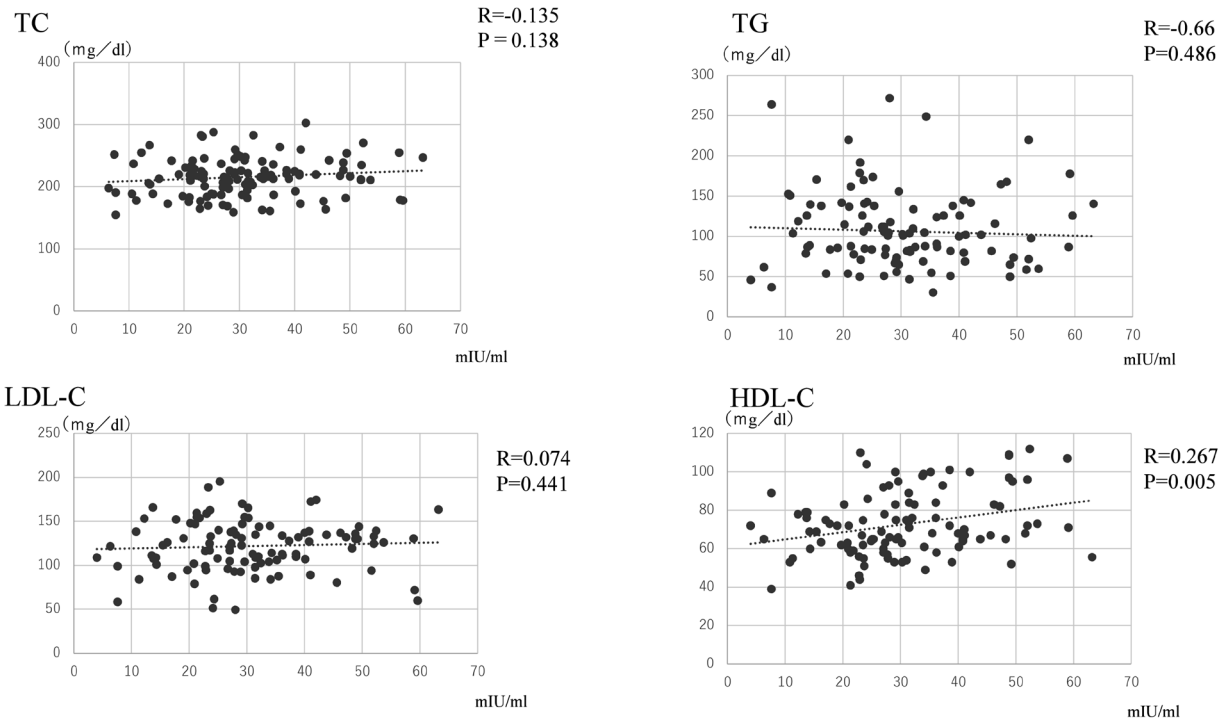

Figure 1B. Associations of LH with lipid parameters before HRT.
The correlation between LH and lipids before HRT administration was examined ; a significant positive correlation was found for HDL cholesterol.

Table 1. FSH and LH levels before and after commencement of HRT

FSH levels before and after commencement of HRT

mIU/ml	before	6 months	1 year
Total	88.5 (11.9-207.3)	49.0 (1.1-124.8) *	45.2 (1.3-197.5) *
Oral	88.4 (11.9-207.3)	48.4 (1.1-124.8) *	44.4 (1.3-197.5) *
Transdermal	87.7 (13.9-187.5)	52.6 (1.1-85.3) *	48.2 (16.5-83.1) *

LH levels before and after commencement of HRT

mIU/ml	before	6 months	1 year
Total	29.2 (4.0-64.3)	20.9 (0.5-51.2)	19.5 (0.5-58.3) *
Oral	29.2 (6.3-64.3)	22.0 (5.5-51.2)	19.2 (0.5-58.3) *
Transdermal	30.9 (4.0-59.1)	20.6 (0.5-28.5)	19.8 (4.4-50.8)

HRT was divided into overall, oral estrogen, and transdermal estrogen groups, and changes in FSH and LH over time were checked before HRT, 6 months after HRT, and 1 year after HRT. Values are indicated as medians (10-90 %tiles).
* P<0.001

Table 2. Baseline levels of lipid parameters and hormonal levels, and estradiol level during HRT

Oral estrogen administration

	Change in reduction rate of FSH		P value
	>48.26% (n=37)	≦48.26% (n=39)	
Baseline LDL (mg/dl)	121.8 (89.2-164.8)	107.6 (81.0-147.7)	0.144
Baseline HDL (mg/dl)	65.0 (52.0-75.0)	69.0 (54.0-94.0)	0.065
Baseline TG (mg/dl)	84.0 (52.2-157.6)	100.0 (66.0-194.0)	0.4
Baseline TC (mg/dl)	218.0 (159.0-260.0)	210.0 (155.0-283.0)	0.491
Baseline FSH (mIU/ml)	90.6 (56.4-127.1)	75.4 (41.0-117.0)	0.187
Baseline E2 (pg/ml)	3.8 (2.0-13.8)	2.4 (2.0-22.3)	0.413
E2 during HRT (pg/ml)	34.4 (15.0-64.0)	17.0 (5.1-42.1)	<0.001
Age (years)	50.0 (41.0-52.0)	48.0 (37-53)	0.032
BMI	21.2 (20.3-26.7)	22.0 (18.9-25.1)	0.895

Transdermal estrogen administration

	Change in reduction rate of FSH		P value
	>46.94% (n=20)	≦46.94% (n=21)	
Baseline LDL (mg/dl)	134.0 (105.0-167.0)	133.8 (60.0-174.2)	0.917
Baseline HDL (mg/dl)	69.0 (44.1-96.4)	75.2 (55.8-109.0)	0.738
Baseline TG (mg/dl)	101.0 (71.7-199.5)	107.0 (74.0-170.0)	0.602
BaselineTC (mg/dl)	231.0 (187.0-283.0)	219.0 (176.0-254.0)	0.076
Baseline FSH (mIU/ml)	82.5 (48.3-134.4)	66.6 (47.2-97.6)	0.042
Baseline E2 (pg/ml)	10.6 (5.0-35.9)	7.5 (5.0-83.5)	0.078
E2 during HRT (pg/ml)	79.0 (44.0-129.0)	44.0 (13.1-108.3)	0.005
Age (years)	49.0 (37.2-52.4)	48.0 (43.1-54.8)	0.559
BMI	19.1 (18.1-25.1)	20.6 (16.5-25.2)	0.935

In the oral estrogen and transdermal estrogen groups of HRT, we divided the decrease in FSH into two groups and examined whether there was a difference in lipid values when the decrease in FSH was greater or less. We also examined whether there was a difference in estradiol levels.

the group with a small reduction rate of FSH in both women with oral estrogen administration and women with transdermal estrogen administration. There were no significant diffences in baseline levels of LDL-C, HDL-C, or TG in the two groups.

As shown in Figure 2, in women with oral estrogen administration, the rate of increase in HDL-C in the group with a large reduction rate of FSH was significantly higher than that in the group with a small reduction rate of FSH (p=0.021). In addition, the rate of increase in TG in the group with a large reduction rate of FSH was significantly higher than that in the group with a small reduction rate of FSH (p=0.001). The rate of decrease in LDL-C in the group with a large reduction rate of FSH was larger than that in the group with a small reduction rate of FSH, but the difference was not significant (p=0.054). In women with transdermal estrogen administration, there were no significant differences in the rates of changes in LDL-C, HDL-C and TG between the two groups.

With regard to the associations of estradiol level during HRT with lipid parameters, we divided the changes in lipid parameters into two groups according to the median estradiol level during HRT (Figure 3). In women with oral estrogen administration, the group with a large increase in estradiol showed a significant decrease in LDL-C (p<0.001) and a significant increase in TG (p=0.003) compared to those in the group with a

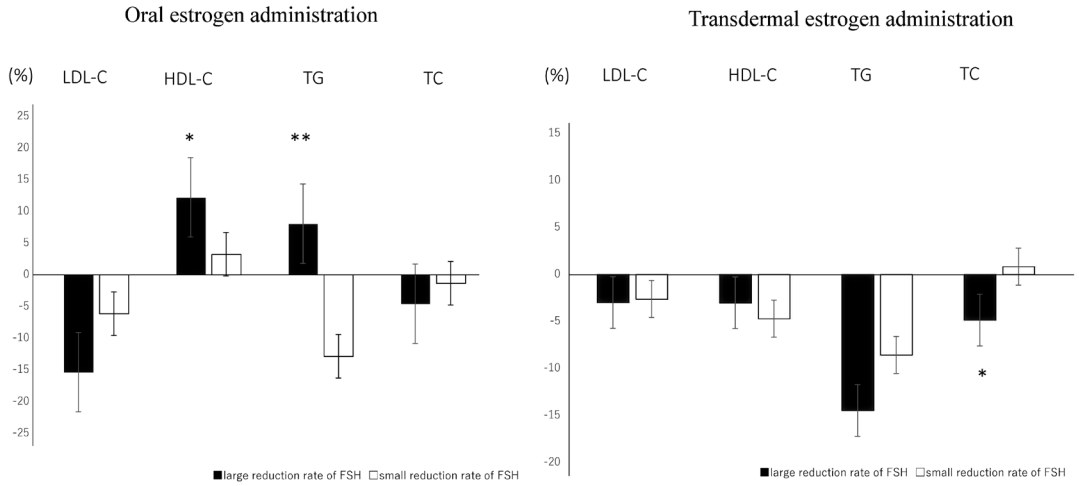

Figure 2. Changes in lipid parameters according to change in FSH during HRT.
In the oral estrogen and transdermal estrogen groups, the decrease in FSH was divided into two groups, large and small, to determine if there was a difference in lipid values between the two groups. The decrease in FSH was divided into large and small groups based on median values, and the percent change in lipids was expressed as a percentage. Closed bar : large change in FSH, Open bar : small change in FSH. *P<0.05 ** P<0.001

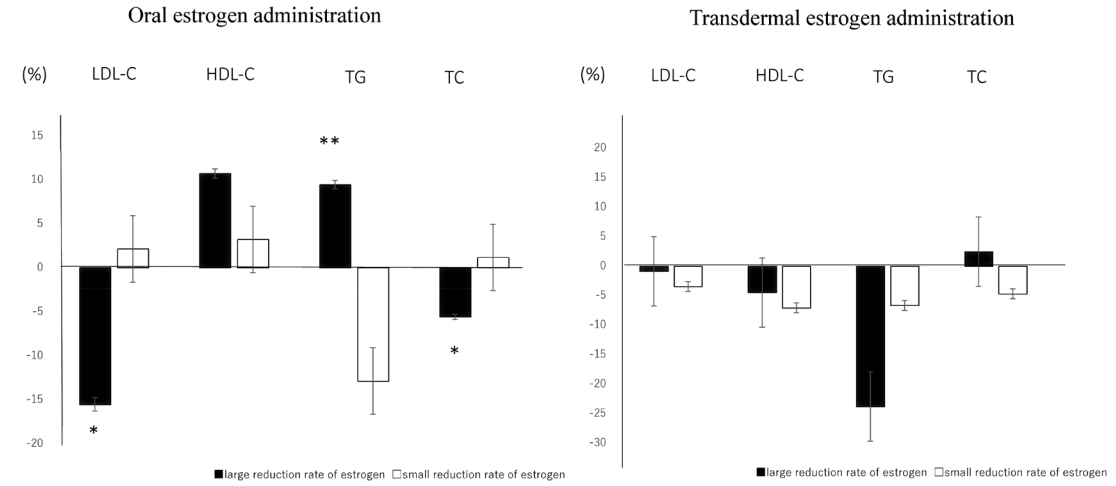

Figure 3. Changes in lipid parameters according to estradiol level during HRT.
In the oral estrogen and transdermal estrogen groups, the rate of increase in estradiol was divided into two groups, large and small, to determine if there was a difference in lipid values between the two groups. The median rate of increase in estradiol was used to divide the patients into large and small groups, and the percentage change in lipids was expressed as a percentage. Closed bar : large increase in estradiol, Open bar : small increase in estradiol. *P<0.05 ** P<0.001

small increase in estradiol. In women with transdermal estrogen administration, there were no significant differences in the rates of changes in lipid parameters between the two groups.

Similarly, we divided the rate of change in LH into two groups according to the median rate of change in LH and compared the lipid profiles. There were no significant changes in lipid profiles between the groups oral and transdermal estrogen administration (data not shown).

DISCUSSION

In Japanese women during the menopausal transition, we showed that a high FSH level was associated with low levels of LDL-C and TG. In addition, we showed that increases in HDL-C and TG were large in the group with a large reduction rate of FSH for women who received oral estrogen administration.

Xu *et al*. reported that FSH level was negatively associated with TG and LDL-C (18). Wang *et al*. also reported that there was a negative association between FSH and TG (17). Negative associations of FSH level with LDL-C level and TG level shown in our study were similar to the results of those previous studies. On the other hand, a positive association between FSH and LDL-C has also been reported (8, 19). Although the reason for the inconsistent results regarding associations between FSH levels and circulating lipid profiles in postmenopausal women is not clear, age and race of the subjects may be related.

On the other hand, during HRT with oral estradiol valerate, women with a large decrease in FSH (decrease by ≧30%) had significantly improved serum levels of TC and LDL-C (8). In the present study, we also showed that there was a significant increase in HDL-C and a tendency for a decrease in LDL-C in the group with a large reduction rate of FSH for women with oral estrogen administration. In addition, a significant increase in TG was found in the group with a large reduction rate of FSH. Wakatsuki *et al*. reported that the conventional dose of CEE (0.625 mg/day) significantly increased plasma TG but that a low dose of CEE (0.3125 mg) did not affect plasma TG (22). We also demonstrated that the effects on lipid parameters were weak in women with a low estrogen level in the present study (Figure 3). Considering the results shown in Figure 2 and Figure 3, changes in lipid parameters according to the reduction rate of FSH are similar to changes in lipid parameters according to the increase in E2 level. The effects on lipid profiles during HRT may basically reflect the action of oral E2 on lipid parameters. In women with transdermal estrogen administration, we showed that the effects of estrogen on lipid profiles were weak since there was no hepatic first-pass effect.

In the present study, a significant increase in HDL-C was found in the group with a large reduction rate of FSH, although the increase in HDL-C in the group with a large increase in E2 was not significant in women with oral administration. The action of FSH together the action of estrogen may be involved in the increase in HDL-C during HRT. El Khoudary *et al*. reported that associations of higher FSH with greater total HDL-P and smaller HDL size were only evident at/after menopause, suggesting that FSH is related to HDL subclasses, lipid content and function of HDL-C in midlife women (23).

There was no significant difference in the reduction rates of FSH (44.9% in the oral group and 37.9% in the transdermal group, p=0.162), although the increases in estradiol level were different (17-34 pg/ml in the oral group and 44-79 pg/ml in the transdermal group). We previously reported that mean estradiol level in women with CEE (0.625 mg) administration was 21.3 pg/ml (22). It has been reported that estradiol level in women with transdermal administration of estrogen ranged from 40 to 60 pg/ml (24, 25). In the female reproductive system, it has been suggested that a low circulating estrogen level fine-tunes GnRH pulses via the negative feedback action of estrogen and that a high circulating estrogen level induces a GnRH/LH surge via the positive feedback mechanism (26). A large increase in the estradiol level may be associated with a large reduction of FSH in both women with oral estrogen administration and women with transdermal estrogen administration.

Oral CEE stimulates the synthesis of LDL-C receptors and also contributes to the reduction of plasma LDL-C synthesis (27, 28). Elevated FSH levels may increase serum LDL-C levels by inhibiting the expression of LDL receptors in liver tissue (8). In the present study, unfortunately, there was no significant difference in the association between decrease in FSH and decrease in LDL-C, but the reduction of LDL-C (-15.4%) in women with a large decrease in FSH tended to be larger than that (-6.1%) in women with a small decrease in FSH (p=0.054).

The results regarding associations of FSH levels with lipid profiles in our cross-sectional study and our study during HRT were different. Although a high FSH level was associated with favorable changes in lipid parameters such as decreases in LDL-C and TG in the cross-sectional study, a large reduction of FSH during HRT was associated with a decrease in LDL-C. The different study designs may be involved in the contradictory results. Basically, there is a difference in the time course between our two studies. During the menopause transition, estradiol levels eventually decline significantly and remain low, whereas FSH levels increase and remain high. The timing and magnitude of increase in FSH varies among individuals. Tepper *et al*. found low-, medium- and high-rising trajectories of FSH over the menopausal transition, suggesting that these different trajectories were strongly related to BMI and ethnicity (29). Lee *et al*. suggested that FSH has stimulatory effects on lipid synthesis and that FSH production may be inhibited by excessive body fat via an unknown mechanism (12). Although associations between reduction of FSH and changes in lipid profiles were found during HRT, the action of FSH is not superior to the action of estrogen on lipid profiles except for HDL-C.

In the present study, a significant positive correlation between LH level and HDL-C was found in women before HRT treatment. However, there were no significant changes in lipid profiles according to change in LH during HRT. To date, associations between LH level and lipid profiles have not been reported. Although both LH and FSH are gonadotrophins, the associations of LH and FSH with reproductive hormones were shown to be different depending on the stage of menopausal transition (30). We showed the time difference in hormonal changes in which FSH reached a plateau later than LH. The associations between FSH levels and lipid profiles may be formed during the menopausal transition.

This study has several limitations. The number of subjects was relatively small. The number of subjects in the transdermal HRT group was particularly small. For HRT, we used progestogen with estrogen in women with a uterus. It has been shown that a progestin such as medroxyprogesterone acetate affects lipid profiles (31). Therefore, the associations between change in FSH and changes in lipid profiles in an estrogen alone group and an estrogen and progestogen group may need to be compared. Also, women with oral CEE and women with oral estradiol were mixed in the same oral group since we focused on the difference between oral administration and transdermal administration. As we did not investigate lifestyle such as diet and exercise habits in peri- and postmenopausal women, the effects of confounding factors such as diet and exercise on associations of FSH and lipids are not clarified.

In conclusion, we demonstrated associations between FSH

level and favorable lipid profiles in a cross-sectional study in Japanese women. During HRT, the action of reduction of FSH on lipid parameters did not exceed the direct action of estrogen.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

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