

PAPER

Effects of hormone replacement therapy on weight, abdominal fat distribution, and lipid levels in Japanese postmenopausal women

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OBJECTIVE: To investigate the effects of hormone replacement therapy (HRT) on weight, abdominal fat distribution, and fasting lipid levels in Japanese postmenopausal women (PMW).

DESIGN: Prospective, 12-month-controlled clinical comparison of women with and without HRT.

SUBJECTS: In all, 35 PMW with HRT (conjugated estrogens, 0.625 mg daily; medroxyprogesterone acetate, 2.5 mg daily; HRT group) and 26 PMW without HRT (control group).

MEASUREMENTS: Weight, abdominal fat distribution by computed tomographic measurements, lipid profiles, and sex hormones were determined at baseline and after 12 months of treatment or observation.

RESULTS: Weight did not change in any group. Visceral abdominal fat increased in controls, but not in the HRT group. Total and low-density lipoprotein cholesterol decreased, and triglyceride (TG) and high-density lipoprotein cholesterol increased in the HRT group; these did not change in the control group. When we divided women into those with android and gynoid types of abdominal fat distribution. Subjects with an android distribution showed reduced visceral fat with HRT, which also decreased the proportion of patients maintaining an android distribution. HRT did not alter abdominal fat distribution in subjects with a gynoid distribution. HRT increased serum TG in the android and the gynoid subgroups.

CONCLUSION: Improved distribution of abdominal fat and fasting lipid levels except for TG may represent beneficial effects of HRT with respect to cardiovascular disease, but caution is warranted concerning TG elevation from HRT performed in PMW. *International Journal of Obesity* (2003) 27, 1044–1051. doi:10.1038/sj.ijo.0802371

Keywords: hormone replacement therapy; estrogen; abdominal fat distribution; menopause; lipid levels

Introduction

Menopause is associated with gains in weight^{1–3} and body fat.⁴ Postmenopausal women (PMW) generally gain weight and develop a fat distribution similar to that in men (android or central) as opposed to that in premenopausal women (gynoid or peripheral).^{1–4} These changes have been attributed to diminished estrogen secretion.^{5,6}

Many menopausal women believe that hormone replacement therapy (HRT) causes weight gain,⁷ but whether this impression is correct remains uncertain. In fact, many clinical studies indicated that HRT prevented or reduced weight gain^{8–18} and body fat gain,^{8–15,18,19} although other investigators found the opposite both for weight^{20,21} and body fat.^{20,21} Thus, the effect of HRT concerning weight and body fat remains controversial.

In most of the above studies dual-energy X-ray absorptiometry (DEXA) or waist-to-hip ratio (WHR) was used as a measure of central body fat. Unfortunately, these methods do not differentiate between intra- and extra-abdominal fat compartments. In recent years, more specific methods have been applied to measurement of abdominal fat

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compartments, including computed tomography (CT) and magnetic resonance imaging (MRI).^{22–24} Only two CT-based reports found visceral fat to be lower in HRT patients than in untreated PMW.^{10,11} However, the CT studies merely compared HRT users with nonusers, with none being longitudinal.

Lipid profiles undergo changes in menopause. Specifically, total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) both increase, while high-density lipoprotein cholesterol (HDL-C) decreases.^{25,26} HRT has been reported to counteract these changes in lipid levels; HRT increases HDL-C and TG and decreases TC and LDL-C in PMW.^{15,27–29} Excess visceral adipose tissue accumulation (android fat distribution) is also associated with alterations in the lipoprotein lipid profile, including elevated TG as well as decreased HDL-C.^{30,31} Thus, HRT might be expected to alter abdominal fat distribution in addition to lipid levels. However, no study has described the effect of HRT on abdominal fat distribution in PMW together with effects on lipid levels.

We investigated the influence of 12 months of HRT on weight and on abdominal fat composition according to CT in Japanese PMW. In addition, since visceral fat deposition is a risk factor for cardiovascular disease, stroke, and type II diabetes mellitus,^{6,32} we studied the effect of HRT on the relation between type of abdominal fat distribution and fasting lipid levels.

Methods

Subjects

In 1997–2000, 75 women, consulting an outpatient for management of clinic menopause at the Cardiovascular Hospital of Central Japan, were asked to participate. Eligibility was determined by a health history questionnaire, a physical examination including gynecologic examination, and endocrine blood tests. The questionnaire contained items concerning medical status and menopausal status. Inclusion in the study required natural occurrence of menopause 1–10 y previously, elevated serum gonadotropins (follicle-stimulating hormone or FSH; >40 mIU/ml) and decreased estradiol or E2; <20 pg/ml), and no concurrent illness. No patient had received HRT before enrollment or had any contraindication to such treatment. All subjects were nonsmokers. We excluded three perimenopausal women and 11 women who did not complete the 12-month trial from the study. Informed consent was obtained from each participant according to the Second Helsinki Declaration, and the study was approved by the Ethics Committee of the Cardiovascular Hospital of Central Japan.

The 61 Japanese PMW who were enrolled (46–61 y old, mean \pm s.d., 53.3 \pm 4.3) were assigned according to preference to an HRT group ($n = 35$) to be given HRT for 12 months, and a control group ($n = 26$) consisting of those who did not wish to receive HRT. All subjects enrolled in the study were

counseled not to change their usual diet or lifestyle habits. One subject in HRT group and one in control group had received lipid medications for at least 2 y before the study. However, these medications were not changed during the study.

Study design

Except for control subjects, each subject received a daily dose of oral HRT (0.625 mg of conjugated equine estrogen combined with 2.5 mg of medroxyprogesterone acetate) for 12 months. All subjects attended to the HRT clinic of the Cardiovascular Hospital of Central Japan once monthly for physical check-ups; at baseline and again at 12 months after HRT initiation, blood sampling and CT were performed.

Blood samples were collected and anthropometric measurements and CT were obtained in the morning after a 12 h fast. Samples were centrifuged and stored at -80°C until assays.

Physical examination

Anthropometric characteristics then were measured, including weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm). The body mass index (BMI) was calculated (weight in kilograms divided by height in meters squared).

Assays

Serum TC and TG concentrations were determined using enzymatic methods (Medca Japan, Konosu, Japan) with an automatic analyzer (Boehringer Mannheim, Germany). Serum concentrations of HDL-C were determined electrophoretically using the HDL Cholesterol Supply Kit (Helena Laboratory, Beaumont, TX, USA). The concentration of LDL-C was calculated according to the Friedewald formula.³³ Serum concentrations of FSH and E2 were analyzed by radioimmunoassay using commercially available kits (Boehringer Mannheim, Germany).

Computed tomography

Visceral abdominal fat (VAF) and subcutaneous abdominal fat (SAF) were measured by CT using a GE High-speed FX scanner (General Electric Yokogawa Medical Systems, Hino, Tokyo, Japan). Subjects were examined in the supine position with both arms extended above their heads. A position for abdominal scanning was established at the L4 to L5 level using a scout image of the body. Adipose tissue, defined as an attenuation range of -150 to -50 Hounsfield units was highlighted for computation of areas of interest. VAF area was quantified after outlining the intra-abdominal cavity at the most internal aspect of the abdominal and oblique muscle walls surrounding the peritoneal cavity and the posterior aspect of the vertebral body. SAF area was quantified by highlighting adipose tissue located between

the skin and the most external aspect of the abdominal muscle wall. The coefficient of variation for repeated analysis of scans of 10 subjects was 1–2%. The ratio between SAF and VAF (S:V ratio) was calculated for each CT and taken to be an indicator of predominantly subcutaneous or visceral fat accumulation.³⁴

Statistical analyses

Data are reported as means \pm s.d. Student's unpaired *t*-test was used to analyze differences in baseline parameters between the HRT group and the control group. The following equations were used: percent change = (value at 12 months – basal value)/basal value \times 100 (%) for S:V ratio of abdominal fat; and difference (delta) between 12-month value and baseline = value at 12 months for the characteristic – the basal value. Student's paired *t*-test was used to analyze differences between values recorded at baseline and again at 12 months. All probability values are two-tailed. A value of $P < 0.05$ was accepted as indicating statistical significance.

Results

Patient characteristics and changes in these variables over the treatment/observation period are shown in Table 1. No significant differences in age were noted between the HRT group and the control group, and baseline weight, BMI, TAF, SAF, VAF, S:V ratio, TC, TG, HDL-C, LDL-C, FSH, and E2 did not differ significantly between the HRT group and the control group. After 12 months of HRT, TC, LDL-C, and FSH had decreased significantly ($P < 0.01$ for all). TG, HDL-C, and E2 had increased significantly ($P < 0.01$ for all). Weight, BMI, TAF, SAF, VAF, and S:V ratio did not change from baseline in the HRT group. In addition, after 12 months of HRT, TAF

and VAF had increased significantly ($P < 0.05$ for both). Weight, BMI, SAF, S:V ratio, TC, TG, HDL-C, LDL-C, FSH, and E2 did not change during the year of observation in the control group. In the control group, TAF had increased significantly ($P < 0.05$). Increased serum concentrations of E2 and decreased FSH following treatment in the HRT group confirmed patient compliance with the regimen.

Declines at 12 months from baseline for VAF, LDL-C, and FSH were significantly greater in the HRT group than in the control group ($P < 0.05$ for all). Increases in TG, HDL-C, and E2 between baseline and 12 months were significantly greater in the HRT group than in the control group ($P < 0.05$ for all; Table 1). No significant differences were noted for percent change in the S:V ratio between the HRT group and the control group (Figure 1).

To determine whether android or gynoid fat distribution at baseline importantly influenced effects of HRT on abdominal fat distribution, subjects were divided into two groups according to the S:V ratio for abdominal fat. Women with an S:V ratio below 1.99 were assigned to the android abdominal fat group, while those with an S:V ratio above 1.99 were assigned to the gynoid abdominal fat group. The cutoff point represented the mean S:V ratio for all subjects in the study. Finally, subjects were divided into four groups: android-HRT ($n = 19$), android-control ($n = 16$), gynoid-HRT ($n = 16$), and gynoid-control ($n = 10$).

Clinical features and their changes over the course of the study are presented in Table 2 for HRT and control subjects with android and gynoid abdominal fat distributions. No significant differences in age were noted between the HRT group and the control group with android and gynoid abdominal fat distribution. At baseline, no significant

Table 1 Characteristics of HRT and control subjects, including changes over 1 y of treatment/observation

	HRT group (n = 35)			Control group (n = 26)		
	Baseline	12 months	Delta	Baseline	12 months	Delta
Age (y)	53.7 \pm 3.7			52.7 \pm 5.0		
Weight (kg)	56.5 \pm 7.7	56.7 \pm 7.6	0.2 \pm 2.3	55.7 \pm 10.0	56.1 \pm 9.1	0.4 \pm 2.4
BMI (kg/m ²)	23.9 \pm 3.0	24.0 \pm 3.0	0.1 \pm 0.9	23.9 \pm 3.8	24.1 \pm 3.6	0.2 \pm 1.0
TAF (cm ²)	311.5 \pm 98.9	313.1 \pm 104.7	1.6 \pm 41.4	302.9 \pm 126.2	322.2 \pm 125.3*	19.3 \pm 40.5
SAF (cm ²)	202.1 \pm 71.0	204.8 \pm 69.9	2.7 \pm 30.0	197.6 \pm 82.3	206.0 \pm 77.5	8.4 \pm 30.1
VAF (cm ²)	109.4 \pm 40.4	108.3 \pm 42.3	-1.1 \pm 21.9#	105.3 \pm 49.5	116.3 \pm 55.5*	10.9 \pm 21.0
S:V ratio	1.96 \pm 0.63	2.01 \pm 0.53	0.05 \pm 0.43	2.02 \pm 0.67	1.95 \pm 0.64	-0.07 \pm 0.44
TC (mg/dl)	192.2 \pm 30.6	180.5 \pm 27.0**	-11.7 \pm 19.2	197.6 \pm 33.5	196.0 \pm 21.7	-1.5 \pm 25.7
TG (mg/dl)	107.4 \pm 54.3	135.3 \pm 67.5**	27.9 \pm 43.3#	116.1 \pm 66.1	124.0 \pm 63.0	7.8 \pm 29.1
HDL-C (mg/dl)	51.1 \pm 13.9	58.3 \pm 13.9**	7.2 \pm 9.3#	49.2 \pm 9.5	49.3 \pm 11.0	0.1 \pm 9.4
LDL-C (mg/dl)	119.7 \pm 29.2	95.2 \pm 26.6**	-24.5 \pm 22.8#	125.2 \pm 30.8	121.9 \pm 28.0	-3.2 \pm 26.1
FSH (mIU/ml)	72.4 \pm 29.4	24.6 \pm 13.0**	-47.8 \pm 25.4#	72.5 \pm 19.9	71.3 \pm 20.8	-1.2 \pm 10.7
E2 (pg/ml)	12.2 \pm 5.0	82.1 \pm 23.3**	69.9 \pm 22.5#	12.6 \pm 4.7	12.8 \pm 7.1	0.2 \pm 7.6

HRT = hormone replacement therapy; BMI = body mass index; TAF = total abdominal fat; SAF = subcutaneous abdominal fat; VAF = visceral abdominal fat; S:V = subcutaneous abdominal fat:visceral abdominal fat; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; FSH = follicle-stimulating hormone; E2 = estradiol. Values are presented as means \pm s.d. Differences (delta) between 12-month values and baseline = value at 12 months – value at baseline. * $P < 0.05$, ** $P < 0.01$ compared with baseline. # $P < 0.05$ compared with delta of control group.

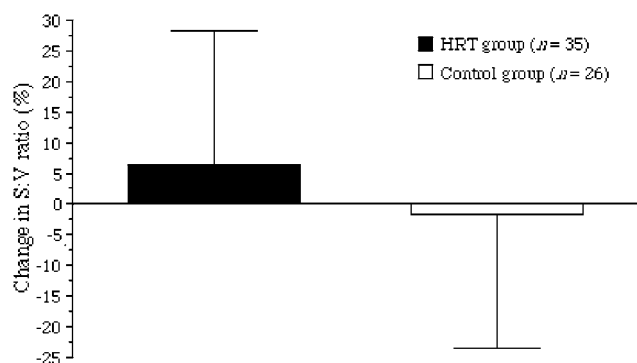


Figure 1 Percent changes in subcutaneous-to-visceral (S:V) ratios for abdominal fat in PMW who received HRT, and in PMW who did not receive HRT (control group), during 1 y of treatment/observation. Closed and open columns indicate percent changes in the S:V ratio for abdominal fat in the HRT group and the control group, respectively. Data are expressed as means \pm s.d.

differences in weight, BMI, TAF, SAF, VAF, S:V ratio, TC, TG, HDL-C, LDL-C, FSH, and E2 were noted between the android-HRT group and the android-control group or between the gynoid-HRT group and the gynoid-control group. In the android-HRT group, TC, LDL-C, and FSH declined significantly ($P < 0.01$ for all) with treatment. SAF, S:V ratio, TG, HDL-C, and E2 increased significantly ($P < 0.05$, $P < 0.01$, $P < 0.05$, $P < 0.05$, and $P < 0.01$, respectively). Weight, BMI, TAF, and VAF were not altered. In the android-control group, VAF had increased significantly ($P < 0.05$) after 12 months of HRT, but weight, BMI, TAF, SAF, S:V ratio, TC, TG, HDL-C, LDL-C, FSH, and E2 were not altered. In addition, in the gynoid-HRT group, LDL-C and FSH decreased significantly ($P < 0.01$ for both). TG, HDL-C, and E2 increased significantly ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively). HRT did not change weight, BMI, TAF, SAF, VAF, S:V ratio, or TC. In the gynoid-control group,

Table 2 Characteristics in HRT and control subjects with android and gynoid abdominal fat distribution, including changes over 1 y

	Android-HRT group (n = 19)			Android-control group (n = 16)		
	Baseline	12 months	Delta	Baseline	12 months	Delta
Age (y)	54.4 \pm 3.2			53.1 \pm 3.6		
Weight (kg)	55.8 \pm 6.9	56.3 \pm 6.7	0.5 \pm 1.9	56.3 \pm 10.5	57.0 \pm 10.2	0.7 \pm 2.1
BMI (kg/m ²)	24.0 \pm 3.0	24.2 \pm 2.9	0.2 \pm 0.8	24.4 \pm 4.1	24.7 \pm 4.2	0.3 \pm 0.9
TAF (cm ²)	305.6 \pm 93.5	315.5 \pm 97.1	9.9 \pm 37.1	317.6 \pm 138.2	340.4 \pm 140.4	22.8 \pm 43.1
SAF (cm ²)	180.7 \pm 55.4	195.7 \pm 58.1*	14.9 \pm 22.7	196.7 \pm 91.2	205.2 \pm 85.5	8.5 \pm 27.2
VAF (cm ²)	124.9 \pm 41.7	119.8 \pm 43.7	-5.1 \pm 22.6#	120.9 \pm 50.7	135.3 \pm 58.1*	14.3 \pm 21.2
S:V ratio	1.49 \pm 0.25	1.73 \pm 0.41**	0.24 \pm 0.31#	1.63 \pm 0.30	1.57 \pm 0.31	-0.06 \pm 0.27
TC (mg/dl)	192.8 \pm 20.9	178.8 \pm 18.8**	-13.9 \pm 15.7	205.4 \pm 35.7	196.2 \pm 24.7	-9.2 \pm 27.5
TG (mg/dl)	118.2 \pm 65.0	144.0 \pm 85.0*	25.8 \pm 45.1	124.2 \pm 71.9	124.9 \pm 64.7	0.7 \pm 24.9
HDL-C (mg/dl)	50.1 \pm 15.2	55.5 \pm 14.4*	5.4 \pm 9.7	48.5 \pm 10.2	49.2 \pm 10.5	0.8 \pm 8.5
LDL-C (mg/dl)	119.1 \pm 22.8	94.6 \pm 22.5**	-24.5 \pm 19.8	132.1 \pm 32.3	122.0 \pm 29.8	-10.1 \pm 28.2
FSH (mIU/ml)	69.1 \pm 35.0	22.0 \pm 13.1**	-47.2 \pm 25.4#	68.2 \pm 12.6	66.4 \pm 13.4	-1.9 \pm 12.1
E2 (pg/ml)	12.4 \pm 5.7	88.8 \pm 24.7**	76.3 \pm 24.2#	12.3 \pm 4.4	11.5 \pm 3.1	-0.9 \pm 2.1
Gynoid-HRT group (n = 16)						
	Baseline	12 months	Delta	Baseline	12 months	Delta
Age (y)	53.0 \pm 4.2			52.1 \pm 6.9		
Weight (kg)	57.3 \pm 8.8	57.2 \pm 8.7	-0.1 \pm 2.7	54.8 \pm 9.5	54.6 \pm 7.3	-0.2 \pm 2.9
BMI (kg/m ²)	23.7 \pm 3.0	23.7 \pm 3.2	0.0 \pm 1.1	23.0 \pm 3.1	23.0 \pm 2.4	0.0 \pm 1.2
TAF (cm ²)	318.4 \pm 107.7	310.2 \pm 116.4	-8.2 \pm 45.2	279.4 \pm 106.7	293.1 \pm 96.0	13.8 \pm 37.6
SAF (cm ²)	227.4 \pm 80.6	215.6 \pm 82.4	-11.8 \pm 31.7	199.0 \pm 70.3	207.2 \pm 67.2	8.3 \pm 35.8
VAF (cm ²)	91.0 \pm 30.8	94.6 \pm 37.4	3.6 \pm 20.7	80.4 \pm 37.6	85.9 \pm 35.2	5.5 \pm 20.7
S:V ratio	2.52 \pm 0.45	2.35 \pm 0.46	-0.17 \pm 0.46	2.65 \pm 0.62	2.56 \pm 0.55	-0.10 \pm 0.65
TC (mg/dl)	191.6 \pm 40.0	182.6 \pm 34.9	-9.0 \pm 22.9#	185.1 \pm 26.5	195.8 \pm 17.1	10.7 \pm 17.5
TG (mg/dl)	94.6 \pm 36.0	124.9 \pm 37.8*	30.3 \pm 42.4	103.2 \pm 56.8	122.5 \pm 63.7	19.3 \pm 33.0
HDL-C (mg/dl)	52.2 \pm 12.6	61.6 \pm 13.0**	9.4 \pm 8.6#	50.4 \pm 8.7	49.5 \pm 12.2	-0.9 \pm 11.1
LDL-C (mg/dl)	120.4 \pm 36.2	96.0 \pm 31.6**	-24.4 \pm 26.7#	114.1 \pm 26.0	121.8 \pm 26.3	7.7 \pm 18.7
FSH (mIU/ml)	76.3 \pm 21.6	27.7 \pm 12.5**	-48.6 \pm 25.1#	79.3 \pm 27.5	79.2 \pm 28.1	-0.2 \pm 8.7
E2 (pg/ml)	11.8 \pm 4.1	74.2 \pm 19.4**	62.4 \pm 18.2#	12.9 \pm 5.3	14.9 \pm 10.8	2.0 \pm 12.1

HRT = hormone replacement therapy; BMI = body mass index; TAF = total abdominal fat; SAF = subcutaneous abdominal fat; VAF = visceral abdominal fat; S:V = subcutaneous abdominal fat: visceral abdominal fat; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; FSH = follicle-stimulating hormone; E2 = estradiol. Values are presented as means \pm s.d. Differences (delta) between 12-month values and baseline = value at 12 months - value at baseline. * $P < 0.05$, ** $P < 0.01$ compared with baseline. # $P < 0.05$ compared with delta in control group.

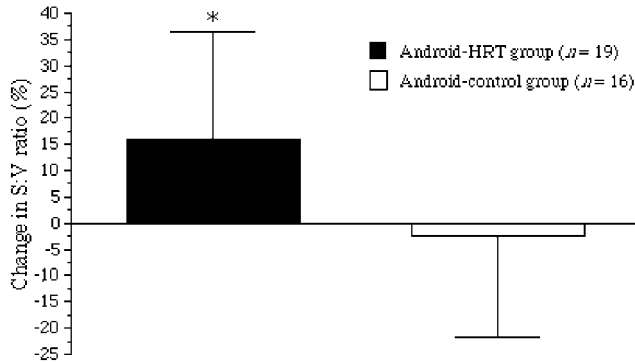


Figure 2 Percent change in subcutaneous-to-visceral (S:V) ratio of abdominal fat in HRT and control subjects with an android abdominal fat distribution at baseline. Closed and open columns indicate percent change in S:V ratio of abdominal fat in the android-HRT group and the android-control group, respectively. Data are expressed as means \pm s.d. * $P < 0.01$ compared with the control group (Student's unpaired *t*-test).

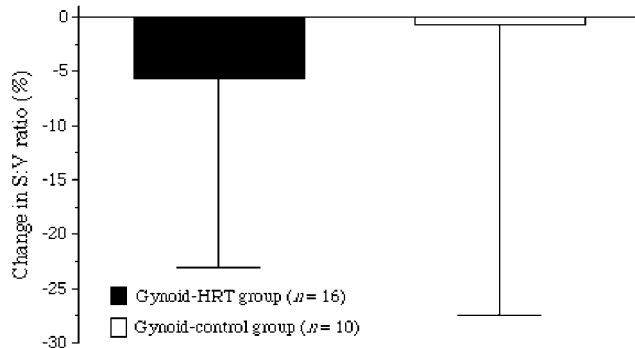


Figure 3 Percent change in subcutaneous-to-visceral (S:V) ratio of abdominal fat in HRT and control subjects with a gynoid abdominal fat distribution at baseline. Closed and open columns indicate the percent change in S:V ratio of abdominal fat in the gynoid-HRT group and the gynoid-control group, respectively. Data are expressed as means \pm s.d.

weight, BMI, TAF, SAF, VAF, S:V ratio, TC, TG, HDL-C, LDL-C, FSH, and E2 did not change.

A significantly greater decline was seen between 12-month and baseline values for VAF and FSH in the android-HRT group than in the android-control group ($P < 0.05$), and significantly greater increases in S:V ratio and E2 were seen in the android-HRT group than in the android-control group ($P < 0.05$; Table 2). The percent increase in S:V ratio of abdominal fat was significantly greater in the android-HRT group than in the android-control group ($P < 0.01$; Figure 2). In addition, a significantly greater decline was seen between 12-month values and baseline for TC, LDL-C, and FSH in the gynoid-HRT group than in the gynoid-control group ($P < 0.05$), while HDL-C and E2 rose significantly more in the gynoid-HRT group than in the gynoid-control group ($P < 0.05$; Table 2). No significant difference in percent

change in S:V ratio of abdominal fat was noted between the gynoid-HRT group and the gynoid-control group (Figure 3).

Discussion

In the Japanese PMW, in this study, HRT did not cause weight gain; instead, HRT inhibited a postmenopausal tendency toward an increase in abdominal fat, especially VAF. HRT also decreased serum TC and LDL-C, while increasing serum TG and HDL-C. In subjects with an android abdominal fat distribution, HRT reduced visceral fat and shifted abdominal fat distribution toward a gynoid pattern. HRT did not alter abdominal fat distribution in subjects with a gynoid pattern. Unfortunately, HRT increased serum TG in the android and the gynoid subgroups.

Data concerning gonadal steroids and changes in weight and abdominal fat distribution have been conflicting. Numerous studies have indicated that HRT prevented or reduced weight gain^{8-15,18} and android (central) fat accumulation.^{8-15,18,19} Manolio *et al*⁸ reported that estrogen users had lower weight, BMI, and WHR than subjects never treated. Espeland *et al*⁹ showed that women randomly assigned to take conjugated equine estrogen (CEE) with or without a progestational agent averaged 1.0 kg less weight gain at the end of 3 y than those assigned to take placebo. CEE treatment also was associated with an average of 1.2 cm less increase in waist girth and 0.3 cm less increase in hip girth. In the long-term prospective, double-blind, placebo-controlled PEPI trial (postmenopausal estrogen/progestins interventions),¹⁵ an increase in weight was demonstrated during menopause. After 36 months, the increase in weight was significantly higher in untreated PMW (+2.1 kg) than in women treated with estrogens (+0.7 kg). In a 15-y prospective and cross-sectional cohort study,¹² no significant differences were evident between HRT users and nonusers for BMI at follow-up, change in weight or BMI between baseline and follow-up, or WHR or fat mass at follow-up. Kristensen *et al*¹³ demonstrated using DEXA that 5 y of HRT significantly reduced fat mass accumulation, especially in the trunk. This effect of HRT was more pronounced in nonobese than obese subjects. Reubinoff *et al*¹⁴ reported that 12 months of continuous daily estrogen and progestin replacement neither prevented nor increased early postmenopausal weight gain; the same was true for fat accumulation measured by infrared methods. Yet HRT minimized increase in WHR, given similar caloric and macronutrient intake among subjects. Using DEXA, Gambacciani *et al*¹⁸ demonstrated that 12 months of continuous estrogen and progestin replacement therapy did not increase weight or body fat, and prevented the postmenopausal shift to a central fat distribution. Haarbo *et al*¹⁹ found that 2 y of combined estrogen-progestogen therapy prevented an increase after menopause in abdominal fat measured by DEXA.

Sites *et al*^{10,11} found that estrogen users had lower weight and BMI, and less visceral adipose tissue demonstrable by CT than patients never treated. Our findings that HRT did not cause gains in weight and BMI, and prevented an increase in VAF distribution, are essentially in agreement. These findings suggest that HRT use may minimize weight gain and selective accumulation of intra-abdominal fat. On the other hand, Aloia *et al*²⁰ reported that 2.9 y of cyclic combined estrogen–progestogen therapy in PMW increased weight and body fat, and decreased the extremity/trunk fat ratio as determined by dual photon absorption. O’Sullivan *et al*²¹ demonstrated that 6 months of treatment with estradiol increased weight and body fat measured by DEXA, via inhibition of lipid oxidation. Differences in findings may reflect differences in type and dosage of HRT, lengths of observation periods, numbers of subjects, or methods used to estimate adipose tissue.

In the present study, HRT increased SAF and the S:V ratio in PMW who had an android abdominal fat distribution at the beginning of treatment. The increase in S:V ratio was greater in HRT users than in nonusers. The ratio between the subcutaneous and the VAF was taken to be an indicator of predominantly SAF or VAF accumulation.³⁴ By these ratios, HRT shifted abdominal fat distribution from android to gynoid in PMW with android fat distribution. The prevalence of an android abdominal fat deposition is greater in PMW than in premenopausal women, which has been attributed to diminished estrogen secretion.⁵ Enzi *et al*³⁴ demonstrated that among women 40–59-y old, PMW had a significantly lower S:V ratio than premenopausal women (1.73 ± 0.28 vs 2.81 ± 0.25), while above age 60 the S:V ratio became much lower than in younger subjects, reflecting a change to an android distribution. In a cross-sectional study using CT, Zamboni *et al*³⁵ found SAF to be greater in premenopausal women, while VAF was greater in PMW. We believe that estrogen therapy contributes to a shift from android to gynoid abdominal fat distribution in PMW.

Although the mechanism by which HRT shifts abdominal fat distribution from android to gynoid remains obscure, sex steroid hormones appear to participate in regulation of adipose tissue distribution. While environmental factors such as smoking, activity, and stress can increase central body fat, gender-associated differences in body fat distribution are largely attributable to circulating sex steroid hormones.³⁶ Enzyme activity of lipoprotein lipase (LPL) in adipocytes has been validated as a reliable indicator of fat formation and accumulation. The opposite process, lipolysis, enzymatically degrades lipids within the adipocyte. Women of reproductive age have a higher femoral than abdominal LPL activity and a higher abdominal than femoral lipolytic activity,^{36–38} and their lipolytic response to noradrenaline has been shown to be more intense in the abdominal than in the femoral region. In PMW, however, no differences in LPL or lipolysis were found between these two regions.³⁸ Postmenopausal estrogen therapy has been shown to increase LPL activity in the femorogluteal region.³⁷ In this

manner, estrogen may contribute to a shift of abdominal fat from android to gynoid.

HRT has important effects on lipids and lipoproteins. Favorable changes in lipids and lipoprotein have been demonstrated in a clinical study evaluating effects of exogenous estrogen on cardiovascular risk factors in women.²⁸ These improvements include an increase in HDL-C and a decrease in LDL-C. Women in the PEPI trial,¹⁵ randomly selected to receive CEE plus continuous or cyclic medroxyprogesterone acetate had smaller increases in HDL-C from baseline than did women who received unopposed estrogen. Walsh *et al*²⁸ and Wakatsuki *et al*³⁹ demonstrated an increase in HDL-C and TG and a decrease in LDL-C and TC levels in PMW following treatment with equine estrogen. In our present study, similar effects on lipid and lipoprotein were observed in PMW.

Estrogen induces changes in lipids and lipoproteins through a variety of mechanisms. For example, estrogen causes a decrease in serum TC and LDL-C and an increase in HDL-C by increasing hepatic LDL receptor activity and suppressing hepatic TG lipase activity.²⁸

Menopause is associated with increased risk of cardiovascular morbidity and mortality.^{40–43} Several epidemiologic studies have shown that HRT reduces these events in PMW.^{44–47} In contrast, some recent, well-controlled large trials such as the Heart and Estrogen/Progestin Replacement Study (HERS), a follow-up study (HERS II), and the Women’s Health Initiative Randomized Controlled Trial failed to show a reduction in coronary heart disease in PMW receiving HRT.^{48–50} In the present study, HRT prevented an increase in VAF and improved fasting lipid levels excluding TG in PMW. In PMW with android distributions, HRT also shifted abdominal fat distribution to a gynoid pattern. This shift in distribution of abdominal fat may be a reason why HRT reduces risk of cardiovascular disease, since visceral obesity is a known risk factor for cardiovascular disease, stroke, and type II diabetes mellitus.^{6,32} However, HRT in the present study remarkably increased serum TG in PMW with an android as well as a gynoid fat distribution. As to TG, elevated TG is a risk factor for coronary artery disease.⁵¹ Furthermore, antioxidant effects of estrogen might be offset in patients showing such a TG increase because estrogen-induced plasma TG increases may produce small low-density lipoprotein particles that are more susceptible to oxidant.³⁹ Therefore, HRT might not have a beneficial net effect on cardiovascular disease in all PMW with an android abdominal fat distribution.

Previous Western studies have reported that women in ethnic minorities, including Hispanics, African-Americans, and Asians, have a higher prevalence of obesity than Caucasian women.^{52,53} In PEPI,¹⁵ however, Hispanic women exhibited significantly smaller longitudinal changes in waist girth than women in the other ethnic groups. Few previous studies have examined associations of HRT with fat distribution according to ethnicity. PEPI¹⁵ data suggested that the impact of hormone therapy on weight and adiposity is fairly

uniform among ethnic groups, but relatively low numbers of minority women in PEPI limited the statistical power of this conclusion. The present study is the first to examine the effect of HRT on body fat distribution in Japanese PMW according to CT.

Several limitations are inherent to the present study, including a relatively small number of subjects and a nonrandomized design. Although this type of study can provide useful information concerning the effects of HRT, observed differences might conceivably be attributable to a selection bias where more health conscious, more healthy women may have chosen HRT.

In conclusion, Japanese PMW undergoing HRT did not gain weight, and an increase in VAF that occurs after menopause was prevented. Fasting lipid levels showed overall improvement. In PMW with android fat distributions, HRT reduced visceral fat and favored a shift to a gynoid abdominal fat distribution, but HRT also increased TG concentrations in PMW with an android as well as a gynoid fat distribution. Improvement in the distribution of abdominal fat and fasting lipid levels except for TG may represent beneficial effects of HRT against cardiovascular disease, but these effects might be offset by the estrogen-induced increase in TG concentrations. The elevation of TG seen with HRT in PMW warrants caution, including careful biochemical follow-up evaluations.

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