Body Composition and Energy Balance: Lack of Effect of Short-Term Hormone Replacement in Postmenopausal Women

Ellen J. Anderson, Helene B. Lavoie, Carrie C. Strauss, Jane L. Hubbard, Julie L. Sharpless, and Janet E. Hall

Postmenopausal women (PMW) commonly believe that hormone replacement (HR) leads to weight gain, and fear of weight gain and/or an actual increase in weight is one of the principle reasons evoked for the discontinuation of HR. However, the potential effects of physiologic HR on body composition have yet to be separated from the effects of lifestyle or aging. Therefore, we examined the effect of short-term hormone replacement and age on alterations in weight, body composition, and energy balance. A prospective study of 28 healthy PMW aged 45 to 55 years (younger PMW, studies completed n = 18) and 70 to 80 years (older PMW, studies completed n = 15) was conducted. The last menstrual period was more than 12 months previously. The women had a body mass index (BMI) less than 30 kg/m^2 and were taking no medication. Subjects were studied at baseline, after 1 month of transdermal estrogen (Estraderm, 50 μg/day) administration (E_2), followed by a further month of transdermal estrogen with progesterone (100 mg per vagina twice daily) for the final 7 days (E_2 + P). Anthropometric measurements and energy assessments were performed at each visit. Physiologic HR was achieved in each subject, and there was no difference between levels achieved in older and younger women. Resting energy expenditure and activity level were positively correlated with fat-free mass ($P < .0001$), while energy intake was not. Resting energy expenditure was lower in older compared with younger PMW when adjusted for fat-free mass ($P < .005$). Energy intake was also lower in the older PMW when corrected for fat-free mass ($P < .0001$); as was activity level ($P < .05$). There was no effect of hormonal treatment on any of the parameters measured. Changes in weight from baseline for E_2 (0.37 ± 0.25 and 0.61 ± 0.27 kg in younger and older) and E_2 + P (0.11 ± 0.38 and 0.28 ± 0.31 kg) were not statistically significant. In addition, there was no difference in BMI, fat mass, fat-free mass, total body water, or waist-to-hip ratio (WHR) between groups or with hormonal treatment. In conclusion, short-term transdermal HR is not associated with significant changes in weight or other anthropometric measures in younger or older PMW. These studies confirm the decrease in energy expenditure that occurs with aging, but indicates that there is no effect of HR on resting energy expenditure.

ALTHOUGH HORMONE REPLACEMENT (HR) has been shown to reduce cardiovascular risk[1-3] and the risk of osteoporosis[4,5]; fear of weight gain and/or an actual increase in weight is one of the principle reasons evoked for the discontinuation of hormonal treatment. The discontinuation of hormonal treatment typically occurs within the initial months of use. The perception that HR contributes to weight gain may be due in part to misinterpretation of scientific data by the lay press and general public.[6,7] A small number of prospective randomized placebo controlled,[8] cross-sectional,[9-11] and long-term prospective[9-12] studies have investigated HR on weight with variable results (Table 1). Importantly, the studies of Wing et al[11] and Kritz-Silverstein et al[9] suggest that age alone or the lifestyle changes associated with aging result in weight gain over time in the absence of HR. The decline in resting energy metabolism associated with age[13-17] would support this hypothesis. Previous studies have not examined early changes in body weight after institution of HR. In addition, it is not possible to assess detailed physiologic parameters such as energy balance in large studies of weight changes in response to hormone therapy, such as those discussed above.

To determine the specific effect of HR on changes in weight, body composition, and energy balance, we conducted short-term studies in which subjects were used as their own control. To determine whether these responses were differentially affected by age, younger and older postmenopausal women (PMW) were studied. In these studies, transdermal estradiol was used to achieve estradiol levels within the follicular phase range and natural progesterone administered to mimic midluteal phase progesterone exposure.

SUBJECTS AND METHODS

Study Population

Healthy PMW aged 45 to 55 years (studies completed n = 18) and 70 to 80 years (studies completed n = 15) were selected on the basis of the following criteria: last menstrual period more than 12 months previously, with a body mass index (BMI) less than 30 kg/m^2 and greater than 20 kg/m^2, on no medication, and specifically on no HR for the past 2 months, normal urinalysis, electrocardiogram, thyroid-stimulating hormone, prolactin, complete blood count, mammogram and Pap smear; and no contraindication to HR. Baseline estradiol (E_2) was less than 30 pg/mL and luteinizing hormone (LH) and follicle stimulating hormone (FSH) were greater than 30 IU/L in all subjects. None of the women studied was attempting weight loss, and all were instructed to continue usual habits. The women had the understanding that non-nutritional outcomes were the focus of the study. In the 28 individuals enrolled, a total of 33 studies were performed because 2 younger and 1 older PMW completed 2 studies, and 1 younger individual enrolled in 3 studies. All repeat studies were separated by a washout period of more than 2 months. This number of studies was chosen to provide a 90% probability of detecting an increase of ≥1 kg,

From the General Clinical Research Center and the Reproductive Endocrine Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA.

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Address reprint requests to Ellen J. Anderson, General Clinical Research Center, MC GRBBA 005, 25 Fruit St, Massachusetts General Hospital, Boston, MA 02114.

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Table 1. Studies on the Effect of Hormone Replacement on Weight

Author	No.	Design	Groups (no.)	Change in Weight (kg)
Espeland[8]	875	Prospective (3 yr), randomized, placebo-controlled	Placebo (166)	2.1 ± 0.4*
			Unopposed CEE (170)	0.7 ± 0.4
			CEE + MPAγ (169)	1.3 ± 0.4
			CEE + MPA^n (170)	0.9 ± 0.3
			CEE + MP (172)	1.3 ± 0.3
Kritz-Silverstein[9]	671	Prospective (15 yr), cross-sectional	Never on HRT (194)	−0.9†
			Intermittent HRT (331)	0.7
			Continuous HRT (146)	0.9
Reubinoff[10]	63	Prospective (1 yr), cross-sectional	Received HRT (34)	2.35 ± 0.64†
			Refused HRT (29)	2.06 ± 1.88
Wing[11]	485	Prospective (3 yr), cross-sectional	Premenopause (279)	2.1 ± 4.1†
			Perimenopause (94)	2.5 ± 3.3
			Natural menopause (61)	1.4 ± 4.9
			Hysterectomy (19)	2.9 ± 5.4
			Hormone users (32)	3.3 ± 4.7
Gambacciani[12]	27	Prospective (1 yr)	No HRT (12)	1.6 ± 0.3‡
			EV + CPA (15)	0.5 ± 0.0§

Abbreviations: HRT, hormone replacement therapy; CEE, conjugated equine estrogen, 0.625 mg daily; MPAγ, medroxyprogesterone acetate, 2.5 mg daily; MPA^n, medroxyprogesterone acetate, 10 mg daily on days 1-12; MP, micronized progesterone, 200 mg daily on days 1-12; EV, estradiol valerate, 2 mg daily on days 1-21; CPA, cyproterone acetate, 1 mg daily on last 10 days of cycle.

*No significant difference between hormone treatment and active treatment arms.

†No significant difference between the groups.

‡$P < .05$ between baseline and follow-up.

§No significant difference between baseline and follow-up.

a change in weight which most individuals judge to be clinically significant.

Study Protocol

The study was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital and informed consent was obtained from each subject before participation. Subjects were studied at baseline, after 1 month of transdermal estradiol replacement (Estraderm, 50 μg/d; Novartis, East Hanover, NJ) and after a further month of transdermal estradiol replacement at the same dose and 7 days of progesterone (progesterone, 100 mg per vagina twice daily), designed to achieve physiologic hormone levels. LH, FSH, E_2, and progesterone (P) were measured at the screening visit to determine study eligibility using radioimmunoassay (RIA) methods previously described.[18-20] E_2 and P serum levels were measured at each visit to verify that appropriate midfollicular phase estradiol and midluteal phase progesterone levels were achieved with hormone administration.

Metabolic Parameters

At each visit, height was obtained by stadiometer and fasting weight by digital scale using standard procedures,[21] and BMI was calculated. Using a metal, spring tension measuring tape, waist measurements were obtained at the umbilicus and hip measurements at the maximum circumference to the nearest 0.1 cm as the mean of 3 measurements and waist-to-hip ratio (WHR) was calculated. Percent body fat composition was measured by tetrapolar bioelectric impedance analysis (BIA 101A; RJL Systems, Clinton Twp, MI) in the supine position.[22,23] This method allows for the determination of body composition indices, including body fat, and percent body fat (using the calculation program [Weight Manager 2.05] supplied with the BIA analyzer), absolute fat mass (% body fat × weight [kg]), and total body water (TBW). The determination of body water and fat-free mass using this method is highly correlated with total body water and fat-free mass determined from body density in healthy subjects ($r = .95$).[24] All measurements, except fasting weight, were completed when the subject had refrained from any excessive activity in the preceding 24 hours, had not consumed alcohol for at least 3 days, and had been postprandial for greater than 2 hours. Complete anthropometric measurements were obtained for each individual at each visit with the exception of WHR in 1 young PMW and measurements at the E_2 + P visit for 1 young PMW.

Energy Balance

Resting energy expenditure was determined by indirect calorimetry (Life Energy Systems, EMS/50, Murray, UT).[25,26] Subjects sat quietly in a thermal neutral room for ≥15 minutes before study commencement. Oxygen consumption and carbon dioxide production were measured continuously with the achievement of a steady state for ≥20 minutes. Subjects were interviewed by nutrition staff trained in the modified Burke diet history technique[27,28] to obtain an estimate of food intake. Subjects were asked open-ended and closed-ended questions to determine food intake and supplement use within the past month. Food models, cups, and measuring tools were used to quantify portion sizes. Nutrient calculations were performed using the Minnesota Nutrition Data System 2.8 (NDS) software, developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN (Food Database version 10A; Nutrient Database version 25). Vitamin/mineral supplements were assessed using the actual supplement label and verified with nutrient composition in the NDS databank. Reported intakes from diet history were analyzed for energy intake and macronutrients. A physical activity questionnaire[29] was verbally administered to estimate total energy expenditure per day. Incomplete nutrient intake was obtained from 3 younger women at the E_2 visit and 5 younger women at the E_2 + P visit. A steady state for measurement of energy expenditure was not achieved in 2 older and 1 younger women at baseline and at the E_2 visit and 1 older and 3 younger women at E_2 + P visit.

Data Analysis

Repeated measures 2-way analysis of variance was used to determine differences in age, weight, BMI, percent body fat, fat mass,

Table 2. Effects of HR on Body Composition in PMW (mean ± SEM)

	Younger			Older		
	Baseline	E_2	E_2 + P	Baseline	E_2	E_2 + P
Weight (kg)	64.4 ± 1.8	64.7 ± 1.9	64.4 ± 1.9	65.2 ± 2.5	65.8 ± 2.6	65.5 ± 2.6
BMI (kg/m^2)	25.0 ± 0.8	25.2 ± 0.8	24.8 ± 0.7	26.2 ± 1.0	26.4 ± 1.0	26.4 ± 1.0
Body fat (%)	29.7 ± 1.1	29.6 ± 1.1	29.2 ± 1.2	32.1 ± 1.6	31.5 ± 1.9	32.1 ± 1.8
Fat mass (kg)	19.4 ± 1.2	19.4 ± 1.2	19.1 ± 1.3	21.4 ± 1.8	21.3 ± 2.0	21.6 ± 2.0
Fat-free mass (kg)	45.0 ± 0.9	45.6 ± 0.9	45.4 ± 1.0	43.8 ± 1.0	44.5 ± 0.9	43.6 ± 1.0
Total body water (%)	51.4 ± 0.9	51.4 ± 0.8	51.4 ± 0.9	49.6 ± 1.2	50.1 ± 1.4	49.3 ± 1.3
WHR	0.90 ± 0.01	0.91 ± 0.02	0.90 ± 0.02	0.94 ± 0.02	0.94 ± 0.02	0.93 ± 0.02

NOTE. No significant differences have been found.

fat-free mass, percent total body water, WHR, energy expenditure, nutrient intake, physical activity, serum hormone levels, and absolute weight change as a function of hormone treatment and age. Previous studies have shown that energy expenditure, nutrient intake, and physical activity are correlated with fat-free mass.[13,17,30,31] Therefore, a regression-based approach[32,33] was used to assess these variables using fat-free mass and age group as covariates. Values are expressed as the mean ± SEM, unless otherwise specified, and $P < .05$ was accepted as significant.

RESULTS

Baseline Characteristics

The mean age ± SEM was 52.4 ± 0.6 years for the younger and 72.3 ± 0.6 years for the older PMW. Estradiol increased from baseline to early follicular phase levels with HR (27.99 ± 1.77, 76.89 ± 4.43, 80.60 ± 5.43 pg/mL; baseline, E_2, E_2 + P; mean ± SEM; $P < .001$). Physiologic progesterone levels (0.48 ± 0.04, 7.09 ± 0.91 ng/mL; E_2, E_2 + P; mean ± SEM; $P < .001$) were also achieved in response to hormone administration.

Body Composition

At baseline, there was no difference between the younger and older PMW in weight, BMI, percent body fat, absolute fat mass, fat-free mass, total body water, or WHR (Table 2). While there was no significant difference in weight change in the younger or older women, individual variability was observed in both the younger and older women (Fig 1). For younger PMW, the mean change in weight was 0.37 ± 0.25 kg with E_2 and 0.11 ± 0.38 kg with E_2 + P. For older PMW, the mean change in weight was 0.61 ± 0.27 with E_2 and 0.28 ± 0.31 kg with E_2 + P. For the group as a whole, there was no effect of E_2 or E_2 + P on percent body fat, total body water, or absolute fat mass.

Energy Balance

Resting energy expenditure and activity level were positively correlated with fat-free mass ($P < .0001$). There was no effect of E_2 or E_2 + P on resting energy expenditure, activity level, or energy intake even when adjusted for fat-free mass (Table 3). Resting energy expenditure across all visits was lower in older compared with younger PMW when corrected for fat-free mass (6,537 ± 115 kJ/24 h younger *v* 6,027 ± 125 kJ/24 h older; $P < .004$). Reported energy intake was also lower in the older PMW when adjusted for fat-free mass (7,106 ± 233 younger *v* 5,668 ± 238 kJ/24 h older; $P < .0001$). In addition, there was a small, but significant decrease in reported activity level in the older PMW when corrected for fat-free mass (10,689 ± 236 kJ/24 h younger *v* 10,003 ± 226 kJ/24 h older; $P < .05$).

DISCUSSION

In this study, we have shown that in estrogen-deficient PMW, short-term transdermal estradiol ± progesterone re-

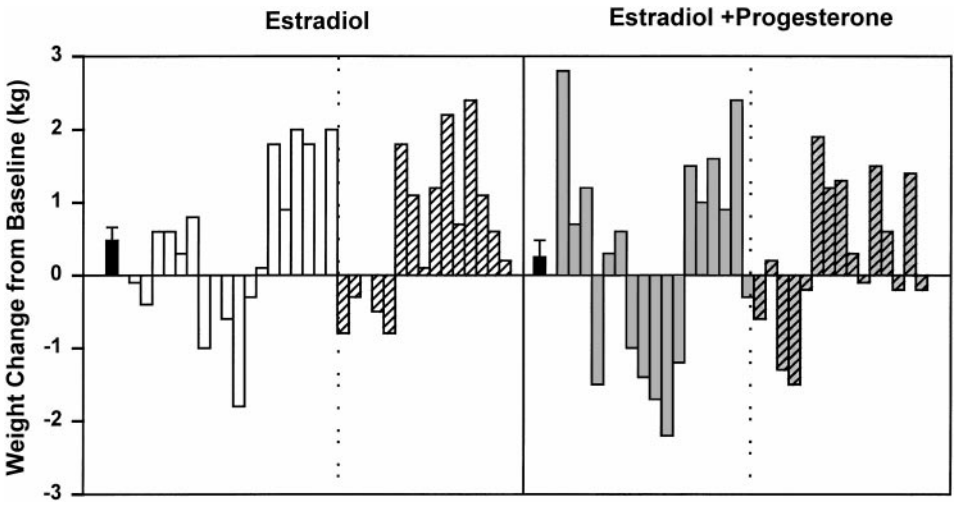

Fig 1. Weight change from baseline for individual younger PMW (open bars, n = 18) and older PMW (hatched bars, n = 15) after 1 month of estrogen replacement and after 1 month of continued estrogen and 7 days of progesterone, as indicated. The mean weight change (±SEM) for the PMW is shown in the black bar for each hormonal treatment.

Table 3. Effects of HR on Energy Balance in PMW Adjusted for Fat-Free Mass (mean ± SEM)

	Younger			Older		
	Baseline	E_2	E_2 + P	Baseline	E_2	E_2 + P
Resting energy expenditure (kJ/24 h)	6,424 ± 170	6,881 ± 232	6,238 ± 173	6,054 ± 197	5,994 ± 266*	6,023 ± 166
Activity level (kJ/24 h)	10,193 ± 399	10,002 ± 373	9,761 ± 380	11,165 ± 438	10,336 ± 398	10,566 ± 367
Energy intake (kJ/24 h)	7,325 ± 448	7,360 ± 360	6,490 ± 387	5,948 ± 491†	5,496 ± 360†	5,573 ± 373

*$P < .02$ *v* younger.
†$P < .05$ *v* younger.

placement to physiologic premenopausal levels does not result in a significant increase in body weight. In addition, there was no change in BMI, percent body fat, fat mass, fat-free mass, percent total body water, or WHR during the 2-month hormone replacement period.

In our population, individual variability in weight change in younger and older women ranged from −1.8 to 2.4 kg with E_2 and from −2.2 to 2.8 kg with E_2 + P, but there was no consistent pattern. The overall absence of an increase in body weight is consistent with most prior studies investigating the relationship of hormonal treatment and weight,[8,9,12] including the only other study, which used natural rather than synthetic progesterone,[8] and a study, which compared the oral versus transdermal route of estrogen administration.[34] Previous studies have variably concluded that hormonal treatment neither prevents nor increases weight gain with no significant difference in the weight gained in women who refused HR and women who took HR[10]; HR is not associated with weight gain[9]; or HR was associated with a small, but insignificant weight gain.[11] Importantly, 2 studies have now shown that groups receiving HR and controls gained weight over 1 to 3 years, but those on hormonal treatment gained less weight than those not on HR.[8,12] Although hormone administration has the potential to contribute to fluid retention[35]; this was not observed in our short-term study, as both total body water and weight remained unchanged.

In the current study, no changes in body fat distribution, determined by WHR and percent body fat calculated by BIA were observed with short-term HR. These findings are consistent with the majority of long-term studies using either dual photon absorptiometry and/or dual energy x-ray absorptiometry, which have demonstrated that HR is not associated with increased body fat and may, in fact, prevent age or lifestyle-associated increases in fat.[1,12,36-38] However, a higher fat mass, determined by BIA, in women receiving hormone therapy compared with women not receiving hormone therapy has been observed in one study.[9] There is some evidence that the route of HR may be important as studies by O'Sullivan et al[34] indicate that oral administration increases fat mass compared with transdermal. In our population, the WHR ranged from 0.90 ± 0.01 to 0.94 ± 0.02 with no change with hormone treatments or with aging. While an increase in upper body fat mass in association with menopause has been observed,[38] our short-term findings are consistent with studies suggesting that the use of HR prevents an increase in abdominal fat mass.[8-10,36]

Previous studies have shown an association of aging with loss of fat-free mass, increase in fat mass, and decrease in energy expenditure.[13-16,31] As the current studies did not follow the same women over many years, changes in body composition with age cannot be examined within an individual, however our cross-sectional study demonstrated a decrease in energy expenditure adjusted for fat-free mass in older compared with younger PMW, confirming previous findings.

The major strength of this study is that the use of subjects as their own control permitted detailed metabolic information to be obtained in addition to changes in body weight. Although small, our prospective study was adequately powered to detect an increase of 1.0 kg with a 90% probability, and thus we can conclude that HR does not result in short-term weight gain in younger or older subjects. In these studies, hormonal therapy was designed to mimic physiologic levels of estrogen and a midluteal phase exposure to progesterone. These studies used transdermal estradiol commonly used as HR in PMW and produced similar progesterone levels to those seen with the use of natural progesterone, which is being used increasingly for postmenopausal hormonal treatment. However, due to our selective, racially homogenous population, extrapolation of these results to women in general should be drawn with caution. Further limitations of the study include the lack of a placebo control group and the lack of blinding.

In conclusion, the results of this study confirm an age-related decrease in energy expenditure, but demonstrate that younger and older PMW should not expect to gain significant amounts of weight on short-term transdermal HR. Weight gain, which has been associated with the menopausal years, is more likely related to a decrease in energy expenditure or to lifestyle changes than to the use of hormone administration. Because of the variability in individual weight changes, assessment of the multiple factors that may affect body weight should be probed before the discontinuation of hormonal therapy.

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