

Effects of the Menopausal Transition on Factors Related to Energy Balance. A MONET group Study:

I. Energy Expenditure

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Abstract

Objectives—Factors that influence weight gain during the menopausal transition are not fully understood. The purpose of this study was to investigate changes in energy expenditure (EE) across the menopausal transition.

Methods—One hundred and two premenopausal women (age: 49.9 ± 1.9 yrs; BMI: 23.3 ± 2.2 kg/m²) were followed for 5 years. Body composition (DXA), physical activity EE (accelerometer), resting EE and thermic effect of food (indirect calorimetry) were measured annually.

Results—Total EE decreased significantly over time in postmenopausal women ($P < 0.05$), which was mostly due to a decrease in physical activity EE ($P < 0.05$). Although average resting EE remained stable over time in postmenopausal women, a significant increase, over the 5-year

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period, was noted in women who were in the menopausal transition by year 5 ($P < 0.05$). Finally, the time spent in moderate physical activity decreased and the time spent in sedentary physical activity increased during the menopausal transition ($P < 0.05$).

Conclusion—These results suggest that menopausal transition is accompanied with a decline in EE mainly characterized by a decrease in physical activity EE and a shift to a more sedentary lifestyle.

Keywords

Energy balance; energy expenditure; menopausal transition; body composition

INTRODUCTION

The menopausal transition is associated with a risk to increase body weight and adiposity¹. Weight gain observed in middle-aged women at this time seems to be more closely associated with chronological aging rather than menopause *per se*²⁻⁵. On the other hand, changes in body composition and in fat distribution are influenced by the hormonal changes occurring at menopause, as well as by chronological aging⁶⁻⁷. Although hormonal changes associated with menopause and chronological aging may play a role in the changes of body weight and composition in women, identifying modifiable factors that can prevent or attenuate these changes is of great relevance⁸.

Few studies have investigated factors associated with energy balance during the menopausal transition. Although resting energy expenditure (REE) decreases with age⁹, the loss of ovarian function and the loss in muscle mass observed in postmenopausal women may also explain decline¹⁰. A 4-year study showed a significant decrease in REE over time in middle-aged women¹¹. However, this decrease was 1.5 times greater in women who became postmenopausal when compared to those who remained premenopausal. Estrogens also appear to have an impact in the regulation of physical activity in both rodents and humans¹²⁻¹³. Lovejoy *et al.*¹¹ showed a significant decrease in leisure-time physical activity during the menopausal transition. Spontaneous physical activity, measured in a whole-room calorimeter, was also decreased by 30 to 40% in both postmenopausal and premenopausal women, suggesting an age-related decline rather than a specific effect of menopause^{11, 14}. Thus, changes in EE could play an important role in weight gain during the menopausal transition. However, at present, little is known about the relationship between EE and menopause.

To our knowledge, there have been only four longitudinal studies related to changes in EE during the menopausal transition^{2, 5, 11, 15}. However, most of them have only measured the physical activity component of EE with self-reported questionnaire^{2, 5, 15}. One study used direct measures of body composition and EE (whole-room calorimeter and accelerometer)¹¹. The accelerometers were worn for only four consecutive days and 24-h EE was obtained in a small subset of women. The thermic effect of food (TEF) and the time spent in physical activity of different intensities have never been investigated during the menopausal transition.

This study was performed to determine changes in factors related to energy balance in women going through the menopausal transition. The objective was to investigate factors related to energy balance that occur in healthy women during the menopausal transition. In the first part of this study, we report changes in EE during the menopausal transition. We hypothesized that women who become menopausal would show greater decrease in EE [REE and physical activity EE (PAEE)]. In the second part of this study, reported in a companion article, we investigated changes in energy intake (EI), macronutrient composition, eating frequency and appetite during the menopausal transition.

METHODS

Participants

Participants were recruited using community advertising and referrals from the Ob/Gyn clinics. Premenopausal women were included if they met the following criteria: (1) premenopausal status (two menstruations in the last 3 months, no increase in cycle irregularity in the 12 months before testing, and a plasma follicular-stimulating hormone level < 30 IU/L as a mean of verification), (2) aged between 47 and 55 years, (3) nonsmoker, (4) BMI between 20 and 29 kg/m², and (5) reported weight stability (± 2 kg) for 6 months or more before enrollment in the study. Exclusion criteria were (1) pregnancy or having plans to become pregnant, (2) medical problems that could have interfered with outcome variables including cardiovascular and/or metabolic diseases, (3) taking oral contraceptives or hormone therapy, (4) high risk for hysterectomy, and (5) history of drug and/or alcohol abuse. As described by Abdunour *et al.*⁷ of the 314 calls received, 102 women were found eligible. Among them, 11 dropped out of the study for personal reasons. Consequently, a total of 91 Caucasian women completed the 5-year longitudinal study. Further details of the MONET menopausal transition study design and recruitment are provided elsewhere⁷.

Since not all women had completed measurements for all of the EE variables every year, the number of participants varies across analyses for each EE variables (n range from 39 to 58). This study received approval from the University of Ottawa and the Montfort Hospital ethics committees, and written consent was obtained from each participant.

Design

The 5-year menopausal transition study was observational with all outcomes measured at baseline and annually for 5 years. As long as women were premenopausal, they were always tested on days 1–8 of the follicular phase of the menstrual cycle, *ie*, when estrogens and progesterone are at their lowest concentrations.

Menopausal status

Menopausal status was determined yearly by self-reported questionnaire about menstrual bleeding and its regularity. Follicle-stimulating hormone (FSH) was measured yearly during the early follicular phase and was used as a mean of verification of the menopausal status. Women were classified as *premenopausal* if they reported no changes in menstrual cycle frequency; *menopausal transition* if they reported irregular cycles characterised by variable cycle length > 7 days different from normal and/or 2 skipped cycles and an interval of 60

days of amenorrhea; and finally women were classified as *postmenopausal* based on their final menstrual period (FMP) and confirmed by 12 months of amenorrhoea and FSH > 30 IU/L ¹⁶.

Anthropometric measurements

Body weight and height were measured with a BWB-800AS digital scale and a Tanita HR-100 height rod (Tanita Corporation of America, Inc, Arlington Heights, IL), respectively, while participants were wearing a hospital gown and no shoes. Body composition was measured by using dual-energy X-ray absorptiometry (DXA; GE-LUNAR Prodigy module; GE Medical Systems, Madison, WI.). Coefficient of variation and correlation for percentage of body fat (%BF) measured in 12 healthy subjects tested in our laboratory were 1.8% and $r = 0.99$, respectively.

Resting EE and TEF

Resting EE and TEF were measured by indirect calorimetry (Deltatrac II metabolic cart; SensorMedics, Yorba Linda, CA). Resting EE was measured for 30 min after a 12-h overnight fast. Subjects had to rest quietly in the supine position for 20 min before the measurement. The first and last 5 min were excluded and only those obtained during min 6 to 25 were used in the calculation. The participant then consumed a standardized breakfast consisting of 2 slices of whole wheat bread (80 g), peanut butter (20 g), raspberry jam (20 g), cheddar cheese 27% milk fat (20 g), and orange juice (250 ml). The total energy content was 575 kcal (2400 kJ), and its food quotient was 0.89 (57% carbohydrates, 13% protein, 30% lipids). Subjects ate everything within 10 minutes. For postprandial EE (PEE), 15-min sampling periods were performed every 30 min for 3 h during the postprandial period ¹⁷. A mean value (in kcal/min) for each of the 6 PEE measurements was calculated. The TEF was obtained by subtracting REE from PEE for each of the mean values obtained for the 6 sampling periods. Total TEF was calculated by multiplying the mean value of each of the 6 sampling periods by 30 min. These 6 values were then added together to obtain TEF for the 180-min period. TEF expressed in percentage was also calculated as the increase in EE (over baseline REE) expressed as a percentage of the energy content of the test meal. EE was calculated according to the Weir equation ¹⁸. Coefficient of variation and correlation for the determination of REE with the Deltatrac II metabolic cart in our laboratory were 2.3% and $r = 0.98$, respectively, as determined in 12 healthy subjects.

Physical Activity EE

Multidirectional accelerometry units were used (Actical; Mini Mitter Co, Inc, Bend, OR). The Actical has been validated to measure physical activity in adults ¹⁹ and has shown better instrument reliability than other accelerometers models ²⁰. It was used to estimate daily EE from physical activities and time spent at sedentary and moderate physical activity intensity. Participants were asked to wear the accelerometer upon waking up and took it off just before going to bed for 7 consecutive days. Such a duration was reported to result in 90% reliability for the measurement of PAEE in both males and females ²¹. The accelerometer was worn over the right hip as it best predicts EE ($r = 0.92-0.97$) ²².

Total EE

Total EE (TEE) was calculated by using the following formula:

$$TEE=(PAEE+REE) \times 1.11 \quad (1)$$

where the factor 1.11 corresponds at the TEF, and was fixed at 10% of TEE.

Statistical analysis

SPSS was used for all analyses (version 17.0; SPSS Inc, Chicago, IL, USA). Two-way repeated-measures analyses of variance (ANOVA), controlled for fat mass (FM) and fat-free mass (FFM) at year 5, were used to determine main effects of time and menopausal status on EE variables. *Post hoc* test were done with Tukey-Kramer and adjustment was used for multiple comparisons. These analyses thus included data collected annually for 5 years. Only cases with complete data at all measurement points were retained. Paired comparison tests were performed to determine differences between year 0 and years before and after menopause onset. In these analyses, year 0 is considered the year within FMP (menopause onset). Data before and after menopause onset were expressed as the percent of the values at year 0, which was fixed at 100%. Data are presented as means \pm SD. All effects were considered significant at $P < 0.05$.

RESULTS

Characteristics of the participants

Baseline characteristics of participants are presented in Table 1. At the onset of the study, women were all premenopausal. By the end of year 5, 4% (n = 4) were still premenopausal, 29% (n = 26) were in the menopausal transition and 67% (n = 61) had become postmenopausal. As reported previously, Abdulnour *et al.*⁷ reported significant increases for FM, %BF, trunk FM and visceral fat during the menopausal transition. No significant changes were observed for body weight and FFM after the 5-year follow-up.

Menopausal status and EE changes over time

Women were divided *post hoc* based on their menopausal status at year 5: 1) women who remained premenopausal (n = 4) and those classified in the menopausal transition at year 5 (n = 26); 2) women classified as postmenopausal for less than 12 months (*Post < 12 months*, n = 22); and 3) women who classified as postmenopausal for more than 12 months (*Post > 12 months*, n = 39). Considering the small number of women who remained premenopausal, they were combined with women who were classified to be in the menopausal transition. No significant differences were found throughout the study for body weight and body composition (*Menopausal Transition*, n = 30) (data not shown). Postmenopausal status at year 5 in the *Post < 12 months* group was confirmed *a posteriori*. Women in this group were contacted after the completion of the 5-year data collection to confirm their menopausal status.

Baseline EE variables were not significantly different between *Menopausal transition*, *Post 12 months* and *Post > 12 months* groups (data not shown). Although Table 2 presents EE data for only years 1 and 5, analyses were performed using data from years 1 through 5. Significant main effects of time were observed for TEF, showing an overall increase for TEF during the 5-year follow-up for all groups (Table 2). Significant *menopausal status x time* interaction was observed for REE, revealing a significant increase in the *Menopausal transition* group only. Significant effects for the *menopausal status x time* interaction were also observed for PAEE and TEE, revealing a significant decrease in the *Post > 12 months* group only. Because the accelerometry data can be influenced by whether time spent awake changed over time, we did two-way repeated-measures ANOVA to determine main effect of time and menopausal status on time spent awake. No significant main effect of time and *menopausal status x time* interaction were observed for this variable (data not shown). There was no main effect of menopausal status on any of the EE variables (Table 2).

Regression analyses were performed to investigate relations between changes in EE and those in body weight and composition. The only significant regression was observed between FFM and PAEE for the *Post > 12 months* group ($r^2 = 0.16$, $P < 0.05$).

Effect of the menopausal transition on EE changes

To further analyze the effect of menopausal transition on EE variables, paired comparison tests were performed to investigate the differences between years relative to FMP in women who became menopausal by the end of the study. These data are expressed as the percent of the values at year 0, which was fixed at 100%, and are shown in Table 3. Year 0 was the year within the FMP (or menopause onset), year 1 was considered as one year after FMP and year -1 was considered as one year before FMP, etc. There were no significant differences in PAEE and TEE in relation to menopause onset. REE was significantly higher at year +2, whereas TEF was significantly higher at year +1 relative to menopause onset. Moreover, TEF was significantly lower in the years preceding onset of menopause (-4 and -3), and %TEF was significantly lower at year -4. Furthermore, time spent in sedentary physical activity tended to increase across the menopausal transition years and was significantly higher at year -1. This variable continued to increase in the postmenopausal years (year +1 and +2) and was significantly higher at year +1. Regarding the time spent in moderate physical activity, it was higher at year -3 and decreased until the onset of menopause (year 0).

DISCUSSION

The present study provides longitudinal data on changes in EE that occur in women during the menopausal transition. We found that TEE was decreased in postmenopausal women, which was mostly explained by a decrease in PAEE. We also observed that the time spent in moderate physical activity was decreased and the time spent in sedentary physical activity was increased during the menopausal transition. Contrary to what was expected, REE remained stable in postmenopausal women and a significant increase was noted in women who were in the menopausal transition by year 5.

There are several possible explanations for the decrease of EE during the menopausal transition. First, TEE tends to decrease in advancing age resulting mainly from changes in REE and PAEE^{10, 23–24}. Second, postmenopausal women no longer experience the luteal phase of the menstrual cycle, which is associated with a rise in EE¹⁰. Third, the loss of FFM in postmenopausal women, which was previously reported^{25–26}, appears to be related with lower REE¹⁰. Finally, estrogens appear to play a role in the regulation of PAEE in both rodents and humans^{12–13}. Indeed, estrogen deficiency can lead to weight gain in animals by decreasing spontaneous physical activity¹³. One study conducted by Lovejoy *et al.* reported similar results to ours in 129 premenopausal women¹¹. In that study, the women (age: 47.2 ± 0.2 yrs; BMI: 27.1 ± 0.6 kg/m²; %BF: 40.9 ± 0.9) were followed for 4 years and those who became postmenopausal by the end of the study showed a significant decrease in EE (sleeping EE, PAEE, spontaneous physical activity). In contrast to Lovejoy's study, we did not observe a decline in REE. In a cross-sectional study of 65 premenopausal and postmenopausal women, Van Pelt *et al.*²⁷ reported that the age-related decline in REE in sedentary women was not observed in women who exercise regularly. In this study, women had a relatively high level of fitness (33.8 ml O₂/kg/min) and a high physical activity level (PAL) (1.7). In the Lovejoy *et al.* study¹¹, the mean PAL was 1.3²⁸, which is associated with a sedentary lifestyle²⁹. This difference in the level of physical activity can explain, in part, why we did not observe a decline in REE during the menopausal transition. Another explanation for this result is that no significant changes in FFM were noted, which appears to be related with changes REE¹⁰.

Similar to Lovejoy *et al.*¹¹, we observed a reduction in TEE of approximately 200 kcal/day in postmenopausal women, which could be enough to cause significant weight gain over time. However, although we observed a decrease in EE in postmenopausal women, the mean body weight changed minimally over time⁷. As discussed in the companion article, this could be explained by a concomitant reduction in EI, which could offset the effects of a decrease in EE on energy balance.

The major findings of the present study are related to changes in PAEE and in time spent in physical activities at different intensities. The decrease in PAEE observed in postmenopausal women is consistent with the findings of other studies^{5, 8, 11, 15, 30}. In addition to the changes in PAEE, we also observed changes in time spent in sedentary and moderate physical activity. These results extend the findings from previous studies demonstrating that, during the menopausal transition, women tend to shift to a more sedentary lifestyle. Associations between physical activity and weight gain during the menopausal transition have been observed in other studies^{2, 5, 15, 30}. In the Healthy Women Study, a prospective study of middle-aged women, Owens *et al.*³⁰ reported that women who had higher levels of physical activity at baseline had less weight gain over time. Moreover, women who increased their physical activity during the 3-year follow-up had the smallest increases in weight. In the SWAN study, Sternfeld *et al.*⁵ also found that physical activity was inversely associated with changes in body weight. Findings from several cross-sectional and longitudinal studies have suggested that regular physical activity may help to attenuate or prevent the tendency for weight gain and adverse changes in body composition that can occur during the menopausal transition^{31–33}. Indeed, it seems that regular physical activity, particularly at moderate to high intensity, could help to minimize changes in body weight

and composition during the menopausal transition^{5, 8, 15, 34}. The most consistent behavioural factor contributing to weight gain during the menopausal transition seems to be a decrease in PAEE.

This study presents some limitations. First, the small sample size and the healthy homogenous population (healthy women with a BMI less than 30 kg/m²) limits the generalizability of our results. However, it is important to mention that 45% of the women aged between 40 to 59 years in the Canadian population present a BMI between 20 and 29 kg/m². Second, women were tested yearly and thus, measurements were not taken exactly 12 months prior, during and 12 months after their final menstrual period. Third, although 67% of the women became postmenopausal by year 5, the relatively short duration of the follow-up, particularly during the postmenopausal period (2 years only), represents another limitation. Finally, we combined women who remained premenopausal (n=4) to those who were in the menopausal transition resulting in the absence of a premenopausal control group. Nonetheless, the prospective design in a very well-characterized cohort of women allows for consideration of within-woman change and is more informative than cross-sectional design. Gold standard measures (DXA) for body composition and objective measures of EE were used. Finally, even if our population consisted of non-obese women, according to their BMI (WHO), 59% had a %BF >30% and 32% had a %BF >35%, which are considered as overweight and obese, respectively, based on norms from the American College of Sports Medicine³⁵.

CONCLUSION

In summary, the present study suggests that menopausal transition is accompanied with a decline in EE mainly characterized by a decrease in PAEE and a shift to a more sedentary lifestyle. Although middle-aged women tend to experience changes in body composition, participation in regular physical activity as they approached and transitioned into menopause may represent a relevant strategy to attenuate the decline in EE and, as a result, the increase in body weight.

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Table 1

Characteristics of the whole sample of subjects at baseline

Variable	n	Value
Age (years)	102	49.9 ± 1.9 (47–55)
Body weight (kg)	102	61.1 ± 6.7 (46.8–79.7)
Waist circumference (cm)	102	78.0 ± 6.6 (62.2–93.7)
BMI (kg/m ²)	102	23.3 ± 2.2 (19.3–28.8)
% Body fat	102	31.3 ± 6.5 (18.2–42.4)
Fat mass (kg)	102	19.2 ± 5.3 (9.6–31.6)
Fat-free mass (kg)	102	41.3 ± 4.5 (27.6–52.9)
REE (kcal/day)	95	1224.1 ± 109.5 (946.0–1460.0)
TEF (kcal/180 min)	93	33.1 ± 8.5 (14.2–66.1)
TEF (%)	93	17.8 ± 3.8 (9.0–30.8)
PAEE (kcal/day)	86	802.4 ± 258.0 (326.3–1904.7)
Time sedentary (min/week)	86	6366.4 ± 746.7 (4601.0–8189.0)
Time moderate (min/week)	86	1598.8 ± 479.4 (628.0–2801.0)
TEE (kcal/day)	85	2249.3 ± 344.5 (1640.4–3662.0)

BMI: body mass index; REE: resting energy expenditure; TEF: thermic effect of food; PAEE: physical activity energy expenditure; Time sedentary: time spent in sedentary physical activity [1–1.5 metabolic equivalents (METs)]; Time moderate: time spent in moderate physical activity (3–6 METs); TEE: total energy expenditure. Values are mean ± SD (all such values).

Table 2

EE variables in response to time and menopausal status at year 5 (Only values at baseline and year 5 are presented)

	Menopausal Transition			Post 12 months		Post > 12 months		Repeated Measures ANOVA P-value		
	Baseline	Year 5	Baseline	Year 5	Baseline	Year 5	Time	Meno	Meno * Time	
n	19	19	14	14	25	25				
REE (kcal/day)	1249.8 ± 115.7	1320.8 ± 145.1*	1222.6 ± 108.1	1213.4 ± 122.5	1213.6 ± 107.7	1232.6 ± 104.8	NS	NS	<0.05	
n	19	19	13	13	24	24				
TEF (kcal/180 min)	31.6 ± 6.8	36.2 ± 9.8*	33.2 ± 6.3	39.2 ± 7.1*	33.2 ± 7.0	33.6 ± 9.2*	<0.01	NS	NS	
TEF (%)	16.8 ± 2.8	18.0 ± 4.4*	17.8 ± 3.0	20.5 ± 3.8*	18.0 ± 3.5	17.8 ± 4.6*	<0.05	NS	NS	
n	12	12	11	11	18	18				
PAEE (kcal/day)	764.5 ± 276.8	890.1 ± 252.1	837.5 ± 259.5	887.7 ± 201.0	940.1 ± 340.7	751.4 ± 314.1*	NS	NS	<0.05	
Time sedentary (min/week)	6376.5 ± 877.8	6219.0 ± 837.7	6103.5 ± 817.1	6271.4 ± 469.8	6244.6 ± 731.0	6875.0 ± 1010.1	NS	NS	NS	
Time moderate (min/week)	1506.8 ± 534.7	1683.5 ± 438.9	1788.1 ± 632.4	1687.9 ± 322.6	1749.8 ± 450.1	1495.3 ± 614.0	NS	NS	NS	
n	10	10	11	11	18	18				
TEE (kcal/day)	2239.8 ± 381.6	2446.9 ± 312.9	2295.0 ± 355.4	2332.2 ± 275.0	2412.2 ± 429.0	2209.9 ± 419.9*	NS	NS	<0.01	

Post 12 months: postmenopausal status 12 months; Post > 12 months: postmenopausal status > 12 months; Meno: menopausal status; EE: energy expenditure; REE: resting EE; TEF: thermic effect of food; PAEE: physical EE; Time sedentary: time spent in sedentary physical activity [1–1.5 metabolic equivalents (METs)]; Time moderate: time spent in moderate physical activity (3–6 METs); TEE: total EE; NS: not significant. Analyses were controlled for fat mass and fat-free mass at year 5. Values are mean ± SD.

* Significant difference over time within menopausal status ($P < 0.05$ by *post hoc* Tukey's test).

Table 3

Changes in EE before and since menopause onset (year 0)

	Years before and since menopause onset						
	-4	-3	-2	-1	0	1	2
n	18	32	48	42	49	28	14
REE (kcal/day)	99.2 ± 6.6	99.3 ± 7.1	100.4 ± 9.8	101.1 ± 8.2	100%	103.0 ± 8.4	107.2 ± 9.6*
n	17	29	44	40	46	27	13
TEF (kcal/180 min)	86.2 ± 19.8*	90.1 ± 23.6*	107.3 ± 51.1	96.5 ± 27.4	100%	111.2 ± 24.2*	107.7 ± 24.6
TEF (%)	89.2 ± 17.7*	93.0 ± 22.7	106.9 ± 44.4	97.3 ± 25.8	100%	107.1 ± 23.7	101.4 ± 23.2
n	16	30	41	36	46	21	12
PAEE (kcal/day)	98.6 ± 29.1	108.2 ± 26.8	104.8 ± 34.5	95.0 ± 29.5	100%	89.5 ± 28.2	96.3 ± 35.8
Time sedentary (min/week)	96.4 ± 10.3	96.9 ± 9.8	100.4 ± 13.2	104.4 ± 13.2*	100%	107.7 ± 12.4*	106.6 ± 13.5
Time moderate (min/week)	110.6 ± 33.1	112.6 ± 26.9*	108.7 ± 36.2	94.7 ± 25.2	100%	90.2 ± 36.6	94.6 ± 26.7
n	16	28	40	36	45	20	12
TEE (kcal/day)	97.9 ± 10.0	100.9 ± 12.5	99.8 ± 13.2	97.6 ± 11.8	100%	95.7 ± 11.0	101.6 ± 12.3

EE: energy expenditure; REE: resting EE; TEF: thermic effect of food; PAEE: physical EE; Time sedentary: time spent in sedentary physical activity [1–1.5 metabolic equivalents (METs)]; Time moderate: time spent in moderate physical activity (3–6 METs); TEE: total EE; Values are mean ± SD for each year expressed as the percent of the values at year 0 (menopausal onset), which was standardized to 100%.

* Significantly different compared to year 0 ($P < 0.05$).