Changes in leptin and peptide YY do not explain the greater than predicted decreases in resting energy expenditure after weight loss

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Abstract:

Context: It is unknown whether leptin and peptide YY (PYY) influence changes in resting energy expenditure (REE), independently of fat mass (FM) and fat-free mass (FFM) in addition to changes in other energy expenditure (EE) components during weight loss.
Objective: The objective of the study was to examine the relationships between leptin, PYY, and body composition with different EE components before and after weight loss and whether changes in leptin and PYY were associated with differences in predicted vs measured REE after the intervention.
Design: This was a randomized controlled design.
Setting: The study was conducted in a laboratory.
Participants: Participants were ninety-three overweight/obese postmenopausal women (aged 58.1 ± 4.8 y; body mass index 32.1 ± 4.3 kg/m^2).
Intervention: Interventions included a 6-month caloric restriction diet alone or caloric restriction diet+resistance training.
Main Outcome Measures: Body composition (dual energy x-ray absorptiometry), REE (indirect calorimetry), total EE (TEE; doubly labeled water), and fasting leptin and total PYY before and after weight loss were measured.
Results: Both interventions yielded significant decreases in weight, FFM, REE, and leptin, whereas a significant time × group interaction was noted for FM (greater decrease in FM in the diet+resistance training group) ($P < .05$ for all outcomes). No significant differences in TEE, physical activity EE, and PYY were noted between baseline and after the intervention. Age, FFM, leptin, and PYY were the best predictors of baseline REE ($R^2 = 0.77$; $P = .0001$), whereas age, FFM, and FM were associated with REE after the intervention ($R^2 = 0.88$; $P = .0001$). The same predictors, except for leptin, were significantly related to TEE at baseline ($R^2 = 0.70$; $P = .0001$) and after the intervention ($R^2 = 0.29$; $P = .0001$), whereas only PYY was a significant

predictor of physical activity EE at baseline and after the intervention. Changes in FM and leptin accounted for 27% of the variance in ΔREE ($P = .0001$). Greater predicted vs measured REE was noted after the intervention ($P = .02$). However, Δ leptin and ΔPYY were not significant predictors of the differences between postintervention measurement and predicted REE. **Conclusions:** Δ Leptin and ΔFM were strong contributors to changes in REE. However, Δ leptin and ΔPYY were not significant predictors of the differences between predicted and measured REE after the intervention.

Keywords: resting energy expenditure | weight loss | leptin | peptide YY

Article:

Abbreviations: CI, confidence interval; EE, energy expenditure; FFM, fat-free mass; FM, fat mass; PAEE, physical activity EE; PYY, peptide YY; REE, resting EE; 1-RM, 1-maximum repetition; TEE, total EE.

Several approaches have been used in an attempt to induce sustainable weight loss in obese individuals. Among them is the combination of caloric restriction and resistance exercise, which can promote weight loss in obese individuals while preserving fat-free mass (FFM) (1, 2). However, a well-documented effect of weight loss is the decrease in resting energy expenditure (REE) (3–5). A recent systematic review reported that the average magnitude in REE reduction is −15.4 kcal/kg of weight loss (4) when assessed during the dynamic phase of weight loss in obese individuals. This review also reported that shorter weight loss trials (duration of 2–6 weeks) and caloric restriction only interventions resulted in greater mean decreases in REE relative to weight loss compared with longer interventions (>6 wk) as well as other types of weight-loss interventions (exercise only, pharmaceutical, surgery, and combination of exercise + caloric restriction) (4). It is often assumed that this reduction in REE is commensurate to changes in weight, presumably because of the strong relationship between body composition and total EE (TEE) (6). However, there is converging evidence that weight reduction may result in greater than predicted decreases in REE during a weight loss intervention (5, 7–14), which may be sustained after the end of the intervention (5, 10, 13, 15, 16). Keys and colleagues (3) were among the first to document significantly greater-than-predicted reductions in REE during the dynamic phase of weight loss, after weight loss, and during weight recovery. These results are further supported by recent findings, reporting greater-than-predicted decreases in REE in response to severe and sustained energy restriction (5, 7) and less stringent weight-loss conditions (8–14), with these decreases lasting up to 6 years after the end of the intervention (13, 15, 16). Leibel et al (10) also demonstrated that decreases in REE were on average 10%–15% greater during the dynamic phase of weight loss vs a 10% weight-loss maintenance period. Collectively, because successful long-term weight loss requires the matching of energy intake to energy expenditure (EE), this implies that even relatively small decreases in REE may predispose weight-reduced individuals to weight regain (5, 8–14). Furthermore, decreases in REE that are greater than that predicted with equations (5, 7–14) may be maintained over time (15, 16), even after weight regain to levels greater than baseline (5).

Given that changes in body mass do not seem to account for all the variance in REE reductions that occur after weight loss (5, 12–16), other factors have been previously investigated. It has been shown that thyroid function and catecholamine excretion (17), as well as changes in leptin (18, 19), among others, provide an independent contribution to changes in energy metabolism

during weight loss. Furthermore, providing obese participants with recombinant leptin after weight loss attenuated some of the disproportionate decline in TEE observed during reduced weight maintenance (20).

Some reports suggest that peptide YY (PYY) might also be related to energy metabolism. Sloth et al (21) were among the first to show that TEE had a tendency to increase after the injection of PYY 3–36. Recent studies have however reported conflicting results; noting positive associations between PYY with postprandial EE (22) and REE (23) and negative associations between PYY and REE (24).

Thus, leptin and PYY are seemingly implicated in fluctuations of REE and TEE. However, it remains to be determined whether PYY is a significant correlate of REE, TEE, and physical activity energy expenditure (PAEE) before and after weight loss. Furthermore, it is unknown whether changes in these peptides influence changes in energy metabolism after weight loss, including the greater-than-predicted decreases in REE. This study assessed the effects of caloric restriction + resistance training and caloric restriction alone interventions on changes in leptin, PYY, and body composition as well as different EE components (REE, TEE, and PAEE). Furthermore, we evaluated the strength of the associations between leptin, PYY and body composition [fat mass (FM) and FFM] with EE components before and after weight loss. We also assessed the strength of the associations between changes in leptin, PYY, and body composition with those of different EE components during the dynamic phase of weight loss. Lastly, we assessed whether changes in REE are greater than predicted and whether changes in leptin and PYY are associated with the potential differences in the predicted vs measured REE postintervention.

Materials and Methods

Participants

Participants were recruited from the Montréal Ottawa New Emerging Team project. Study methodology details can be found in a report by Brochu et al (25). This study was designed to investigate, using a randomized controlled design, the impact of a 6-month caloric restriction and 12-month weight maintenance on the following: 1) metabolic, inflammation, and hormonal profiles, 2) body composition, 3) EE, and 4) psychosocial profiles in overweight/obese postmenopausal women. Participants were recruited through newspaper advertisements, and data were collected from 2003 to 2006. Participants were randomly assigned in a 1:2 fashion to a caloric restriction diet alone or a caloric restriction diet + resistance training because the women who completed the 6-month diet alone were also asked to participate in a 12-month follow-up with or without the resistance training program. The participants who completed all required measurements during the 6-month intervention are presented herein (n = 65 for the diet alone group; n = 28 for the diet + resistance training group). The inclusion criteria, which are published elsewhere (21), were as follows: 1) body mass index 25 kg/m^2 or greater, 2) cessation of menstruation for more than 1 year and an FSH level of 30 IU/L or greater, 3) sedentary (<2 h/wk of structured physical activity), 4) nonsmoker, 5) low to moderate alcohol consumption (fewer than two drinks per day), 6) no known inflammatory disease, and 7) no use of hormone replacement therapy. After a physical examination and biological testing, all participants had no

history or evidence of the following: 1) cardiovascular disease, peripheral vascular disease, or stroke; 2) diabetes (75 g oral glucose tolerance test); 3) known renal and liver disease; 4) asthma requiring therapy or plasma cholesterol greater than 8 mmol/L; 5) systolic and diastolic blood pressures greater than 160 and 100 mm Hg, respectively; 6) history of alcohol or drug abuse; 7) history of inflammation disease or cancer; 8) orthopedic limitations; 9) weight fluctuation of ±2 kg in the last 6 months, 10) untreated thyroid or pituitary disease; and 11) medications that could affect cardiovascular function and/or metabolism. The Université de Montréal Ethics Committee approved the study and informed consent was obtained from all participants.

Caloric restriction intervention

Participants took part in a 6-month weight-loss program aimed at reducing weight by 10%, as previously described (25). For 4 weeks prior to and after the weight-loss intervention, we minimized weight variations within a ±2 kg range, at which time all outcome measurements were performed. To determine the level of caloric restriction, baseline REE was multiplied by a physical activity factor of 1.4, which is equivalent to a sedentary state (26), and 800 kcal was then subtracted from this result (27). However, this caloric restriction was reduced when the calculated daily energy requirements were below 1000 kcal (in these cases, the mean reduction was 633 kcal). Prescribed energy intake during the intervention ranged from 1000 to 1790 kcal. Diet macronutrient composition was standardized to 55%, 30%, and 15% of energy intake from carbohydrates, lipids, and proteins, respectively. Participants met with the study dietitian weekly to review their prescribed diet and dietary recommendations and to discuss compliance throughout the weight-loss trial. During these meetings, the dietitian reviewed the diet restriction with participants and provided them with measures to help adherence to the dietary prescription. Participants were also invited to meet with the dietitian bimonthly for nutritional education classes (60–90 min each). The average rate of participation in these classes were 28.1% ± 30.2% and 29.9% ± 28.8% in the diet only and diet + resistance training groups, respectively [P = NS, as previously reported (25)]. During the weight-loss intervention, participants in the diet only group were instructed not to change their physical activity habits.

Resistance-training intervention

The 6-month resistance-training program included four progressive phases that were performed weekly on 3 nonconsecutive days. Phase 1 included an introduction to training (3 wk, 15 repetitions or ∼65% of maximum, two to three sets per exercise with 90–120 sec between sets), whereas phases 2–4 saw a progressive increase in the intensity and duration of the exercises performed (phase 2: 5 wk, 12 repetitions, or ∼70% of maximum, two to three sets per exercise with 90 sec between sets; phase 3: 9 wk, 8–10 repetitions, or ∼75%–80% of maximum, two to four sets per exercise with 120–180 sec between sets; phase 4: 8 wk, 10–12 repetitions, or ∼70%–75% of maximum, three to four sets per exercise with 60–90 sec between sets). Each training session started with 10 minutes of low-intensity warm-up on the treadmill (ie, walking). The resistance-training program included leg press, chest press, lateral pull-downs, shoulder press, arm curls, and triceps extensions. An exercise physiologist supervised all training sessions, and he/she adjusted the workload, if necessary, to maintain the number of repetitions prescribed. All participants performed a 1-maximum repetition (1-RM) test every 4 weeks to adapt the

workload accordingly. If none of the trials yielded a 1-RM, the Wathan equation was used to extrapolate the 1-RM (28).

Anthropometry

Weight was measured to the nearest 0.1 kg on a calibrated scale (Balance Industrielle Montréal), and height was obtained with a standard stadiometer (Perspective Enterprises). Total FM and FFM were measured using dual-energy x-ray absorptiometry (General Electric Lunar Prodigy; software version 6.10.019). The measured intraclass coefficient correlation of FM and FFM measurements with this technique was 0.99 in 18 volunteers.

Resting energy expenditure

REE was measured after a 12-hour fast by indirect calorimetry for 40 minutes (10 min acclimatization period and 30 min of measurements) while the participants were fasting. Concentrations of CO_2 and O_2 were measured using the ventilated hood technique with a SensorMedics δ Track II (Datex-Ohmeda). The intraclass correlation for REE measured with this technique, which was determined using test-retest conditions, is 0.921 (n = 19).

Physical activity energy expenditure and TEE

TEE was measured over 10 days with the doubly labeled water technique, as previously described (29). PAEE was calculated with the following equation: PAEE = (TEE × 0.90) − REE. PAEE is therefore defined as energy use not related to the energy cost of food ingestion and digestion and to the energy cost of REE.

Calculation of predicted REE after intervention

A stepwise multiple regression analysis was used to determine the best predictors of baseline REE in this cohort. The independent predictors entered into the model were age, FM, FFM, height, leptin, and PYY at baseline. FFM, age, leptin, and PYY met the entry criteria of $P \leq .05$ and were used to compute the following equation: REE (kilocalories per day) = 485.08 + (23.18*FFM) + (−6.35*age) + (2.14*leptin) + (0.70*PYY), with an R^2 of 76.8% and a SE of the estimate of 94 kcal/d. This equation was then used to predict REE after the intervention. The calculated mean REE with this equation at baseline was essentially the same as that measured at baseline (REE: 1312 ± 191 vs 1312 ± 168 kcal/d; $P = 1.00$), thus indicating a strong validity of this equation to estimate REE after intervention.

Calculation of compliance to the caloric restriction intervention and energy imbalance

A ratio between expected and actual changes in body energy stores was calculated. As such, compliance was calculated based on the prescribed caloric restriction at baseline, but was adjusted for changes in TEE, measured with doubly labeled water, at baseline and after the intervention [ie, ([TEE with doubly labeled water (baseline) − prescribed energy intake (baseline)] + [TEE with doubly labeled water (after intervention) − prescribed energy intake (baseline)]/2)*180 d]. We then divided actual changes in body energy stores using equivalents of

9400 kcal/kg of FM loss and 1200 kcal/kg of FFM loss (14) by the total calculated energy deficit. The average daily energy imbalance was also determined by multiplying the change in FM and FFM by their respective energy densities of 9400 and 1200 kcal/kg (14) and then divided by the number of days of the intervention (180 d).

Blood sampling

Venous blood samples were collected to measure fasting total PYY and fasting leptin levels. An iv catheter was inserted into an antecubital vein of the nondominant arm. All samples were placed into tubes containing EDTA. Blood samples were then centrifuged at 3500 rpm at 4°C and stored at −80°C until assayed. Leptin and total PYY (includes both PYY 1–36 and 3–36) were assayed in duplicates with commercially available ELISA kits [human leptin ELISA kit-EZHL-80SK and human PYY (total) ELISA kit-EZHPYYT-66K; Millipore Corp]. In our laboratory, the intrakit coefficient of variation for leptin and PYY were 3.4% and 7.1%, respectively. All samples for every participant were assayed using the same kit.

Statistical analyses

Statistical analyses were performed using SPSS (version 17.0; SPSS Inc). Repeated-measures ANOVA with intervention (diet only or diet + resistance training) as the between-subject variable evaluated changes between baseline and postintervention values for FM, FFM, REE, TEE, PAEE, leptin, and PYY as well as the differences between predicted and measured REE after the intervention. Secondary analyses of these same outcomes corrected for the degree of caloric restriction were also performed. Pearson correlations were performed between body composition and hormone variables with EE components at baseline and postintervention as well as between the changes in these variables of interest. Forward stepwise linear regressions were then used to determine the overall contribution of age, height, FM, FFM, leptin, and PYY to REE, PAEE, and TEE at baseline and after the intervention as well as the contribution of ΔFM, ΔFFM, Δ leptin, and ΔPYY to ΔREE, ΔPAEE, and ΔTEE in response to the intervention. Effects were considered significant at $P < .05$ and data are presented as mean ± SD.

Results

Participant characteristics prior to and after weight loss are presented in Table 1. Both interventions yielded significant decreases in weight and FFM, whereas a significant time × group interaction was noted for FM (ie, greater decrease in FM in the diet + resistance training group) (25). The interventions also led to significant decreases in REE in both groups, whereas no significant differences in TEE and PAEE were noted (27). Fasting absolute (nanograms per milliliter) and relative (nanograms per milliliter per kilogram of fat mass) leptin levels were significantly lower after the intervention compared with baseline, whereas no significant differences in fasting PYY levels were noted between baseline and after the intervention. Fasting PYY was, however, greater in the diet + resistance training group compared with the diet only group, independently of the intervention time. After correcting for the degree of caloric restriction, the changes in weight, FFM, leptin, and REE were no longer significant, which is supported by significant interactions between these outcomes and the degree of caloric restriction ($P < .05$ for all outcomes). Correlational analyses further support these results, in which

significant associations were noted between Δweight (r = −0.23; P = .03), ΔFFM (r = −0.23; P = .02), Δ leptin (r = −0.21; P = .04), and ΔREE (r = −0.25; P = .02) with the degree of caloric restriction. The calculated compliance to the caloric restriction for the entire intervention was 19% and was positively associated with ΔREE (r = 0.49, P < .0001) and Δweight (r = 0.85, P < .0001). Additionally, the magnitude of energy imbalance was related to ΔREE (r = 0.49, P < .0001) and Δweight (r = 0.9, P < .0001). Baseline fasting leptin and PYY were associated with Δweight (leptin: r = 0.27; P = .01; PYY: r = −0.21; P = .05) and ΔFFM (leptin: r = 0.39; P = .0001; PYY: r = −0.26; P = .01). Δ leptin was also associated with Δweight (r = 0.64; P = .0001), ΔFM (r = 0.64; P = .0001) and ΔFFM (r = 0.21; P = .04), whereas no significant associations were observed between ΔPYY with changes in weight or body composition (results not shown).

Table 1. Participants Characteristics Assessed at Baseline and After the Weight-Loss Intervention According to Intervention Group (Caloric Restriction Only, n = 65; Caloric Restriction + Resistance Training, n = 28)

	Baseline	After Intervention	Mean Difference
Body weight, kg[a,b]			
Caloric restriction only	83.5 (14.5)	78.6 (13.8)	−4.8 (4.6)
Caloric restriction + resistance training	81.5 (11.2)	74.8 (10.9)	−6.7 (4.5)
FM, kg[a,c]			
Caloric restriction only	37.8 (8.8)	33.9 (9.2)	−3.9 (3.6)
Caloric restriction + resistance training	37.9 (7.3)	31.8 (8.1)	−6.1 (4.1)
FFM, kg[a,b]			
Caloric restriction only	45.6 (7.3)	44.7 (6.2)	−0.9 (2.4)
Caloric restriction + resistance training	43.6 (5.5)	43.0 (4.2)	−0.5 (2.3)
REE, kcal/d[b,d]			
Caloric restriction only	1318 (208)	1262 (206)	−56 (92) or −11.4 (20.2) kcal/kg of weight loss
Caloric restriction + resistance training	1298 (146)	1230 (154)	−67 (110) or−10.1 (24.4) kcal/kg of weight loss
TEE, kcal/d[d]			
Caloric restriction only	2475 (380)	2408 (368)	−67 (364) or−13.7 (79.1) kcal/kg of weight loss
Caloric restriction + resistance training	2528 (366)	2412 (339)	−117 (331) or−17.3 (73.6) kcal/kg of weight loss
PAEE, kcal/d[d]			
Caloric restriction only	909 (281)	905 (293)	−4 (334) or−0.8 (72.6) kcal/kg of weight loss
Caloric restriction + resistance training	978 (242)	940 (272)	−38 (301) or−5.7 (66.9) kcal/kg of weight loss
Leptin, ng/mL[b]			
Caloric restriction only	38.7 (17.0)	31.2 (16.7)	−7.4 (13.3)
Caloric restriction + resistance training	35.1 (13.5)	24.8 (16.2)	−10.3 (12.2)
Leptin, ng/ml · kg of fat mass[b]			
Caloric restriction only	1.0 (0.3)	0.9 (0.4)	−0.1 (0.3)
Caloric restriction + resistance training	0.9 (0.3)	0.7 (0.4)	−0.2 (0.3)
PYY, pg/mL[e]			
Caloric restriction only	96.2 (47.6)	100.9 (51.0)	4.7 (31.5)
Caloric restriction + resistance training	120.2 (38.6)	124.5 (36.1)	4.4 (31.4)

Values are expressed as means (SD).

[a] Data are adapted from Brochu et al (25).

[b] Significant difference between baseline and after the intervention (P < .05).

[c] Significant time × group interaction (P < .05).

[d] Data are adapted from St Onge et al (27).

[e] Significant difference between intervention groups (P < .05).

Table 2 presents the correlations between body composition and hormone variables with EE components. REE and TEE were positively correlated with FM, FFM, and leptin at baseline and after the intervention. TEE was also negatively associated with PYY at baseline and after the intervention. PAEE was positively associated with FM at baseline and negatively associated with PYY at both baseline and after the intervention.

Table 2. Correlations Between Body Composition Variables, Leptin, and PYY With EE Components

	FM, kg	FFM, kg	Leptin, ng/mL	PYY, pg/mL
REE				
Baseline	r = 0.61; *P* = .0001	r = 0.84; *P* = .0001	r = 0.41; *P* = .0001	r = −0.05; *P* = .64
After intervention	r = 0.67; *P* = .0001	r = 0.83; *P* = .0001	r = 0.40; *P* = .0001	r = 0.02; *P* = .83
TEE				
Baseline	r = 0.52; *P* = .0001	r = 0.56; *P* = .0001	r = 0.40; *P* = .0001	r = −0.37; *P* = .0001
After intervention	r = 0.41; *P* = .0001	r = 0.43; *P* = .0001	r = 0.22; *P* = .04	r = 0.25; *P* = .02
PAEE				
Baseline	r = 0.22; *P* = .04	r = 0.10; *P* = .34	r = 0.21; *P* = .05	r = −0.42; *P* = .0001
After intervention	r = 0.01; *P* = .92	r = −0.07; *P* = .50	r = −0.02; *P* = .84	r = −0.29; *P* = .004

Table 3 presents the significant independent predictors of REE, TEE, and PAEE at baseline and after the intervention. The combination of age, FFM, leptin, and PYY was the best predictor of baseline REE, whereas the combination of age, FFM, and FM predicted the greatest amount of variance in REE after the intervention. The combination of age, FFM, FM, and PYY was the best predictor of baseline TEE, whereas age, PYY, and FFM were significant predictors of this variable after weight loss. Age and PYY were significant predictors of PAEE at baseline, whereas only PYY was a significant predictor of PAEE after the intervention.

Significant associations were noted between ΔREE with ΔFM (r = 0.48; *P* = .0001) and Δ leptin (r = 0.47; *P* = .0001). These results are further supported by regression analyses, suggesting that the combination of ΔFM and Δ leptin accounted for approximately 27% of the variance in ΔREE [R^2 = 0.27; β = 7.69; 95% confidence interval (CI) 1.8–13.5 for FM and β = 2.04; 95% CI 0.3–3.8 for leptin; *P* = .0001]. ΔFFM was significantly correlated with ΔTEE (r = 0.24; *P* = .02) and was the only variable found to be a significant predictor of ΔTEE (R^2 = 0.06; β = 35.23; 95% CI 5.4–65.0 *P* = .02). Changes in none of the variables were significantly associated with ΔPAEE (results not shown).

Significantly greater predicted vs measured REE values were observed after weight loss (Figure 1). This significant effect disappeared after correcting for the degree of caloric restriction. The degree of energy restriction was positively associated with the difference between predicted and measured REE postintervention (r = 0.30; *P* = .004), thus suggesting that participants with the greatest degree of energy restriction had greater decreases in their actual REE, compared with predicted values postintervention. However, the calculated compliance to the energy restriction (r = 0.03, *P* = .77) and energy imbalance (r = 0.04; *P* = .66) were not associated with greater-than-predicted decreases in REE. Lastly, Δ leptin and ΔPYY were not associated with the differences between postintervention measured and predicted REE (leptin: R^2 = 0.00; β = .07; 95% CI −1.4–1.6; *P* = .93; PYY: R^2 = 0.01; β = −.27; 95% CI −0.9–0.4; *P* = .40).

Table 3. The Amount of Variance (R^2) and the Standardized Regression Coefficient (β) for the Significant Predictors of REE, TEE, and PAEE at Baseline and After Weight Loss (n = 93)

Dependent Variable	Model	Significant Predictor(s)	R^2	β	95% CI for β
Baseline REE	1	FFM	0.70	.84[a]	20.2–26.6
	2	FFM+	0.73	.85[a]	20.8–27.0
		Age		−.16[b]	−10.9 to−2.1
	3	FFM+	0.74	.81[a]	19.4–25.8
		Age+		−.15[b]	−10.2 to−1.6
		Leptin		.14[c]	0.3–3.0
	4	FFM+	0.77	.83[a]	20.1–26.3
		Age+		−.16[b]	−10.5 to−2.2
		Leptin+		.18[b]	0.8–3.5
		PYY		.17[b]	0.26–1.1
Baseline PAEE	1	PYY	0.18	−.42[a]	−3.6 to−1.4
	2	PYY+	0.22	−.41[a]	−3.5 to−1.3
		Age		−.21[c]	−22.3 to−1.5
Baseline TEE	1	FFM	0.31	.56[a]	20.9–39.9
	2	FFM+	0.39	.59[a]	23.1–41.1
		Age		−.29[b]	−35.6 to−10.1
	3	FFM+	0.45	.54[a]	20.6–38.2
		Age+		−.27[b]	−33.5 to−9.0
		PYY		−.25[b]	−3.3 to−0.7
	4	FFM+	0.48	.41[a]	11.8–32.8
		Age+		−.24[b]	−31.1 to−6.9
		PYY+		−.23[b]	−3.1 to−0.6
		FM		.22[c]	1.4–18.4
Post-weight-loss REE	1	FFM	0.70	.83[a]	24.0–31.7
	2	FFM+	0.76	.67[a]	18.1–26.5
		FM		.30[a]	3.7–9.1
	3	FFM+	0.78	.71[a]	19.7–27.8
		FM+		.27[a]	3.2–8.4
		Age		−.16[b]	−10.4 to−2.4
Post-weight-loss PAEE	1	PYY	0.09	−.29[b]	−2.9 to −0.6
Post-weight-loss TEE	1	FFM	0.19	.43[a]	15.4–38.8
	2	FFM+	0.25	.48[a]	18.2–41.1
		Age		−.25[b]	−32.1 to −4.8
	3	FFM+	0.29	.46[a]	17.4–39.9
		Age+		−.23[c]	−30.8 to −3.9
		PYY		−.20[c]	−2.8 to −0.2

[a] $P < .001$.
[b] $P < .01$.
[c] $P < .05$.

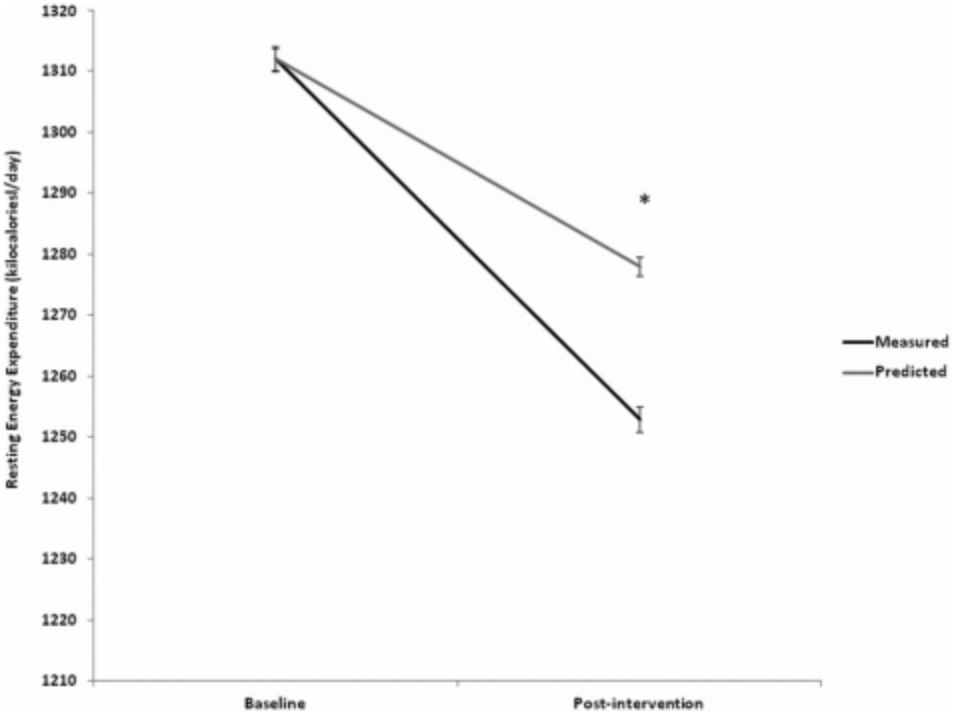

Figure 1. Measured and predicted REE at baseline and after the intervention.
Values are presented as means for 93 participants with SEM represented by vertical bars. *, $P = .02$.

Discussion

This is the first study to include all components of EE (REE, TEE, and PAEE), which were objectively assessed with gold standard measurements before and after weight loss using two different interventions in obese postmenopausal women. Furthermore, this study assessed the potential predictors of these components of EE before, during, and after weight loss. Our results indicate that age, FFM, leptin, and PYY were the best predictors of baseline REE, whereas age, FFM, and FM predicted the greatest amount of variance in REE after intervention. These same predictors, except for leptin, were significantly related to TEE at baseline and after the intervention, whereas only PYY was a significant predictor of PAEE at both baseline and after the intervention. Additionally, ΔFM and Δ leptin were strong contributors to ΔREE. However, Δ leptin and ΔPYY were not significant predictors of the greater-than-predicted decrease in REE after weight loss.

The reduction in leptin adjusted for changes in FM after both interventions in the present study are similar to those previously reported by Doucet et al (18) after weight loss in obese men and women as well as that reported by Rosenbaum et al (30) after weight loss in normal-weight and obese women. Additionally, baseline leptin was negatively associated with Δweight and ΔFFM, which contrasts other studies that reported negative associations between baseline leptin with Δweight and ΔFM (31, 32). It is possible that interindividual factors, which impact leptin levels (eg, age, menopausal status, sex), may in part explain these differences in results.

The combination of Δ leptin and ΔFM were the best predictors of ΔREE during weight loss (~27% of the variance explained). These results extend previous findings (18), indicating that Δ

leptin was the best predictor of REE changes in men, whereas ΔFM was the strongest predictor of ΔREE in women. These significant associations may also in part explain the decrease in REE, which occurred in both intervention groups because all participants had similar decreases in weight, independently of the intervention.

The present study also noted greater predicted vs measured REE after weight loss, which concurs with previous findings (5, 7–14). This metabolic adaptation was affected by the degree of caloric restriction, in which participants with the greatest prescribed caloric restriction saw greater decreases in their measured vs predicted REE after the intervention. However, compliance to the prescribed caloric restriction and energy imbalance, which were calculated based on actual changes in energy reserves, were not associated with this greater-than-predicted decrease in REE. Doucet et al (8) noted that Δ leptin was significantly related to the difference between measured and net predicted exercise EE (ie, difference between sitting and exercise EE) in men after weight loss, whereas the present study noted no such association between Δ leptin and differences in postintervention measured vs predicted REE. A recent study by Knuth et al (14) reported no significant associations between residual leptin changes and the degree of metabolic adaptation after weight loss, despite noting significant correlations between the degree of metabolic adaptation with Δ leptin and the degree of average energy imbalance. It may be hypothesized that changes in leptin may in part contribute to changes in REE during weight loss but that other factors, including the degree of caloric restriction and energy imbalance, may also be partly responsible for explaining the greater-than-predicted changes in REE (3, 5, 14).

Even though Δ leptin was found to be a significant predictor of ΔREE during weight loss, our results indicate that age, FFM, and PYY, in addition to leptin, significantly predicted REE at baseline, whereas FFM, FM, and age better predicted the variance observed in REE after weight loss. Additionally, leptin was not associated with TEE and PAEE at baseline and after the intervention. These results indicate that the short-term depression of REE during the dynamic phase of weight loss may be in part mediated by changes in leptin, whereas weight maintenance may be more so influenced by the depletion of energy stores and age. However, much of the variance, especially for TEE and PAEE, remains unexplained by the predictors measured in the present study. Hence, more studies are needed to evaluate other potential factors that could be related to different EE components at baseline, during and after weight loss.

Factors other than those measured in the present study have been shown to modulate REE changes during weight loss. One such example is the effect of sympathetic nervous system activity and catecholamine changes on decreased REE and TEE after weight loss (17, 33, 34). Decreases in 24-hour noradrenalin excretion during a 3-week low-energy diet have been previously reported (34). This decrease may play an important role in weight loss as the use of sympathomimetics in combination with a weight-loss regimen yielded greater decreases in FM in addition to lower depressions of REE after the intervention (35). Rosenbaum et al (17) also noted that changes in catecholamine excretion explained approximately 25%–40% of changes in TEE and REE after weight loss and that significant reductions in T_3 release occurred in response to weight loss. Additionally, Johannsen et al (12) noted a significant association between changes in TSH levels and the degree of metabolic adaptation associated with weight loss (ie, greater increases in TSH were associated with the smallest metabolic adaptations to weight loss). Hence, the effects of the sympathetic nervous system and thyroid hormones, in addition to leptin, should

be taken into consideration when aiming to determine the factors involved in predicting changes of REE and TEE during weight loss. Another factor that may influence EE changes during weight loss is the potential decrease seen in REE as a result of the decreased size and energy metabolism of individual organs (36). However, it seems that after accounting for changes in FM, FFM, and organ EE, approximately 40% of the decrease in REE is not accounted for by organ and tissue mass (37). Other biological factors thus most likely contribute to the greater-than-predicted changes in REE and TEE that result from weight loss, which may be the result of an adaptive response of physiological mediators that have adjusted to feast-famine cycles throughout human evolution (38).

PYY was found to be a significant, negative predictor of REE at baseline and was the only endocrine factor measured in the present study that was correlated with TEE and PAEE at baseline and after the intervention. There is evidence to show that PYY exerts influence over various components of EE (21–24). More specifically, cross-sectional analyses showed that fasting PYY is negatively associated with REE in normal-weight and obese men and women (24), whereas Hill et al (23) observed a positive association between 24-hour mean PYY and REE in normal-weight, premenopausal women. However, neither of these studies reported significant associations between PYY and TEE (23, 24). Doucet et al (22) reported that total postprandial PYY was a correlate of postprandial EE in weight-stable, premenopausal women. Furthermore, the infusion of PYY 3–36 showed a tendency ($P = .06$) to increase TEE, compared with the infusion of a saline solution or PYY 1–36 in weight-stable men (21). There is a possibility that if PYY does affect REE and TEE, these changes may be partially due to the action of PYY on neuropeptide Y (39). PYY 3–36 binds to specific receptors, including Y5 receptors in neuropeptide Y, located within the nuclei of the hypothalamus (40). The intracervical infusion of Y5 agonists in rats has been associated with reductions in oxygen consumption and TEE (39). Taken together, results from the present study add to those previously reported, suggesting that PYY is a predictor of REE, TEE, and PAEE prior to and after weight loss. However, more work is needed in humans to garner an understanding as to how PYY affects these components of EE.

The present findings are limited to a sample of postmenopausal women, which limits generalizability to other populations. Only fasting PYY and fasting leptin concentrations were measured in our participants. The EE measurements prior to and after the intervention may not account for the actual energy cost of exercising, which may translate into slight increases in REE due to increased energy requirements for recovery (41). The compliance equation used assumes a linear decrease in TEE from baseline to postintervention, which may not be the case. Furthermore, a potential drift in weight of ±2 kg during the time of measurements could compromise certain metabolic measurements, including REE. However, studies (5, 13) have shown that metabolic adaptation seems to persist after weight loss and this even when participants regained the weight lost. Hence, participants in the present study would most likely still be displaying lower-than-predicted REE values, even if weight may have fluctuated during this period. Lastly, the correlations computed between different variables cannot infer causality.

In conclusion, leptin and PYY were significant correlates only of baseline REE, whereas age and bodily tissues explained most of the variance in REE after the intervention. PYY was significantly associated with TEE and PAEE at baseline and after the intervention. ΔFM and Δ

leptin were strongly correlated with ΔREE. However, Δ leptin and ΔPYY were not significant predictors of the greater-than-predicted decrease in REE after the intervention. These novel results suggest that we cannot exclude the possibility that other biological factors in addition to leptin may account for the greater-than-predicted decreases in REE observed after weight loss. More studies are needed to explore different underlying biological factors, which may contribute to the variance in different EE components at baseline, during and after weight loss as well as explain the greater-than-predicted adaptive responses to weight loss.

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References

1. Hunter GR, Byrne NM, Sirikul B, et al. . Resistance training conserves fat-free mass and resting energy expenditure following weight loss. Obesity (Silver Spring). 2008;16:1045–1051.
2. Jakicic JM, Clark K, Coleman E, et al. . American College of Sports Medicine position stand. Appropriate intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc. 2001;33:2145–2156.
3. Keys A, Brozek J, Henschel A. The Biology of Human Starvation. St Paul: North Central Publishing; 1950.
4. Schwartz A, Doucet E. Relative changes in resting energy expenditure during weight loss: a systematic review. Obes Rev. 2010;11:531–547.
5. Dulloo AG, Jacquet J. Adaptive reduction in basal metabolic rate in response to food deprivation in humans: a role for feedback signals from fat stores. Am J Clin Nutr. 1998;68:599–606.
6. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. J Clin Invest. 1986;78:1568–1578.
7. Weyer C, Walford RL, Harper IT, et al. . Energy metabolism after 2 y of energy restriction: the biosphere 2 experiment. Am J Clin Nutr. 2000;72:946–953.

8. Doucet E, Imbeault P, St Pierre S, et al. . Greater than predicted decrease in energy expenditure during exercise after body weight loss in obese men. Clin Sci (Lond). 2003;105:89–95.

9. Doucet E, St Pierre S, Almeras N, Despres JP, Bouchard C, Tremblay A. Evidence for the existence of adaptive thermogenesis during weight loss. Br J Nutr. 2001;85:715–723.

10. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332:621–628.

11. Miller DS, Parsonage S. Resistance to slimming: adaptation or illusion? Lancet. 1975;1:773–775.

12. Johannsen DL, Knuth ND, Huizenga R, Rood JC, Ravussin E, Hall KD. Metabolic slowing with massive weight loss despite preservation of fat-free mass. J Clin Endocrinol Metab. 2012;97:2489–2496.

13. Camps SG, Verhoef SP, Westerterp KR. Weight loss, weight maintenance, and adaptive thermogenesis. Am J Clin Nutr. 2013;97:990–994.

14. Knuth ND, Johannsen DL, Tamboli RA, et al. . Metabolic adaptation following massive weight loss is related to the degree of energy imbalance and changes in circulating leptin. Obesity. (Silver Spring) 2014;XXX.

15. Astrup A, Gotzsche PC, van de Werken K, et al. . Meta-analysis of resting metabolic rate in formerly obese subjects. Am J Clin Nutr. 1999;69:1117–1122.

16. Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr. 2008;88:906–912.

17. Rosenbaum M, Hirsch J, Murphy E, Leibel RL. Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. Am J Clin Nutr. 2000;71:1421–1432.

18. Doucet E, St Pierre S, Almeras N, Mauriege P, Richard D, Tremblay A. Changes in energy expenditure and substrate oxidation resulting from weight loss in obese men and women: is there an important contribution of leptin? J Clin Endocrinol Metab. 2000;85:1550–1556.

19. Verdich C, Toubro S, Buemann B, et al. . Leptin levels are associated with fat oxidation and dietary-induced weight loss in obesity. Obes Res. 2001;9:452–461.

20. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. J Clin Endocrinol Metab. 2002;87:2391–2394.

21. Sloth B, Holst JJ, Flint A, Gregersen NT, Astrup A. Effects of PYY1–36 and PYY3–36 on appetite, energy intake, energy expenditure, glucose and fat metabolism in obese and lean subjects. Am J Physiol Endocrinol Metab. 2007;292:E1062–E1068.

22. Doucet E, Laviolette M, Imbeault P, Strychar I, Rabasa-Lhoret R, Prud'homme D. Total peptide YY is a correlate of postprandial energy expenditure but not of appetite or energy intake in healthy women. Metabolism. 2008;57:1458–1464.

23. Hill BR, De Souza MJ, Williams NI. Characterization of the diurnal rhythm of peptide YY and its association with energy balance parameters in normal-weight premenopausal women. Am J Physiol Endocrinol Metab. 2011;301:E409–E415.

24. Guo Y, Ma L, Enriori PJ, et al. . Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. Obesity (Silver Spring). 2006;14:1562–1570.

25. Brochu M, Malita MF, Messier V, et al. . Resistance training does not contribute to improving the metabolic profile after a 6-month weight loss program in overweight and obese postmenopausal women. J Clin Endocrinol Metab. 2009;94:3226–3233.

26. Tremblay A, Pelletier C, Doucet E, Imbeault P. Thermogenesis and weight loss in obese individuals: a primary association with organochlorine pollution. Int J Obes Relat Metab Disord. 2004;28:936–939.

27. St Onge M, Rabasa-Lhoret R, Strychar I, Faraj M, Doucet E, Lavoie JM. Impact of energy restriction with or without resistance training on energy metabolism in overweight and obese postmenopausal women: a Montreal Ottawa New Emerging Team group study. Menopause. 2013;20:194–201.

28. Karelis AD, Tousignant B, Nantel J, et al. . Association of insulin sensitivity and muscle strength in overweight and obese sedentary postmenopausal women. Appl Physiol Nutr Metab. 2007;32:297–301.

29. St Onge M, Mignault D, Allison DB, Rabasa-Lhoret R. Evaluation of a portable device to measure daily energy expenditure in free-living adults. Am J Clin Nutr. 2007;85:742–749.

30. Rosenbaum M, Nicolson M, Hirsch J, Murphy E, Chu F, Leibel RL. Effects of weight change on plasma leptin concentrations and energy expenditure. J Clin Endocrinol Metab. 1997;82:3647–3654.

31. Labayen I, Ortega FB, Ruiz JR, Lasa A, Simon E, Margareto J. Role of baseline leptin and ghrelin levels on body weight and fat mass changes after an energy-restricted diet intervention in obese women: effects on energy metabolism. J Clin Endocrinol Metab. 2011;96:E996–E1000.

32. Shih LY, Liou TH, Chao JC, et al. . Leptin, superoxide dismutase, and weight loss: initial leptin predicts weight loss. Obesity (Silver Spring). 2006;14:2184–2192.

33. Dulloo AG, Jacquet J. An adipose-specific control of thermogenesis in body weight regulation. Int J Obes Relat Metab Disord. 25(suppl 2001);5:S22–S29.

34. Menozzi R, Bondi M, Baldini A, Venneri MG, Velardo A, Del Rio G. Resting metabolic rate, fat-free mass and catecholamine excretion during weight loss in female obese patients. Br J Nutr. 2000;84:515–520.

35. Astrup A, Buemann B, Christensen NJ, et al. . The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. Metabolism. 1992;41:686–688.

36. Elias M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, eds. Energy Metabolism: Tissue Determinants and Cellular Corollaries. New York: Raven Press; 1991:61–80.

37. Bosy-Westphal A, Kossel E, Goele K, et al. . Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure. Am J Clin Nutr. 2009;90:993–1001.

38. Prentice AM. Starvation in humans: evolutionary background and contemporary implications. Mech Ageing Dev. 2005;126:976–981.

39. Hwa JJ, Witten MB, Williams P, et al. . Activation of the NPY Y5 receptor regulates both feeding and energy expenditure. Am J Physiol. 1999;277:R1428–R1434.

40. Keire DA, Bowers CW, Solomon TE, Reeve JR Jr. Structure and receptor binding of PYY analogs. Peptides. 2002;23:305–321.

41. Melby C, Scholl C, Edwards G, Bullough R. Effect of acute resistance exercise on postexercise energy expenditure and resting metabolic rate. J Appl Physiol (1985). 1993;75:1847–1853.