Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? An examination of the set-point theory[1–3]

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ABSTRACT

Background: Obese persons generally regain lost weight, suggesting that adaptive metabolic changes favor return to a preset weight.

Objective: Our objective was to determine whether adaptive changes in resting metabolic rate (RMR) and thyroid hormones occur in weight-reduced persons, predisposing them to long-term weight gain.

Design: Twenty-four overweight, postmenopausal women were studied at a clinical research center in four 10-d study phases: the overweight state (phase 1, energy balance; phase 2, 3350 kJ/d) and after reduction to a normal-weight state (phase 3, 3350 kJ/d; phase 4, energy balance). Weight-reduced women were matched with 24 never-overweight control subjects. After each study phase, assessments included RMR (by indirect calorimetry), body composition (by hydrostatic weighing), serum triiodothyronine (T_3), and reverse T_3 (rT_3). Body weight was measured 4 y later, without intervention.

Results: Body composition–adjusted RMR and T_3:rT_3 fell during acute (phase 2) and chronic (phase 3) energy restriction ($P < 0.01$), but returned to baseline in the normal-weight, energy-balanced state (phase 4; mean weight loss: 12.9 ± 2.0 kg). RMR among weight-reduced women (4771 ± 414 kJ/d) was not significantly different from that in control subjects (4955 ± 414 kJ/d; $P = 0.14$), and lower RMR did not predict greater 4-y weight regain ($r = 0.27$, NS).

Conclusions: Energy restriction produces a transient hypothyroid-hypometabolic state that normalizes on return to energy-balanced conditions. Failure to establish energy balance after weight loss gives the misleading impression that weight-reduced persons are energy conservative and predisposed to weight regain. Our findings do not provide evidence in support of adaptive metabolic changes as an explanation for the tendency of weight-reduced persons to regain weight. *Am J Clin Nutr* 2000;72:1088–94.

KEY WORDS Overweight, obesity, weight loss, body composition, thyroid hormones, energy expenditure, metabolic rate, set-point theory, postmenopausal women

INTRODUCTION

Observations that obese persons tend to regain lost weight have raised suspicion that metabolic factors are important contributors to body weight regulation. The resultant set-point theory holds that the body has a homeostatic feedback system for controlling its fat stores. Homeostatic mechanisms include an adaptation in the energy efficiency of metabolic processes, making them more or less wasteful, as needed, to maintain fixed fat stores and body weight (1). The notion that weight regain may be due to such an adaptive down-regulation in resting metabolic rate (RMR) after weight loss has prompted controversy and different interpretations of the same data (2).

Support for the concept that variations in RMR contribute to weight gain comes from several reports. Pima Indians with a low RMR relative to their body size were found to have greater weight gain than others with normal RMRs (3). In a recent review of studies of obese persons who underwent weight loss, Astrup et al (4) concluded that weight-reduced persons have an RMR that is lower than that in lean control subjects. In metabolic ward studies, the data of Leibel et al (5) suggested that weight loss and weight gain result in adaptive changes in RMR that serve to return individuals to their previous body weight. By contrast, others found no evidence that RMR differs between obesity-prone and obesity-resistant individuals (6). Two studies examined individuals who reported that they suffered from diet-resistant obesity, potentially because of an abnormally low RMR, although no evidence was found for alterations in metabolic efficiency (7, 8).

The purpose of this report was to examine the distinct effects of energy restriction compared with those of weight loss on the possible down-regulation of thyroid hormones and RMR, which might favor weight regain. Data reported herein are selected from a larger data set of analyses of hemodynamic and metabolic effects of weight loss and regain in 48 women who were

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studied extensively. Hence, previous reports have been published on selected aspects of these studies, including changes in hemodynamics (9), energy expenditure and substrate utilization (10, 11), serum leptin concentrations (12), and blood pressure and lipids (13, 14). This paper provides new data analyses on body composition–adjusted changes in RMR and concurrent changes in thyroid hormones that occurred throughout 4 consecutive study phases, including energy balance in the overweight state, early energy restriction, sustained energy restriction after normalization of body weight, and return to energy balance in the normal-weight state. These new analyses are included with some previously reported data on comparisons of weight-reduced women with control subjects and on 4-y follow-up (11, 14) for the sake of a more complete and coherent examination of the question: Is there evidence to support the set-point theory of metabolic regulation of body weight?

SUBJECTS AND METHODS

Subjects

Subjects included 24 overweight women and 24 never-overweight control subjects. The overweight women were between the ages of 49 and 67 y. The control subjects were between the ages of 46 and 66 y. All were postmenopausal. The overweight women were selected to have an initial body mass index (BMI; in kg/m^2) between 25 and 30, placing them in the overweight category (15). This BMI range was chosen to increase the likelihood that the women could lose ≥10 kg and reach a normal body weight (BMI: 19–25) within a reasonable time frame. All overweight women had a family history of overweight or obesity in ≥1 first-degree relative, increasing the likelihood that they had a familial, as well as a personal, predisposition to obesity. After reduction to a normal body weight, the 24 weight-reduced women were pair-matched with respect to fat-free mass (FFM; ±5 kg), fat mass (FM; ±5 kg), and age (±5y) with 24 never-overweight women (BMI < 25) who had no family history of overweight or obesity.

All women were white except for one who was of Japanese descent. Subjects were nonsmokers and were not taking medications known to affect metabolic rate, fuel utilization, heart rate, or thyroid status. Normal glucose tolerance was documented by fasting and 2-h postprandial blood glucose concentrations after an oral glucose load. Institutional Review Board approval was received for the study, and all subjects provided informed consent.

Study design

For the overweight women, the study entailed 4 study phases during 2 General Clinical Research Center (GCRC) admissions: two 10-d phases in the overweight state and two 10-d phases in the reduced, normal-weight state. Just before the first admission, subjects were provided a macronutrient-controlled diet for 2 wk from the GCRC and energy intake was adjusted until weight variation was <1% on ≥5 consecutive occasions, usually over ≈10 d. Subjects were then admitted to the GCRC and maintained in energy balance for another 10 d (phase 1) before being started on a 3350-kJ(800 kcal)/d diet for 10 d (phase 2). They were discharged and followed as outpatients of the GCRC and continued to consume the 3350-kJ/d diet until they achieved the study goals of losing a minimum of 10 kg and reaching a BMI < 25. All 24 women successfully reached these goals and completed the 4 phases of study. Although the women were relatively sedentary, physical activity was restricted throughout the study to usual walking and to occasional, nonintensive recreational activities.

During the ambulatory period of weight reduction, the women received all of their meals through the GCRC research kitchen. They were seen twice weekly by the GCRC dietitian (BD), who measured body weight, monitored dietary adherence, and provided meals until the next visit. During all study phases (inpatient and outpatient, energy balance and energy restriction), meals consisted of foods prepared by the research kitchen, except for frozen entrées (Stouffer's Lean Cuisine; Nestlé Food Co, Solon, OH) at lunch and dinner. Meal composition was ≈64% carbohydrate, 14–20% fat, and 16–22% protein. For these female subjects, who were overweight but not obese, we found that the 3350-kJ/d weight-reduction diet was well tolerated and resulted in a safe rate of weight loss. No attempts were made to alter the subjects' self-selected patterns of physical activity. On losing ≥10 kg and reaching a BMI < 25, the women were readmitted to the GCRC and continued to consume the 3350-kJ/d diet for 10 d (phase 3). They were returned to energy-balance conditions for the final 10 d at the GCRC (phase 4). Despite their history of weight stability, the never-overweight control subjects were also provided all meals by the GCRC on an outpatient basis for 10 d to ensure energy balance. They were then admitted for 1 full day and 1 night before evaluation.

The 4-y follow-up data were obtained as reported previously (11). In summary, no attempt was made to modify weight-control behaviors after discharge from the GCRC after phase 4, and subjects were not informed that they would receive follow-up. Each year after discharge, the women were contacted by phone to ask their current body weight. In the fourth year, after this information was obtained by phone, they were asked to return to the GCRC for measurement of their weight. Among the weight-reduced women, 21 of 24 (88%) returned to be weighed. Because there was no significant difference between self-reported and measured weights, and because the correlations between weight gain and body composition–adjusted RMR were similar whether the 3 women with only self-reported weights were included, the reported weights of these 3 subjects were included in the final analysis. Among the control subjects, 23 of 24 women (96%) returned after 4 y for weight measurements (one had died during the follow-up period).

Study measures

The subjects' body weights were measured by using an electronic scale in the morning after the subjects had fasted overnight and immediately after they had voided. During evaluations at the GCRC, subjects were weighed in a hospital gown. The average of 3 readings was recorded with the subject stepping off the scale between weighings. The same scale was used for all GCRC measurements, including follow-up weights. The following measures were obtained at the end of each 10-d study phase at the GCRC. After subjects had fasted overnight, blood was drawn for measurement of serum triiodothyronine (T_3) and reverse T_3 (rT_3), which were analyzed by ^{125}I radioimmunoassay (16). At least 2 h after venipuncture and after subjects had rested an additional 30 min in the supine position, RMR was measured over a 30-min period by indirect calorimetry using a thermoplastic ventilated-hood canopy system (17). Body composition was determined by underwater weighing (18) with residual lung volume obtained using the closed-circuit oxygen-dilution method (19). Percentage body fat was calculated by using the formula of Siri (20).

TABLE 1
Age and body-composition characteristics of 24 postmenopausal women, assessed in the overweight state and after weight loss to the normal-weight state, and of pair-matched never-overweight control subjects[1]

Study measures	Weight-reduced subjects (n = 24)		Never-overweight control subjects (n = 24)
	Overweight state	Normal-weight state	
Age (y)	59 ± 5		57 ± 5
Body weight (kg)	74.4 ± 7.6	61.5 ± 6.7[2]	58.2 ± 5.8[2]
Body mass index (kg/m^2)	27.9 ± 1.8	23.0 ± 1.5[2]	21.3 ± 1.6[2,3]
Fat mass (kg)	31.7 ± 5.8	21.3 ± 4.9[2]	19.3 ± 4.5[2]
Fat-free mass (kg)	42.3 ± 3.9	40.0 ± 3.8	38.9 ± 3.2[4]
Percentage body fat (%)	42.6 ± 4.5	34.4 ± 5.4[2]	32.9 ±5.2[2]

[1] $\bar{x}$ ± SD. Measurements were obtained under energy-balanced conditions. Comparisons of subjects in the overweight and normal-weight states were based on paired t tests. Comparisons of the normal-weight and never-overweight groups were based on Student's t tests.
[2,4] Significantly different from overweight state: [2] $P < 0.001$, [4] $P < 0.05$.
[3] Significantly different from normal-weight state, $P < 0.001$.

To confirm that 10 d of energy balance in phase 4 was sufficient to stabilize RMR after having followed the 3350-kJ/d diet for several months, a subgroup of 8 weight-reduced women was maintained in energy-balance conditions for an additional 10 d. RMR values after 10 and 20 d of energy balance were not significantly different (4729 ± 117 and 4880 ± 176 kJ/d, respectively).

Statistical analysis

Repeated-measures analysis during 4 study phases

Descriptive data are presented as means ± SDs unless indicated otherwise. Repeated-measures analysis of variance (ANOVA) was used to evaluate changes in thyroid hormones and absolute values of RMR within the 24 overweight women across the 4 study phases. Repeated-measures analysis of covariance (ANCOVA) was used to adjust RMR for changes in body composition, with use of FFM and FM as covariates in the model. Specifically, we used longitudinal data analysis of the repeatedly measured outcome data with SAS PROC MIXED (21). This provided flexibility in fitting the appropriate covariance structure of the repeatedly measured outcome data. Use of ANCOVA to adjust RMR to changes in body composition obviated any potentially misleading results obtained by using the ratios of RMR and FFM due to lack of linearity of the relation and a nonzero intercept. RMR means, adjusted for the significant covariates in the model, were calculated. Contrasts to perform pairwise comparisons of adjusted RMRs between individual study phases were also set up in the same model. The effect of weight reduction (compared with energy restriction) on thyroid hormones and RMR was evaluated by comparing average values in phases 1 and 2 (overweight phases) with average values in phases 3 and 4 (normal-weight phases). Similarly, the effect of energy restriction (compared with energy balance) was evaluated by comparing average values in the 3350-kJ/d diet phases (2 and 3) with average values in the energy-balanced phases (1 and 4). This approach obviates any unknown, but potentially confounding, effect of length of GCRC stay on the outcome variables. That is, subjects in phases 1 and 3 had been in the GCRC for 10 d at the time of assessment, whereas subjects in phases 2 and 4 had been in the GCRC for a total of 20 d at the time of assessment.

Comparison of weight-reduced and control subjects

Comparison of RMRs, adjusted for FFM and FM, between weight-reduced and control subjects was done by using ANCOVA. The degree of association between weight gain at 4-y follow-up and variation in body composition–adjusted RMR in the weight-reduced state was determined by using Pearson product-moment correlation. In some instances data reported herein may differ slightly from values reported previously, depending on the method of statistical analysis. For example, comparisons of RMR values in an analysis that simultaneously entails overweight, weight-reduced, and control subjects, or that entails only weight-reduced compared with control subjects, will give slightly different mean values than an analysis that entails within-subject analyses across the 4 study phases. The results are affected by the number of groups entered into the analysis and whether the analysis entailed a repeated-measures or nonrepeated- measures approach.

RESULTS

Body-composition changes

Age and body-composition characteristics of the 24 women in the overweight and normal-weight states and of the 24 never-overweight control subjects are shown in **Table 1**. The average length of time required for the overweight women to reach a normal weight was 15.4 ± 2.5 wk (range: 12–20 wk), at an average rate of weight loss of 0.93 ± 0.14 kg/wk (range: 0.7–1.2 kg/wk). Body weight fell an average of 12.9 ± 2.0 kg (range: 11.5–20.2 kg). Body weights at the end of each 10-d study phase were as follows ($\bar{x}$ ± SEM): phase 1 (overweight, energy balance), 74.0 ± 1.6 kg; phase 2 (overweight, energy restriction), 71.8 ± 1.5 kg; phase 3 (normal weight, energy restriction), 61.4 ± 1.4 kg; and phase 4 (normal weight, energy balance), 61.3 ± 1.4 kg. Weight, BMI, FM, and percentage body fat decreased significantly between phases 1 and 4; mean FFM tended to decrease, but not significantly. The weight-reduced and control subjects were not significantly different in terms of body weight, FFM, FM, or percentage body fat.

Metabolic responses to energy restriction compared with weight reduction

Changes in thyroid hormones and RMR in response to energy restriction and weight reduction are shown in **Table 2**. FFM and FM were found to be significant, independent covariates of RMR during weight loss (both $P < 0.01$). Hence, to determine whether there was an effect on RMR of energy restriction independent of

TABLE 2
Resting metabolic rate (RMR) and thyroid hormone status in 24 postmenopausal women, assessed in energy-balanced and energy-restricted phases, in the overweight state and after weight loss to the normal-weight state[1]

	Overweight state		Normal-weight state		Energy restriction effect (Phases 1, 4 compared with 2, 3)		Weight reduction effect (Phases 1, 2 compared with 3, 4)	
Study measures	Phase 1 (energy balance)	Phase 2 (energy restriction)	Phase 3 (energy restriction)	Phase 4 (energy balance)	Mean change	*P*	Mean change	*P*
RMR, absolute (kJ/d)	5482 ± 540[2]	5089 ± 716[3]	4641 ± 490[3,4]	4859 ± 460[3,5]	−276	<0.01	−565	<0.001
RMR, adjusted for FFM and FM (kJ/d)[6]	5198 ± 511	4909 ± 657[3]	4880 ± 473[3]	5089 ± 473[5]	−247	<0.01	−71	NS
Serum rT_3 (μg/L)	0.19 ± 0.04	0.23 ± 0.05[3]	0.22 ± 0.04[3]	0.18 ± 0.03[4,5]	0.39	<0.001	−0.10	NS
Serum T_3 (μg/L)	1.35 ± 0.20	1.18 ± 0.29[3]	1.25 ± 0.20	1.26 ± 0.20	−0.09	<0.03	0	NS
Serum T_3:rT_3	7.37 ± 1.9	5.32 ± 1.7[3]	5.93 ± 1.5[3,4]	7.20 ± 1.8[4,5]	−1.66	<0.001	0.22	NS

[1] FFM, fat-free mass; FM, fat mass; T_3, triiodothyronine; rT_3, reverse T_3.
[2] $\bar{x}$ ± SD.
[3] Significantly different from phase 1, $P < 0.05$.
[4] Significantly different from phase 2, $P < 0.05$.
[5] Significantly different from phase 3, $P < 0.05$.
[6] Adjusted by repeated-measures ANCOVA with FFM and FM as covariates.

changes in body composition, RMR values were adjusted for FFM and FM across the 4 study phases. Mean adjusted RMR fell significantly within 10 d of the start of the 3350-kJ/d diet (6% decline from phase 1 to phase 2; $P < 0.02$), and was still significantly reduced while the women continued to consume the energy-restricted diet after reaching the normal-weight state (6% decline from phase 1 to phase 3; $P < 0.05$). The mean body composition–adjusted RMR of the 2 energy-restricted phases (2 and 3) was significantly lower than that of the 2 energy-balanced phases (1 and 4) by 247 kJ(59 kcal)/d, or 5%.

In contrast with the significant effects of energy restriction, body composition–adjusted RMR values were not changed significantly by weight reduction. That is, there was no significant difference in the mean adjusted RMR between the overweight, energy-balanced state (phase 1) and the normal-weight, energy-balanced state (phase 4). Nor was there a significant difference in mean adjusted RMR between the overweight, energy-restricted state (phase 2) and in the normal-weight, energy-restricted state (phase 3) (**Figure 1**). The mean of the RMR values in the 2 overweight phases (1 and 2) was within 71 kJ(17 kcal)/d, or 1% of the mean of the RMR values in the reduced, normal-weight phases (3 and 4) (Table 2).

The mean concentration of serum rT_3, the biologically inactive form of T_3, was significantly higher in the 2 energy-restricted phases than in the 2 energy-balanced phases. Conversely, the mean values of T_3 and the T_3:rT_3 were significantly lower in the energy-restricted phases than in the energy-balanced phases. T_3:rT_3 fell within 10 d of energy restriction ($P < 0.001$, phase 2 compared with phase 1) and remained depressed during continued energy restriction in the normal-weight state ($P < 0.001$, phase 3 compared with phase 1). On returning to energy balance in the normal-weight state, the ratio rose significantly ($P < 0.01$, phase 4 compared with phase 3) to a value that was not significantly different from that in the baseline overweight state (phase 4 compared with phase 1) (Figure 1).

Comparison of weight-reduced with control subjects

The body composition–adjusted RMR of the weight-reduced women in phase 4 (4771 ± 414 kJ/d) was not significantly different from that of the control subjects (4955 ± 414 kJ/d). (Note that in this statistical analysis, the RMR value of 4771 kJ/d for the weight-reduced women in phase 4 is slightly different from the value of 5089 kJ/d shown in Table 2 for the same subjects because the latter analysis entailed use of within-subject repeated-measures ANCOVA across the 4 study phases.) The observed mean difference in RMR between the weight-reduced and control groups was 184 kJ/d. On the basis of post hoc power analysis, the study had a power of 80% to detect a significant difference in RMR of 314 kJ(75 kcal)/d, and 92% power to detect a significant difference of 419 kJ/d(100 kcal)/d between the weight-reduced and control subjects, if such clinically significant differences existed.

After an average of 4 y of follow-up (50 ± 2 mo), the weight-reduced women regained 87 ± 44% of their lost weight (range: 19–216%), and only 4 of the 24 women (16%) maintained a normal BMI of <25. The average amount of weight gain was 10.9 ± 5.4 kg (range: 2–26 kg). By contrast, the control subjects gained 1.7 ± 2.4 kg (range: −2 to 7 kg) over a comparable period of follow-up (48 ± 1 mo), and all maintained a normal BMI. The body composition–adjusted RMR of the women in the weight-reduced, energy-balanced state (phase 4) showed a nonsignificant positive, rather than a negative, association with weight regain at 4 y ($r = 0.27$, $P = 0.21$), as shown in **Figure 2**. The results were similar after we excluded the 3 women for whom follow-up weights were reported but not measured ($r = 0.34$, $P = 0.14$).

DISCUSSION

Metabolic responses to energy restriction compared with weight reduction

The results of this study indicate that energy restriction caused significant decreases in RMR and in T_3:rT_3 that were independent of changes in body mass. RMR fell 6% within 10 d of energy restriction and remained 6% below baseline despite 3–5 mo of continued energy restriction and an average weight loss of 13 kg. Within 10 d of restoring energy balance in the normal-weight state, body composition–adjusted RMR and T_3:rT_3 returned to the values of the overweight state. These findings suggest that if metabolic measures are obtained in weight-reduced individuals before energy balance is fully restored, results would give the misleading impression that weight-reduced

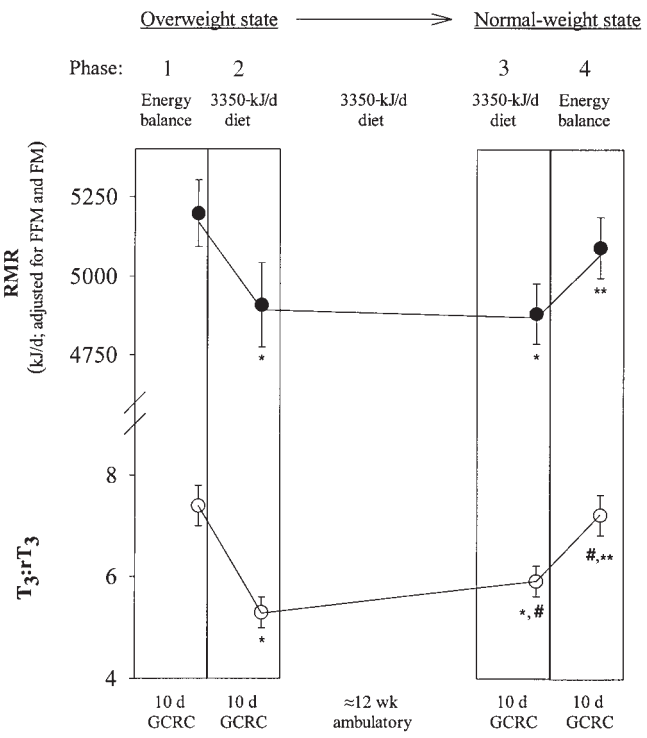

FIGURE 1. Mean (±SEM) resting metabolic rate (RMR) adjusted for fat-free mass (FFM) and fat mass (FM), and serum ratio of triiodothyronine (T_3) to reverse T_3 (rT_3) in 24 overweight women during 4 phases of weight reduction. *Significantly different from phase 1. #Significantly different from phase 2. **Significantly different from phase 3 (all, $P < 0.05$). GCRC, General Clinical Research Center.

persons are hypometabolic and prone to weight regain, in concert with the set-point theory.

The findings also suggest that thyroid concentrations, especially T_3:rT_3, may be useful in documenting that subjects have been returned to an energy-balanced state. Astrup et al (22) found that body composition–adjusted RMR was significantly lower in 28 weight-reduced than in 28 nonobese women. Although the weight-reduced women were reported to have been weight stable for ≥3 mo before testing, their plasma T_3 concentrations were significantly reduced, and the reduced RMR values were explained, statistically, by the reduced T_3 concentrations. The authors suggested that the weight-reduced women may not actually have been in energy balance or that their low thyroid meausres resulted in low RMR and, in turn, contributed to their obesity. Welle et al (23) showed substantial reductions in T_3 concentrations during low energy intake in 6 obese women, although they could not conclude that the hormone changes mediated the declines in RMR. A series of studies by Danforth et al (24, 25) lend support to our findings of the responsiveness of thyroid hormones to changes in energy balance. The investigators found that energy restriction was accompanied by decreases in serum concentrations of T_3 and in T_3:rT_3. Danforth (24) speculated that changes in these thermogenic hormones, in conjunction with decreased sympathetic activity, might be responsible for the observed fall in RMR during energy restriction. Of note, they found that when energy balance was restored after periods of weight change, T_3 and rT_3 concentrations returned to baseline. Collectively, these findings and ours suggest *1*) that energy restriction but not weight reduction is associated with a relative hypothyroid state, and *2*) that although thyroid hormone concentrations may not have a cause-effect relation with RMR, these concentrations may help document the presence of energy balance after weight loss.

The results of our study do not support the concept of an adaptive metabolic response to weight loss because once energy balance was restored, thyroid hormones normalized and RMR returned to a value that was appropriate for the reduced body mass. In an animal study, Reed and Hill (26) found no evidence of disproportionate declines in RMR after weight loss. Several human studies have also shown that weight loss does not cause disproportionate declines in RMR (27–32). Two reviews of human studies concluded that single or repeated bouts of weight loss cause changes in RMR that are appropriate for the changes in body composition (33, 34). In a prospective study similar to the one reported here, we evaluated 32 premenopausal women in the overweight state and after reduction to the normal-weight state, each during 4 wk of energy balance (35). No down-regulation in body composition–adjusted sleeping metabolic rate or RMR was found. By contrast, some investigators have reported a greater than expected decline in RMR after weight loss (36–38). Leibel et al (5) reported that weight loss caused a reduced ratio of RMR to FFM; however, when the authors adjusted RMR for changes in FFM and FM by using a regression-based analysis, the changes in RMR were not significant, weakening support for the set-point theory. Elliot et al (39) measured RMR in 7 obese women during a modified fast and after 8 wk of self-reported weight stability. RMR fell during energy restriction but rebounded only partially on return to a stable weight. However, RMR was only adjusted for FFM and not FM, which fell significantly and which is known to contribute to RMR (40). Wadden et al (41) obtained repeated measurements of RMR in 18 women during energy restriction and after refeeding and found that FFM-adjusted RMR returned to normal after discontinuation of energy restriction.

Comparison of weight-reduced with never-obese control subjects

As another approach to examining the set-point theory of metabolic adaptation, investigators have compared RMRs in formerly obese individuals with those in never-obese control subjects. Our results indicated that RMR values were not significantly different between weight-reduced women and never-overweight control subjects. Wyatt et al (6) also found that body composition–adjusted RMR was not significantly different in weight-reduced subjects from that in weight-matched control subjects (6). Astrup et al (4) recently conducted a meta-analysis of 12 studies of formerly obese and control subjects. Results based on individual data indicated that RMR was slightly (2.9%) but not significantly lower in the weight-reduced subjects after adjustment for differences in FFM and FM with use of an appropriate linear regression technique. By contrast, when the data were expressed as an RMR-FFM ratio, the results indicated that metabolic rate was ≈5% lower in the weight-reduced subjects. As pointed out by Hill and Wyatt (42), results based on RMR-FFM ratio tend to give falsely low RMR values in the group with a higher FFM (43, 44), which was the case in the formerly obese subjects in the meta-analysis. As well, it was not always clear if and how long the weight-reduced subjects were weight stable before RMR was assessed.

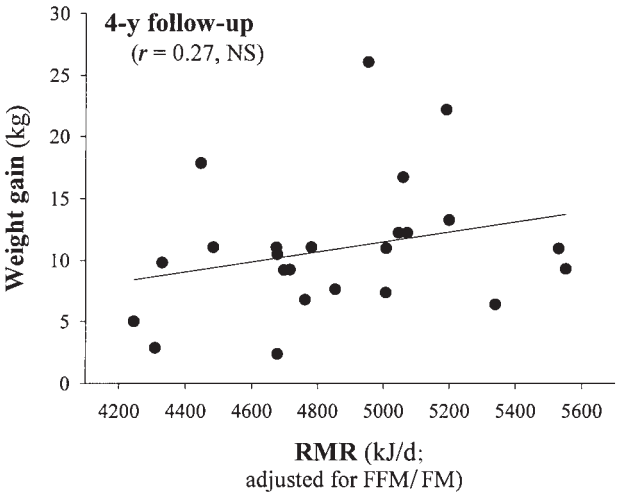

FIGURE 2. Relation of 4-y weight regain to resting metabolic rate (RMR) measured in 24 weight-reduced women under energy-balanced conditions. Follow-up data are shown 4 y from the time the women had achieved an average weight loss of 12.9 kg and had reached a normal body mass index (in kg/m^2), eg, <25.

RMR as a predictor of weight gain

We described previously the significantly different 4-y weight-gain patterns of these formerly overweight and never-overweight women (14). The never-overweight women had a mean increase in BMI of from 21.3 to 21.8, and 100% maintained a BMI < 25. The mean BMI of the overweight women fell from 28 to 23 after weight loss, and then rose again to 27 after 4 y. Only 16% maintained a BMI < 25. Notably, individual variations in body composition–adjusted RMR in the weight-reduced state did not correlate with the weight-regain patterns. Nor was there a trend for greater weight regain among the women with a lower RMR, as shown in Figure 2.

The observed mean difference in 4-y weight gain of the weight-reduced compared with the control groups was 9.2 kg (10.9−1.7 kg). On the basis of a previously published prediction model, a weight difference of this magnitude, if due solely to variation in RMR, would have required that the RMR of the weight-reduced women be ≈523 kJ(125 kcal)/d lower than that of the control subjects (45). By contrast, we observed a nonsignificant difference in mean body composition–adjusted RMR of only 184 kJ(44 kcal)/d, which would have predicted a final weight-gain difference of just 3.5 kg. The current study had more than adequate statistical power (92%) to detect a clinically significant difference in RMR of ≥419 kJ(100 kcal)/d between the weight-reduced and control groups if such a difference existed. Thus, our findings suggest that factors other than variation in RMR explained most of the difference in weight gain of the obesity-prone and obesity-resistant women.

Study limitations

This study entailed a relatively small and homogeneous group of 48 postmenopausal white women. Although the small size and population homogeneity were necessary for this study, which involved tight metabolic control and extended periods of time at the GCRC, these factors limit the applicability of the results to other study groups. We cannot exclude the possibility that differences in subject characteristics may explain conflicting results between our study and those obtained in different weight, sex, age, and ethnic groups. Furthermore, it is possible that greater amounts of weight loss among more severely obese persons may be associated with metabolic adaptations not observed in this study.

Summary and conclusions

The major findings of this study were the following: *1*) Acute and sustained energy restriction was characterized by low concentrations of thyroid hormones and body composition–adjusted RMR, which, on restoration of energy balance, returned to pre-weight-loss values. *2*) Measured in energy-balanced conditions, RMRs of the weight-reduced women were normal relative to those of never-overweight control subjects and did not explain weight regain patterns. These findings indicate the importance of ensuring an energy-balanced state before measuring RMR after weight loss. Even after months of energy restriction, RMR normalized within 10 d of energy balance, as reflected by a return to the euthyroid state. The results also suggest that adaptive down-regulation of RMR is not a characteristic of weight-reduced individuals and does not explain their weight-regain tendency. The weight-gain tendency of obesity-prone persons appears to be caused by factors other than variations in metabolic rate.

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