Weight loss and change in resting metabolic rate

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Weight loss and change in resting metabolic rate[1-3]

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ABSTRACT The relation between change in resting metabolic rate (RMR) and change in fat-free mass (FFM) after weight loss is not well understood and is often inappropriately expressed in kilocalories per unit of FFM. We measured RMR and FFM in 35 obese patients enrolled in a conservative weight-loss program. RMR per kilogram FFM was not different after weight loss. However, the regression of ΔRMR on ΔFFM revealed that the decline in RMR tended to be greater than could be accounted for by loss of FFM. At initial test and retest, body fat (Fat) was not a predictor of RMR after FFM had been taken into account but ΔFat significantly contributed to the prediction of ΔRMR when added to the equation after ΔFFM. Thus, people losing larger amounts of weight had declines in RMR greater than could be accounted for by loss of FFM. Self-reported age of onset of obesity was not related to ΔRMR. *Am J Clin Nutr* 1990;52:981–6.

KEY WORDS Resting metabolic rate, obesity, weight loss, fat-free mass

Introduction

There is disagreement about the nature of the decline in energy requirements after weight loss in obese human subjects. Although postobese people are undeniably hypometabolic relative to when they were obese, it is not clear whether the decline in energy requirement is proportional to the loss of fat-free mass (FFM) that occurs during weight loss or is disproportionally greater.

Evidence is available for both animals and humans that resting metabolic rate (RMR) declines during a hypocaloric diet (1–3). Several investigators have provided evidence for such decreases in humans when RMR was remeasured at the end of or shortly after a period of weight loss produced by dieting, even if RMR was expressed per unit of FFM (4–6). These studies did not establish whether the decrease is temporary or enduring. However, one study of seven obese women found a depressed RMR-FFM ratio up to 8 wk after massive weight loss on a modified fast (7).

In a cross-sectional study, differences in metabolic rate were observed between postobese women and matched lean control subjects during both waking and sleeping periods, with postobese women expending less energy during comparable periods (8). However, half of the postobese subjects were restricting food intake and were still losing weight at the time of the measurements. Data were not provided separately for the weight-stable postobese subjects. In addition, lean control subjects had significantly more FFM than did the postobese subjects, so the two groups were not exactly matched.

In contrast, other researchers have not found disproportionate decreases in metabolic rates after weight loss. For example, in one study of 19 women who had a mean loss of 30 kg, there was no change in metabolic rates from expected values derived from a regression line based on pre-weight-loss data (9). Another study presented data on 14 postobese women from a low-energy-diet and behavior-modification slimming program who stabilized at or near desirable weight compared with 18 matched control subjects. RMR per kilogram FFM was not different between these groups (10).

An additional problem with this research is how to express the response of RMR to change in body weight. FFM is the major determinant of RMR in nondieting subjects (11, 12) and ever since the work of Miller and Blythe (13), the RMR-FFM ratio has been commonly used. However, the simple RMR-FFM ratio may not be suitable for the expression of change because the regression line of RMR on FFM has a nonzero intercept (14, 15). Hence, a change in FFM may move a data point from one location on the regression line to another location also on the line without maintaining a constant RMR-FFM ratio. This issue was recently discussed by Ravussin and Bogardus (16).

In view of these problems, we studied changes in RMR of obese subjects after weight loss in a conservative weight-loss program that used both RMR-FFM ratios and residuals from the regression line of RMR on FFM as measures of RMR change, with the aim of comparing the results obtained by the two measures and of elucidating the nature of the change in RMR.

Subjects and methods

Data for this study were obtained from patients enrolled in the Weight Control Unit (WCU) of the Obesity Research Center at St Luke's–Roosevelt Hospital Center. The WCU operates an outpatient weight-loss program with behavior modification, nu-

trition education, exercise, and psychological components (17, 18). As part of the WCU program, patients are retested at intervals after their initial entry testing. The subjects for this study consisted of all patients who were initially tested and then retested after an interval of between 9 and 42 mo [15 ± 5.3 mo ($\bar{x} \pm$ SD)] for whom measures of RMR and body composition were recorded on both occasions and who had no history of medication or medical problems that might affect metabolic rate. None of the subjects were diabetic (fasting glucose values were 4.9 ± 1.0 mmol/L) but because some were hyperinsulinemic they demonstrated an element of insulin resistance.

Forty-four patients met these criteria. Eight of these weighed more on retest than initial test and were excluded from this analysis, and one patient whose initial weight was > 3 SDs from the mean of the sample was excluded as an outlier, leaving an n of 35. Subjects' weights were relatively stable at the time of retest; the weight change of the subjects for whom weights during the 3-mo preceding retest were available was −0.73 ± 2.1 kg/mo.

Metabolic rate was measured by indirect calorimetry in a temperature-controlled, quiet room. The equipment consisted of a polarographic oxygen analyzer for measuring oxygen consumption (Beckman OM-11, SensorMedics Corp, Anaheim, CA), a nondispersive, infrared medical analyzer for measuring carbon dioxide production (Beckman LB-2), and a computer capable of printing out the analysis of the expired air and the calculated respiratory quotient (Monro, Litton Business Systems, Orange, NJ). Equipment was recalibrated on every testing day with standard gases of known concentration. Measurements were taken by use of a mask during a 15-min period of stable oxygen consumption in the morning after a 12–14-h fast and after a rest of ≥ 30 min. The mean within-individual SD for repeated measurements of RMR in our laboratory is 57 kcal/d, which corresponds to an error coefficient of variation of 3.8%.

FFM was calculated from measures of total body potassium (TBK) made by counting the essential ^{40}K photons in a 4π gamma counter and using the ^{42}K correction for body geometry and adiposity (19). The measurement error for TBK using these methods is estimated to be 4% (19). Equipment was recalibrated with ^{40}K and ^{137}Cs standards every day of testing.

Adipose tissue aspirations from subcutaneous tissue located at the upper outer quadrant of both buttocks were performed on the same day that body composition measurements were made. Mean fat-cell size (weight) was assessed by a photomicrographic method (20).

Plasma insulin (21), triiodothyronine radioimmunoassay (T$_3$RIA), triiodothyronine resin uptake (T$_3$RU), thyroxine radioimmunoassay (T$_4$RIA), and thyroid stimulating hormone (TSH) were measured for a subsample of the group. Thyroid hormones were measured by use of radioimmunoassay kits (Diagnostic Products Corp, Los Angeles).

All testing and procedures that were not part of regular clinical care were approved by the Institutional Review Board of St Luke's–Roosevelt Institute for Health Sciences, and written informed consent was obtained from the patients.

Other variables included in the data set were age, height, sex, self-reported age of onset of obesity, body mass index (BMI) calculated as body weight (kg) divided by height squared (m^2), body-fat weight (Fat) calculated by subtracting FFM from total body weight, waist circumference measured at the level of the lowest rib, and hip circumference measured 5 cm below the tip

of the iliac crest. The variables preceded by a Δ symbol were obtained by subtracting the initial value from the retest value, eg, ΔFFM equals retest FFM minus initial FFM.

Characteristics of the WCU patients studied are shown in Table 1.

Data analyses were performed by use of multiple linear regression (*PROC REG* and *BMDP2R*) and analysis of covariance (*BMDP2V*) programs provided by Statistical Analysis System Inc (Cary, NC) and BioMedical Data Programs (BMDP; Los Angeles). Differences between regression equations were tested by comparing the confidence intervals around the slopes and intercepts with the difference in values of the slopes and intercepts. Other specific tests are described with the results. Probabilities < 0.05 were considered significant.

Results

Weight, FFM, and RMR changes observed on retest are shown in Table 1. The mean difference in body weight between initial test and retest was 18.3 ± 14.3 (± SD) kg, a loss of 19% of initial body weight, of which 5.1 kg was FFM, indicating that ∼72% of the weight loss was made up of fat. The 24-h RMR (RMR24) per kilogram of body weight was significantly higher on retest, as might be expected given the higher proportion of FFM making up the body weight on retest (initial 14.9 vs retest 16.4 kcal · 24 h^{-1} · kg body wt^{-1}; $t = 3.6$, df = 34; $P < 0.01$).

The regression equations of RMR on FFM using the data from initial testing and retesting are, respectively,

$$\text{RMR24} = 356 + (22.9 \times \text{FFM}_{kg}) \qquad (r^2 = 0.53)$$

and

$$\text{RMR24} = 421 + (20.5 \times \text{FFM}_{kg}) \qquad (r^2 = 0.58)$$

These data are shown in **Figure 1**. The coefficients and intercepts of these equations differ from zero at $P < 0.0001$ and $P < 0.06$ for initial testing and $P < 0.0001$ and $P < 0.01$ for retesting, but the equations were not significantly different from each other. The values are similar to those reported by other researchers (12, 13). The correlations between RMR24 and FFM at initial test and at retest were 0.73 and 0.76, respectively; hence, FFM explains 53% and 58% of the variance in RMR. No other variable explains more of the variance in RMR than does FFM, nor does any other variable in our data set add significant amounts of

TABLE 1
Characteristics of sample patients at initial test and retest*

	Initial test	Retest	Difference
Sex	28 F, 7 M		
Age (y)	40 ± 11.5		
Height (cm)	164 ± 9.5		
BMI	36.3 ± 8.0	29.6 ± 6.7	−6.7 ± 5.0
Weight (kg)	98.2 ± 23.8	79.8 ± 18.6	−18.3 ± 14.3
Fat (kg)	49.8 ± 16.7	36.6 ± 14.5	−13.2 ± 13.1
FFM (kg)	48.4 ± 9.9	43.3 ± 8.1	−5.1 ± 3.8
24-h RMR (kcal)	1463 ± 310	1308 ± 221	−156 ± 173
W/H†	0.86 ± 0.09	0.85 ± 0.07	−0.01 ± 0.07

* $\bar{x} \pm$ SD. BMI, weight (kg)/height^2 (m^2).
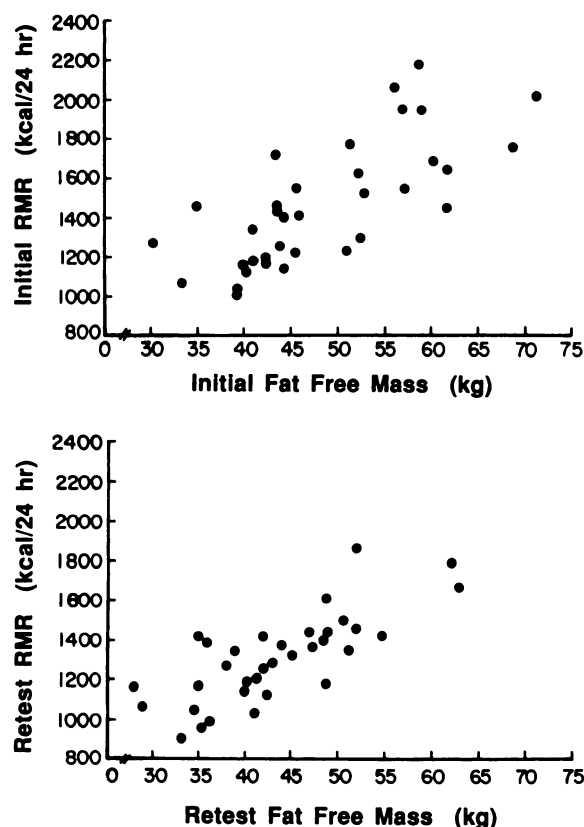
† Waist-to-hip ratio.

FIG 1. Fat-free mass vs RMR (kcal/24 h) for 35 subjects at initial testing (upper panel) and on retest after weight loss (lower panel).

explained variance once FFM is entered. Specifically, adding Fat or %Fat to the regression of RMR on FFM makes no significant additional contribution.

Because > 40% of the variance in RMR was not accounted for by FFM, we examined the residuals from the regression lines to investigate whether the unaccounted variance was due to noise in our measures or to intersubject variability. The correlation of residuals from the first equation with residuals from the second equation shows a robust linear relationship ($r = 0.66$; $P < 0.01$), indicating within-subject stability in the nature of each individual's deviation from the regression line (**Fig 2**). Subjects who had RMRs greater than predicted by the regression line at initial test tended to be above the corresponding regression line at retest as well. This is evidence that the deviations from the regression line reflect stable individual differences and not merely random error.

The central question of this study concerns the relation of RMR to FFM after weight loss. In this sample, RMR, when expressed per kg of FFM, is not different from initial test to retest (30.3 vs 30.5 kcal · 24 h⁻¹ · kg FFM⁻¹; $t = 0.11$, df = 34; NS). Expressed in this traditional way, the change in RMR appears to be entirely accounted for by loss of FFM.

The test of whether weight loss affected the RMR of FFM as estimated from the regression lines was carried out by an analysis of covariance, with repeated measures of RMR and FFM as a covariate. In this statistical procedure the RMR values are adjusted for the amount of FFM present at test and retest and the adjusted values are compared. If the decline in RMR is purely a function of loss of FFM, then the adjusted RMR values at

retest will not be significantly different from those at initial testing. The analysis also tests whether, within subjects, the change in RMR is related to the change in FFM.

The results of the analysis of covariance show that, as discussed above, FFM (the covariate) is strongly related to RMR ($F = 48.1$, df = 1,33; $P < 0.0001$); that within subjects the changes in FFM are related to the changes in RMR ($F = 5.44$, df = 1,33; $P < 0.03$); and that after adjustment for FFM, the RMR is somewhat lower on retest than initial test although the difference is not statistically significant ($F = 2.1$, df = 1,33; $P = 0.16$).

The equation expressing the relation of ΔRMR to ΔFFM within subjects is

$$\Delta RMR24 = -68 + (17.3 \times \Delta FFM_{kg})$$

ΔFFM accounts for 14% of the variance in ΔRMR.

An examination of the partial correlations between ΔRMR and difference scores for the other variables in the data set, after the effect of ΔFFM had been controlled for, revealed a significant remaining correlation to ΔFat (partial $r = 0.49$; $P < 0.005$). When ΔFat is added to the equation the result is

$$\Delta RMR24 = -8 + (13.0 \times \Delta FFM_{kg}) + (6.1 \times \Delta Fat_{kg})$$

The t and P values for the terms in this equation are as follows: intercept $t = -0.17$, $P = 0.8$; ΔFFM $t = 1.95$, $P < 0.06$; ΔFat $t = 3.18$, $P < 0.003$. The SEE is 144 kcal. This two-variable equation accounts for 35% of the variance in ΔRMR (**Fig 3**).

The increase in variance accounted for by the two-variable equation over the one-variable equation is highly significant ($P < 0.001$). After these two variables are entered into the equation, the intercept is trivially different from zero and no other variable in our data set makes a significant contribution toward accounting for variance in ΔRMR. Thus, in this sample there is no relation of Fat to RMR in the between-subjects analysis but there is a significant relation of ΔFat to ΔRMR in the within-subjects analysis.

Several additional analyses were conducted to investigate supplementary hypotheses regarding weight loss and change in RMR. In the covariance analysis the change in RMR after adjusting for loss of FFM was not significantly different from zero for the sample as a whole. Yet the regression equations indicated that ΔFat is linearly related to ΔRMR after ΔFFM had been
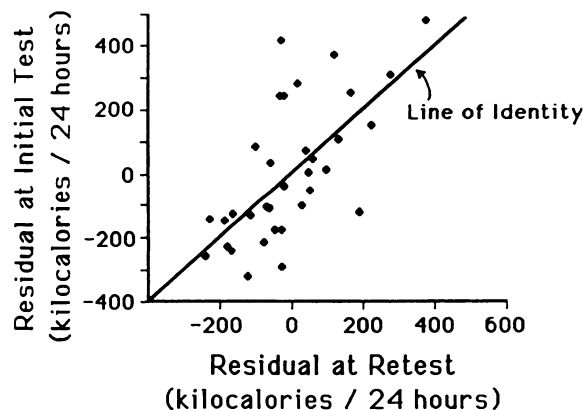

FIG 2. The residuals of the regression equation of 24-h RMR predicted from FFM at initial testing vs the residuals of the corresponding regression equation at retesting.
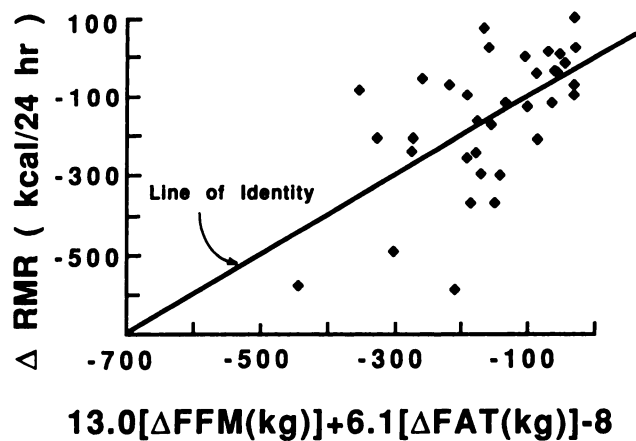
$$13.0[\Delta FFM(kg)]+6.1[\Delta FAT(kg)]-8$$

FIG 3. Measured ΔRMR (kcal/24 h) vs ΔRMR predicted from a regression equation that uses ΔFat and ΔFFM (kcal/24 h).

corrected for. It is possible then that a significant decline of RMR in relation to FFM is seen only after a larger weight loss than that shown on average in this sample. To investigate this possibility the subjects were grouped into categories according to percent of body weight lost between initial test and retest: 0–< 6%, 6–< 16%, 16–< 25%, ≥ 25%. The unadjusted mean RMRs for these groups are shown in **Table 2**. A repeated-measures analysis of covariance was performed with RMR as the repeated measure, percent of body weight lost as a grouping variable, and FFM as a covariate. There is a significant interaction between the percent of weight lost and the amount of change in RMR from test to retest ($F = 3.51$, df = 3,30; $P < 0.03$). That is, after adjusting for FFM the groups that showed the larger percent weight loss show greater declines in RMR. The adjusted mean RMRs are given in Table 2. Post hoc comparisons on the adjusted means indicate that only the difference in the > 25% group is statistically significant ($P < 0.01$). Subjects in this group lost an average of 37.5 kg body wt (range 25.4–57.6 kg). These results are consistent with the result of the previous analysis, because, in a two-compartment model of body composition, once FFM is taken into account the only remaining contributor to body weight is fat. Hence, this analysis confirms the finding that after adjustment for decreased FFM, declines in RMR are related to amount of fat lost.

When the preceding analysis is repeated using a simple RMR-FFM ratio as the dependent measure, the results are rather different. There is no interaction between percent of weight lost and change in the RMR-FFM ratio ($F = 0.60$, df = 3,31; NS). That is, the means do not indicate a decreasing RMR-FFM ratio with increasing amount of weight lost (Table 2). The analysis of variance was repeated with subjects classified according to amount of weight lost rather than percent change in weight, and it produced a similar nonsignificant outcome. Thus, the use of the RMR-FFM ratio as the dependent measure does not lead to the same conclusions as the use of regression analyses.

Another specific hypothesis that we investigated was the possibility that large declines in RMR after weight loss are seen mainly in persons with early-onset obesity. A repeated-measures analysis of covariance was carried out using FFM as a covariate and self-reported age of onset of obesity to classify subjects into four groups: 0–5, 6–10, 11–20, and 21–40 y old at onset. The

analysis shows no main effect for onset age on RMR ($F = 0.46$, df = 3,30; NS), no significant RMR change from test to retest ($F = 1.56$, df = 1,30; NS), and no interaction between these two factors ($F = 0.26$, df = 3,30; NS). Repeating the analysis using analysis of variance with onset age as a grouping variable and RMR-FFM ratio as the dependent measure led to the same conclusion: no reliable differences in RMR:FFM as a function of age of obesity onset ($F = 0.67$, df = 3,31; NS), no significant change in RMR:FFM from initial test to retest ($F = 0.05$, df = 1,31; NS), and no interaction between the two factors ($F = 0.08$, df = 3,31; NS).

Adipose cell weights (ADPWT) at test and retest were available for 31 subjects. Mean initial cell weight was 0.785 ± 0.15 μg and mean retest cell weight was 0.592 ± 0.25 μg. The difference was statistically significant ($t = 4.9$, df 30; $P < 0.01$). The correlations between ΔRMR/ΔFFM and ΔADPWT were not significant ($r = 0.27$; NS). However, the partial correlation of ΔRMR and ΔADPWT, after the effect of ΔFFM has been removed, is substantial ($r = 0.55$; $P < 0.01$), as might be expected given the significant role that ΔFat plays in the regression equation.

Twenty-nine subjects had plasma T_3RU, T_3RIA, T_4RIA, and TSH as part of their test and retest. Only the change in T_3RIA was significant, with retest values lower than initial test values (2.0 ± 0.5 vs 1.7 ± 0.3 nmol/L, $t = 4.3$, df = 16; $P < 0.01$). Changes in thyroid hormones did not correlate significantly with ΔRMR/ΔFFM or with ΔRMR residuals after ΔFFM had been entered.

Mean fasting plasma insulin values ($n = 27$) were as follows: initial 316 ± 201 pmol/L, retest 230 ± 208 pmol/L. The decrease was not quite statistically significant ($t = 1.8$, df = 26; $P < 0.07$). ΔInsulin was not significantly correlated with either ΔRMR/ΔFFM or with residuals of ΔRMR after ΔFFM had been entered.

Waist-to-hip ratios on test and retest ($n = 32$) were as follows: initial 0.856 ± 0.086, retest 0.845 ± 0.067. The difference was

TABLE 2
Cell means for unadjusted RMR, RMR adjusted for FFM, and RMR-LBM ratio, by percent weight loss*

	Percent weight loss			
	0–< 6% ($n = 8$)	6–< 16% ($n = 8$)	16–< 25% ($n = 9$)	≥ 25% ($n = 10$)
Unadjusted RMR (kcal/24 h)				
Initial test	1269	1476	1348	1713
Retest	1221	1408	1168	1421
RMR adjusted for FFM (kcal/24 h)				
Initial test	1281	1416	1400	1542
Retest	1268	1433	1345	1367
RMR-LBM ratio (kcal · 24 h^{-1} · kg FFM^{-1})				
Initial test	28.0	30.6	32.0	30.2
Retest	28.4	31.9	32.5	29.2

* $\sqrt{MSE}$ for unadjusted RMR and for RMR adjusted for FFM: between subject 227, within subject 104; for RMR-LBM ratios: between subject 6.0, within subject 2.6.

not significant. Changes in waist-to-hip ratio were not reliably correlated with ΔRMR/ΔFFM or with ΔRMR residuals after ΔFFM had been entered.

Discussion

The manner in which the relation of RMR to FFM is expressed can alter the conclusion drawn regarding the relationship between change in RMR and change in FFM after weight loss. In this study the RMR-FFM ratio did not change with weight loss. Yet, at the same time, regression analyses showed that RMR declined to a greater degree than would be expected from loss of lean mass alone and that the amount of this additional decline was significantly correlated with the amount of fat lost.

The strong relation found in this study of ΔFat to ΔRMR after ΔFFM was controlled for may appear puzzling because fat was not significantly related to metabolic rate after FFM was adjusted for on initial test or retest. It is known, however, that there is considerable familial variation in RMR. For example, Bogardus et al (11) reported a range of 500 kcal/24 h in RMR among families. Hence, the influence of fat on RMR, which appears to be of the order of 6 $kcal \cdot 24 \ h^{-1} \cdot kg^{-1}$, could easily be obscured by the large individual variation in FFM energy expenditure. In contrast, the covaried within-subject measures and the within-subject changes would control the error introduced by this individual variation and, thus, be more sensitive to any underlying association between fat and RMR. Garby et al (22) estimated the resting energy expenditure of fat in a cross-sectional sample and their result (6.4 $kcal \cdot 24 \ h^{-1} \cdot kg^{-1}$) was statistically significant only with the largest sample size ($n = 104$). Bernstein et al (18) also found a significant influence of fat on RMR in a sample of 202 men and women. They estimated the energy cost to be 6.36 $kcal \cdot 24 \ h^{-1} \cdot kg \ fat^{-1}$, with FFM measured by TBK.

The use of cross-sectional data to make these estimates of the metabolic cost of fat stores requires the assumption that both fat and FFM have specific and constant metabolic rates per unit weight. It may be, however, that people who are fatter also have characteristically lower energy expenditure per unit-FFM (23), in which case the cross-sectional analyses would underestimate the metabolic cost of fat. The close agreement of our results, which are based on longitudinal data and therefore control for stable individual differences, with the cross-sectional studies is reassuring. The use of change measures over time to detect the effect of fat loss is, however, not without its own flaws. For instance, the failure of ΔFFM to account more adequately for ΔRMR may reflect a disproportionate loss of metabolically active (brain, heart, liver, kidney) vs inactive (bone mineral, collagen, extracellular fluids) FFM compartments. If so, the metabolic rate of the remaining FFM would be lowered [eg, see the discussion in Lawrence et al (24)]. There is indeed evidence that tissue nitrogen loss during calorie restriction is a complex function of degree and length of deprivation and of nutrient composition of the diet and is specific to the tissue studied (25). This possibility could be investigated when new methods for body composition measurements become available that permit the development of body composition models with finer and more metabolically relevant compartments.

Other investigators reported lower 24-h energy expenditure (26) or reduced nonresting energy expenditure (27) after weight loss. Our study, using a large number of subjects from a con- servative weight-loss program, found an effect on RMR even after several months had elapsed and weight loss had stabilized before RMR remeasurement. These results are consistent with the findings of Elliot et al (7). Whether this effect will persist after a longer time than that investigated here is not known although if the decreased RMR is indeed the result of decreased energy costs for fat stores then it would be expected to endure indefinitely. The implication for postobese people is that loss of fat will be accompanied by decreased metabolic rate unless it is compensated for by adding metabolically active lean tissue.

This study highlights the importance of methodological considerations in resolving questions about weight loss and RMR. As we have demonstrated, how the dependent measure is expressed is critical. Other likely important factors are the rate and amount of weight loss, the elapsed time between weight loss and remeasurement of RMR, the availability of accurate and discriminating measures of body composition, and the study design.

Regarding study design, Ravussin et al (23) show that preobese people may have lower RMRs than those less susceptible to weight gain. Consequently, studies using matched groups of subjects are not as powerful as studies using repeated measures on the same subjects, not only because of the greater uncontrolled error variance of between-subject designs but also because it is questionable whether postobese subjects' preobese RMRs are comparable to the matched control subjects' RMRs.

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