Metabolic Predictors of Obesity

Contribution of Resting Energy Expenditure, Thermic Effect of Food, and Fuel Utilization to Four-year Weight Gain of Post-obese and Never-obese Women

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Abstract

This prospective study was designed to identify abnormalities of energy expenditure and fuel utilization which distinguish post-obese women from never-obese controls. 24 moderately obese, postmenopausal, nondiabetic women with a familial predisposition to obesity underwent assessments of body composition, fasting and postprandial energy expenditure, and fuel utilization in the obese state and after weight loss (mean 12.9 kg) to a post-obese, normal-weight state. The post-obese women were compared with 24 never-obese women of comparable age and body composition. Four years later, without intervention, body weight was reassessed in both groups.

Results indicated that all parameters measured in the post-obese women were similar to the never-obese controls: mean resting energy expenditure, thermic effect of food, and fasting and postprandial substrate oxidation and insulin-glucose patterns. Four years later, post-obese women regained a mean of 10.9 kg while control subjects remained lean (mean gain 1.7 kg) ($P < 0.001$ between groups). Neither energy expenditure nor fuel oxidation correlated with 4-yr weight changes, whereas self-reported physical inactivity was associated with greater weight regain.

The data suggest that weight gain in obesity-prone women may be due to maladaptive responses to the environment, such as physical inactivity or excess energy intake, rather than to reduced energy requirements. (*J. Clin. Invest.* 1995. 95:980–985.) Key words: obesity • substrate oxidation • body composition

Introduction

The development of successful strategies to prevent the development of obesity depends largely on the ability to identify factors predictive of weight gain. It has recently been proposed that certain characteristics of energy metabolism may precede the obese state and contribute to its development (1). For instance, although resting and 24-h energy expenditure are increased in the obese state, several longitudinal studies have found that relatively low rates of energy expenditure predict greater weight gain in pediatric (2, 3) and adult persons (4). However, a relationship between resting energy expenditure and long-term weight gain was not found in a recent 10-yr study of 775 individuals (5).

Respiratory quotient (RQ),[1] as a reflection of carbohydrate and fat oxidation, has also been suggested to be a metabolic index which predicts subsequent weight gain (1). In one study a higher 24-h RQ (reflecting greater carbohydrate and less fat oxidation) was found to correlate with greater risk of weight gain, independent of low energy expenditure (6). Findings of the Baltimore Longitudinal Study were supportive in that a higher resting RQ correlated with subsequent weight gain, at least among lean men (5). As another reflection of pattern of fuel utilization, insulin sensitivity and, hence, tendency to greater carbohydrate utilization has been reported to predict greater weight gain among Pima Indians (1) and among already obese persons (7) but not among lean persons (7).

To better understand the relationship between various metabolic factors and predisposition to obesity, we conducted a longitudinal study of moderately obese women before and after reduction to a normal-weight, post-obese state, and then followed their weight regain patterns for an average of 4 yr. These women were pair-matched with never-obese women whose weight patterns were also followed an average of 4 yr.

Methods

Subjects. The experimental subjects were 24 postmenopausal, moderately obese women with a mean body mass index (BMI) of 27.9±1.8 kg/m^2. They averaged 59±5 years of age (range 49–67). They underwent evaluation in the General Clinical Research Center (GCRC) at the University of Alabama at Birmingham in the obese state and after reduction to normal and stable body weight. They also had reassessment of body weight on the GCRC an average of 4 yr later. All subjects had normal glucose tolerance confirmed before admission to the study by normal blood glucose levels fasting and 2 h after an oral glucose load. Familial predisposition to obesity was indicated by a history of obesity in one or more first-degree relatives.

After reduction to normal body weight, the women in the post-obese state were pair-matched with respect to fat-free mass (±5 kg), fat mass (±5 kg), and age (±5 years) with 24 never-obese, postmenopausal, non-diabetic women who had no family history of obesity and who served as control subjects. The average age of the control group was

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1. *Abbreviations used in this paper:* BMI, body mass index; CHO, carbohydrate; FFM, fat-free mass; FM, fat mass; REE, resting energy expenditure; RQ, respiratory quotient; TEF, thermic effect of food.

57±5 years (range 46–66). The control subjects were admitted to the GCRC and underwent the same metabolic evaluation as the experimental subjects and had reassessment of their body weight on the GCRC an average of 4 yr later. All study subjects were Caucasian except for one who was of Japanese descent. None of the subjects was taking hormone replacement therapy or other medications known to affect any of the metabolic parameters. The subjects were informed of the study protocol and gave written consent; the study was approved by the Baptist Medical Centers and the University of Alabama at Birmingham Institutional Review Boards.

Experimental protocol. GCRC evaluations were designed to assess body composition, energy expenditure, and fuel utilization in all subjects under weight-stable and diet-controlled conditions. Details of this phase of the study have been published elsewhere (8). Before the initial evaluation on the GCRC, energy intake was adjusted in the obese subjects until weight varied less than 1% on at least 5 consecutive occasions (usually over about 10 d). Subjects were then admitted to the GCRC, and minor adjustments in energy intake were continued in order to ensure stable weight. After 10 d and nights on the GCRC, measures of body composition, energy expenditure, and substrate utilization were assessed. Subjects were then placed on a balanced deficit diet providing 3350 kJ (800 kcal) per day. All meals were provided and they were followed as outpatients of the GCRC until each subject had lost at least 10 kg and had attained a normal body weight (defined as a BMI of ≤ 25 kg/m^2). The average duration of the outpatient weight loss phase was 15.4 wk. Subjects were then readmitted to the GCRC in the normal-weight, post-obese state. Energy intake was again adjusted to maintain stable weight for 10 d while residing in the GCRC, and body composition and metabolic parameters were reassessed at the end of the 10-d period of controlled diet composition, energy intake, and physical activity. Despite a history of weight-stability, the never-obese control subjects were also provided all meals from the GCRC on an outpatient basis for 10 d to ensure control of energy balance and diet composition. They were then admitted to the GCRC for one full day and an overnight before evaluation. During both inpatient and outpatient phases of the study, for both experimental and control subjects, meals consisted of natural foods, all of which were prepared by the GCRC research kitchen except for Lean Cuisine entrees, which were kindly provided by Stouffer's Food Corporation (Solon, OH). The energy content of the diet was 23% protein, 22% fat, and 55% carbohydrate.

No attempt was made to modify the subjects' weight control behaviors following final discharge from the GCRC. After a minimum of 3 yr after discharge (mean 4.2 years; range 3.0–5.5 yr), all 24 subjects were contacted by phone and were asked their current body weight. After volunteering this information, they were asked to return to the GCRC for measurement of their weight, and 21 of the 24 post-obese subjects (88%) did so. Since there was no significant difference by paired t test between self-reported weights and the weights recorded on the GCRC, self-reported weights were used for the three subjects who did not return to the GCRC. The control subjects were also contacted, and 23 of 24 (96%) returned for the follow-up assessment of body weight (one had died during the follow-up period). Immediately prior to this follow-up, they completed a questionnaire which included information about attempts to control body weight since discharge. One post-obese subject, who reported being a former member of Weight Watchers®, attended four meetings since discharge; two others briefly tried liquid formula diets, the longest for 2 mo; a fourth tried Nutri/System® for 2 mo. Except for self-imposed attempts to control calorie intake and exercise, there were no other formal weight control efforts in this group during the period since discharge. One never-obese subject used a liquid diet supplement during one of the follow-up years; two others belonged to Weight Watchers® during part of the follow-up (extent of involvement unknown). The questionnaire also included information about their typical exercise patterns, indicating the frequency, duration, and type of exercise performed during the entire follow-up period. Regular exercise was defined as a positive response to the question, "Did you exercise regularly during the follow-up period?" Occasional exercise was defined as exercise performed regularly during part of the follow-up period, or exercise performed irregularly during the entire follow-up period.

Body composition. Body weight was determined using an electronic scale, taken fasting and immediately post-voiding in the morning, with the subject dressed in a hospital gown. The average of three 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. Body composition was determined by underwater weighing using a standard protocol (9) with residual lung volume obtained using the closed-circuit oxygen dilution method (10). Percent body fat was calculated using the fomula of Siri (11). Waist circumference was measured just below the 10th rib at the mid-axillary line with the subject standing. Hip circumference was measured at the level of the iliac crests, also with the subject standing.

Metabolic measurements. Following a 12-h fast, blood was drawn for serum insulin, determined by radioimmunoassay (Corning Medical, Inc., Medfield, MA). A 24-h urine collection was completed the morning of the measurements of energy expenditure and substrate utilization and analyzed for urea nitrogen. At least 2 h after venipuncture and an additional 30 min of rest in the supine position, resting energy expenditure (REE) was measured for 30 min with a computerized, open-circuit, indirect calorimetry system by using a ventilated canopy. Oxygen was measured with a Sybon/Taylor oxygen analyzer (model OA 540; Servomex, Norwood, MA). Carbon dioxide was measured with a LIRA model 202 infrared analyzer (Mine Safety Appliance, Mars, PA). The oxygen analyzer is sensitive to ±2 ml O_2/min out of 242 ml O_2/min, and the carbon dioxide analyzer is sensitive to ±2 ml CO_2/min out of 218 ml CO_2/min. This indicates that, in the calibration procedure, the measured rate of oxygen consumption or carbon dioxide production differs from the actual amount by less than 1% for each instrument (12). Assuming 20.2 kJ/liter O_2, an oxygen consumption of 242 mL/min corresponds to 7042 kJ/24 h. Our instrumentation is able to detect differences of 58.6 kJ/24 h [(2 ml per min/242 ml per min) 7042 kJ per 24 h]. REE was measured continuously and values were obtained at 3-min intervals. Energy expenditure and substrate oxidation were calculated from the nonprotein respiratory quotient values by using equations described by Jequier and Felber (13) and Ferrannini (14).

After determination of REE, the subjects drank a mixed liquid meal (Sustacal, Mead Johnson, Evansville, IN), which had the same proportional caloric composition as the study diet, with the volume adjusted to provide 60 kJ (14.3 kcal) per kg FFM. The subjects sipped the formula through a flexible tube over 15 min so that the hood would remain in place. Measurements were interrupted for 10 min after 2 h and again after 4 h so the subjects could void. The duration of the thermic effect of food (TEF) was from ingestion of the meal until either the metabolic rate returned to the preprandial baseline rate or until 6 h had passed. The average value obtained for REE was extrapolated over the 6-h period, and the TEF was computed as the increase in caloric expenditure over REE. The caloric expenditure above REE was identified as TEF (kJ/6 h) and was expressed as a percent of the calories ingested. The effect of the formula intake on fuel utilization was expressed as the change in respiratory quotient (RQ) from the fasting to the postprandial state. The latter was taken as the average RQ value during the relatively stable 3-h period between 1 and 4 h after formula ingestion.

Statistics. Descriptive data are presented as means±SD, unless indicated otherwise. Analysis of covariance was used to compare the relationship between REE and body composition, controlling for the group status (i.e., obese, post-obese, or never-obese). Obese status was the grouping variable, and FFM, fat mass (FM), and age were the covariates. FFM and FM were found to be significant, independent determinants of REE; hence, both the absolute and adjusted REE (i.e., adjusted for FFM and FM) were used to compare subjects in the obese, post-obese and never-obese states. By contrast, age was not found to be a significant predictor of REE in this study set, perhaps because the subjects were all selected to be in a very narrow age range. The regression equation for the adjusted REE was derived and is presented in the Results section. The analysis of covariance tests for differences in the

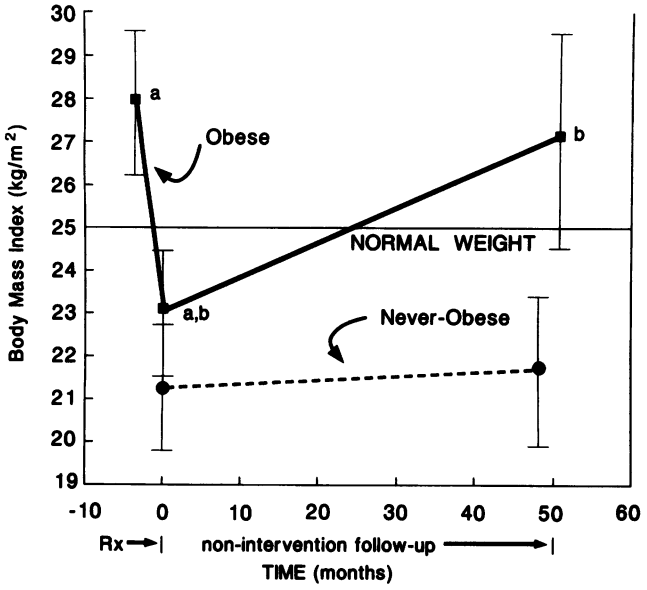

Figure 1. Weight gain pattern (as body mass index, mean±SD) of 24 obese women after being reduced to normal body weight, compared to 23 never-obese women. Corresponding letters indicate differences between means at $P < 0.001$.

adjusted REE means among the groups were examined only after establishing that there was homogeneity of the slopes of the regression lines of the test-comparison groups. The Bonferroni procedure (15) was used to compare differences in the means among the obese, post-obese, and never-obese groups. One subject in the post-obese state had a fasting RQ well outside the expected range (i.e., 1.35); hence, her data were deleted from the analyses of the related metabolic parameters. The associations between the various metabolic parameters and weight change during follow-up were obtained using Pearson correlation coefficients after establishing that the data were normally distributed.

Results

Body composition. Table I shows the body weight and body composition characteristics of the subjects in the obese and post-obese states, and of the never-obese controls. The obese women lost an average of 12.9±2.0 kg, representing a 17% decrease, and their average BMI fell from 27.9 to 23.0 kg/m^2. As designed, fat mass and FFM were similar in the post-obese and never-obese subjects: average fat mass differed by 9% (2.0 kg, ns), and average FFM differed by 3% (1.1 kg, ns). Changes in BMI during follow-up are shown graphically in Fig. 1. The average lengths of follow-up of the two groups were not significantly different: post-obese subjects, 50±2 mo (range 36 to 66); never-obese subjects, 48±1 mo (range 39 to 53). The average weight gain during follow-up of the post-obese women was 10.9±5.4 kg. Their average weight at final follow-up was not significantly different from their starting obese weight, although the individual responses in weight regain were quite variable (range 2 to 26 kg). Only four of 24 subjects maintained a normal BMI of < 25. By contrast, the never-obese women gained an average of just 1.7±2.4 kg (range −2 to +7 kg), and all maintained a BMI of < 25. The difference in average weight gain of the post-obese and never-obese subjects was statistically significant ($P < 0.001$). Body fat pattern, expressed as the waist:hip ratio, remained statistically unchanged through the obese (0.87±0.05), post-obese (0.86±0.05), and follow-up states (0.88±0.05).

Metabolic parameters. Energy expenditure was adjusted for FFM and fat mass (FM) since both components of body composition have been previously reported to be significant independent contributors to REE (16). FFM and FM were found to be significant and independent determinants of REE in these subjects (both at $P \leq 0.002$). The regression equation for REE, which includes both terms FFM and FM, was derived from the data on the combined group of 48 subjects (24 obese subjects prior to weight loss + 24 controls). The $r^2 = 0.61$ ($P < 0.001$). The regression equation is shown below along with standard errors and probability values:

$$\begin{aligned} \text{REE (kJ)} &= \text{constant} + \text{FFM (kg)} + \text{FM (kg)} + \text{SEE} \\ &= 811.4 + 90.1\ \text{FFM} + 27.6\ \text{FM} + 409.4 \\ &\quad (\pm 629.4) \quad (\pm 17.1) \quad (\pm 8.3) \\ &\quad (P = 0.20) \quad (P < 0.001) \quad (P = 0.002) \end{aligned}$$

The group mean values for the various metabolic parameters are given in Table I. REE was significantly lower after weight loss, even when adjusted for FFM. However, when REE was adjusted for both FFM and FM, there was no significant difference in REE between the obese and post-obese states. There were no significant differences in any of the adjusted and nonadjusted measures of REE between the post-obese and the never-obese subjects. The average value for TEF was lower in the obese subjects compared to controls ($P < 0.05$); however, it rose after weight loss such that there was no longer a significant difference in TEF between the post-obese and never-obese control subjects.

The average fasting nonprotein RQ was also lower in the obese subjects compared to controls ($P < 0.05$) but rose after weight loss to an average value in the post-obese state that was no longer significantly different from the never-obese controls. As shown in Fig. 2, the contribution of the substrates to total resting energy expenditure changed with weight loss, with a shift from fat to carbohydrate utilization. However, fasting oxidation rates for carbohydrate and fat were similar in the post-obese and never-obese subjects. Protein oxidation rates were not statistically different in the obese, post-obese, and never-obese groups. The mean change in RQ values with formula ingestion were not statistically different among the three study groups. There was no significant correlation between the individual fasting RQ values measured in the obese and post-obese states ($r = -0.11$, ns). As well, there was no significant correlation between fasting RQ and REE values measured in the obese or in the post-obese state, whereas RQ was inversely correlated with REE among the never-obese subjects ($r = -0.48$, $P < 0.05$), implying that increased fat oxidation was associated with higher REE in this group.

The correlation coefficients between the various metabolic parameters and 4-yr weight gain are shown in Table II. None of the measures of energy expenditure or substrate utilization correlated significantly with long-term weight change, including REE, TEF, patterns of substrate utilization, and glucose and insulin areas. By contrast, fasting serum insulin levels in the obese and post-obese states were significantly and positively correlated with long-term weight gain, with a similar trend in the never-obese subjects.

Physical activity. Among the 24 post-obese subjects, those who reported exercising regularly during the entire follow-up period (5 subjects) gained a mean of 6.0±8.8 kg, those who

Table I. Body Composition and Metabolic Characteristics of 24 Women in the Obese and Post-obese (Normal-weight) States, and of 24 Never-obese Controls

	Experimental subjects		Controls
	Obese state	Post-obese state	Never-obese
Body composition parameters			
Weight (kg)	74.4±7.6[ab] (59.7–93.6)	61.5±6.7[a] (47.8–74.3)	58.2±5.8[b] (46.0–67.9)
Body mass index (kg/m^2)	27.9±1.8[a] (25.2–27.9)	23.0±1.5[a] (20.6–25.3)	21.3±1.6[a] (17.7–23.7)
Body fat (%)	42.6±4.5[ab] (34.6–49.1)	34.4±5.4[a] (23.0–41.3)	32.9±5.2[b] (22.9–42.1)
Fat mass (kg)	31.7±5.8[ab] (21.0–45.5)	21.3±4.9[a] (12.5–30.3)	19.3±4.5[b] (11.0–27.8)
Fat-free mass (kg)	42.3±3.9[c] (34.3–50.4)	40.0±3.8 (32.1–46.8)	38.9±3.2[c] (33.5–45.1)
Metabolic parameters			
REE (kJ/d)	5482±451[ab] (4292–6548)	4896±426[a] (4269–6083)	4867±584[b] (3927–6066)
REE adjusted for FFM (kJ/d)*	5339±460[cd]	4914±441[c]	4992±456[d]
REE adjusted for FFM + FM (kJ/d)*	5088±543	5008±425	5152±473
TEF (percent energy ingested)	8.2±2.4[c] (4.2–13.0)	8.8±2.8 (3.1–13.4)	9.8±2.6[c] (6.4–14.6)
Fasting nonprotein RQ	0.89±0.10[c] (0.73–1.12)	0.94±0.08 (0.74–1.12)	0.96±0.12[c] (0.66–1.17)
Fasting fat oxidation (percent REE)	36.1±16.2[c] (8.1–63.0)	25.6±18.2 (−15.1–69.1)	23.1±22.7[c] (−4.8–80.9)
Fasting CHO oxidation (percent REE)	36.2±17.2[cd] (3.1–66.9)	51.3±18.0[c] (9.0–93.0)	49.6±20.7[d] (−10.0–74.6)
Fasting serum insulin (pmol/liter)	117±57[c] (30–240)	79±47[c] (12–168)	96±48 (12–234)
Postprandial RQ response[‡]	0.09±0.05 (0.00–0.18)	0.07±0.06 (−0.07–0.19)	0.07±0.06 (−0.07–0.22)
6-h glucose area (mmol/liter · min)	287±130 (121–508)	255±101 (95–411)	198±86 (77–354)
6-h insulin area (pmol/liter · min)	110±78 (15–321)	77±40 (8–166)	78±28 (34–129)

The controls were selected to be of similar body composition as the experimental subjects in the post-obese state. (Data are presented as means±SD; ranges are presented in parentheses for the descriptive parameters.) [ab] Different from values with corresponding letters at $P < 0.001$; [cd] different from values with corresponding letters at $P < 0.05$; [c] different from value with corresponding letter at $P = 0.06$. * Adjusted for FFM and FM using analysis of covariance. [‡] Change in total RQ from baseline to average of 1–4 h postprandial response.

exercised occasionally (9 subjects) gained 11.6±9.3 kg, and those who did not exercise (9 subjects) gained 12.8±7.8 kg. Only the difference in weight gain between regular exercisers and nonexercisers was statistically significant ($P < 0.05$).

Discussion

The results of the current investigation provide three interesting findings. (*a*) Among these post-obese and never-obese women, who were pair-matched on the basis of age and body composition, there were no differences found in the measured metabolic parameters which might have explained the predisposition to obesity of the experimental subjects. (*b*) There were relatively few formal attempts at weight control by any of the subjects during the 4 yr of follow-up; nevertheless, there were very clear differences in weight gain patterns according to whether or not they were predisposed to obesity. As a group, the women

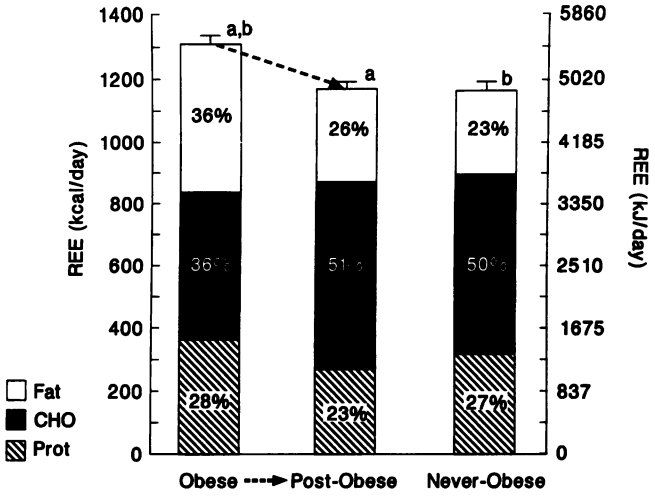

Figure 2. Resting energy expenditure (REE, as mean±SE) and substrate utilization of 24 women in the obese and post-obese states compared to 24 never-obese women. Corresponding letters indicate differences between mean REE values at $P < 0.001$.

predisposed to obesity regained essentially all of their lost weight, albeit with great variability, whereas all of the never-obese women maintained a normal weight. (*c*) Despite this difference, neither resting energy expenditure, the thermic effect of food, nor the patterns of fasting or postprandial fuel utilization were predictive of long-term weight gain in either group.

The strengths of this study include its tight control of study conditions, the rigorous nature of the subject selection, careful comparison of post-obese with pair-matched never-obese controls, and the long-term follow-up. Weaknesses include the homogeneity of the study population (white, postmenopausal, nor-

Table II. Pearson Correlation Coefficients of Various Metabolic Parameters with 4-yr Weight Gain Among Women in the Obese and Post-obese (Normal-weight) States, and Among Never-obese Controls

	Experimental subjects		Controls
	Obese state	Post-obese state	Never-obese
Energy expenditure			
REE (kJ/d)	0.25	0.38	0.17
REE/kg FFM	−0.03	0.09	0.23
TEF (percent energy ingested)	−0.11	−0.02	0.03
Substrate utilization			
Fasting nonprotein RQ	0.11	−0.17	0.04
Postprandial RQ response[§]	−0.08	0.17	−0.07
Fat oxidation (percent REE)	−0.03	0.14	0.03
CHO oxidation (percent REE)	0.00	−0.10	0.03
Protein oxidation (percent REE)	0.08	−0.16	−0.27
Insulin-glucose levels			
Fasting serum insulin (pmol/liter)	0.47*	0.58[‡]	0.26
6-h insulin area (pmol/liter · min)	0.11	0.28	0.03
6-h glucose area (mmol/liter · min)	0.37	−0.05	0.09

[§] Change in total RQ from baseline to average of 1–4 h postprandial response. * $P < 0.05$; [‡] $P < 0.01$.

moglycemic women), which limits its applicability to other groups; the small sample size; and the fact that nonresting energy expenditure was not measured. We attempted to simulate, as nearly as feasible, the "pre-obese" state by studying subjects who were of normal body weight but who were clearly predisposed to obesity on the basis of having been obese and having a family history of obesity in first-degree relatives. Conceivably, the prior history of obesity could have permanently altered their metabolic parameters, although this seems most unlikely since they had normal parameters in the post-obese state compared with controls.

Regarding the sample size, it is quite possible that a larger study sample could have given statistical significance to the small correlations found between the metabolic factors and weight gain, or to the small differences in energy expenditure between the post-obese and the never-obese subjects. However, even if statistically significant, the modest correlation coefficients of REE would explain only between 1 and 14% of the variance of subsequent weight gain, and the correlations were positive, suggesting that higher levels of energy expenditure contributed to greater weight gain, which is an unlikely case. The difference in average weight gain of the post-obese versus the never-obese subjects over the 4-yr period was 9.2 kg (i.e., 10.9 kg weight gain for the post-obese vs. 1.7 kg gain for the never-obese women). Even if the mean differences in energy expenditure were statistically significant, is it likely that such a small degree of energy "economy" could account for the significantly greater weight gain observed in the obesity-prone group? According to a prediction model to assess the theoretical impact of a persistent reduction in energy expenditure on long-term weight gain (17), a difference in weight gain of this magnitude would require a lower initial energy expenditure of approximately 500 kJ (120 kcal) per day. The mean TEF value observed in the post-obese subjects was 1% lower than that of their never-obese counterparts. A difference of 1% of ingested calories represents a potential daily economy of no more than 65 kJ (15 kcal) and would explain a difference in weight gain of only ~ 1 kg. The difference in REE (adjusted for body composition) between the post-obese and never-obese subjects was 144 kJ/d (34 kcal/d). Even the combination of these small numerical differences in TEF and REE would predict a weight gain of just 3.6 kg, which is only about one-third of the actual, measured difference in weight gain of the post-obese versus the never-obese women.

Although we did not obtain measurements of physical activity-related energy expenditure, our finding that weight gain was not predicted by reduced resting and postprandial energy expenditure but was predicted by self-reports of physical inactivity suggests that the nonresting component of energy expenditure may be an important factor in the etiology of obesity. This possibility is supported by the data of Weigle et al. (18) who found that decreased nonresting energy expenditure accounted for over 70% of the decrease in estimated 24-h energy expenditure of 7 subjects studied before and after weight loss.

It has been suggested that inherent abnormalities in energy expenditure or fuel utilization may contribute to weight gain, although the data are inconsistent. Among predominantly obese Pima Indians, Ravussin et al. (4) found that 24-h energy expenditure (but not REE) was significantly associated with subsequent rate of weight gain, suggesting that nonresting energy expenditure may be an important factor in the development of obesity. In a mixed population of normal-weight and obese adults, Seidell et al. (5) reported no association of REE with long-term weight change. Amatruda et al. (19) studied 18 obese females before and after reduction to normal body weight and then followed 10 of them for 18 to 34 mo. Not only were their resting and total energy expenditure measurements similar to those of 14 never-obese control subjects, but there was no evidence that reduced energy expenditure in the 10 subjects predicted their weight regain during the 1 to 3-yr period of follow-up. Thus, it did not appear that low energy expenditure was a predisposing factor to weight gain.

In several relatively small pediatric studies, normal-weight children were selected on the basis of their familial predisposition to obesity. In one such study of 18 infants, weight gain over one year was predicted by a relatively low average daily energy expenditure, but not by REE or TEF, again suggesting that energy expenditure of physical activity accounted for the differences in weight gain patterns (2). The results of a study of 25 healthy preschoolers were less clear but supported the notion that low daily energy expenditure among predisposed children facilitates weight gain (3). By contrast, a retrospective analysis of data on 33 normal infants, who were selected without regard to their predisposition to obesity, showed that usual energy expenditure did not predict subsequent two-year weight gain (20).

There is also variability among studies regarding the potential contribution to weight gain of differences in substrate oxidation (4–6). In part, this may be explained by variations in pretest conditions since substrate oxidation is readily influenced by energy imbalance, as well as by changes in diet composition and body composition (21). Overfeeding is accompanied by a rise in fasting RQ during the dynamic phase of weight gain (22). Hence, as pointed out by Schutz (21), it is important to separate the extent to which an inherently high RQ (low-fat, high-carbohydrate oxidation state) contributes to weight gain versus overfeeding itself. The influence of body composition was demonstrated in the present study wherein reduction of percentage body fat was associated with a shift from fat to carbohydrate oxidation, despite energy balance and identical diet composition (see Fig. 2). Being leaner is not only associated with a higher RQ, it is also predictive of a tendency to gain weight (5). Thus, unless subjects have similar body composition, the contribution of a relatively high RQ to subsequent weight gain must be distinguished from a potentially confounding effect of having a lower initial body fat.

In our present study of normoglycemic women, higher fasting insulin levels predicted greater weight gain, especially in the women predisposed to obesity, raising the possibility that hyperinsulinemia contributes to the obese state. There is relatively little published information on insulin level as a predictor of weight gain, although several recent abstracts have addressed this issue and have noted very different associations. For example, insulin levels did not predict weight gain patterns of lean adults followed eight years (7) or of monozygotic twins after short-term overfeeding (23). By contrast, among obese individuals, lower insulin levels predicted greater weight gain (7), and among Pima Indians, who are generally obese, lesser insulin resistance and reduced insulin secretion predicted greater weight gain (24, 25). The explanation for these findings and the differences among the weight groups is not clear. Hyperinsulinemia may precede and contribute to a state of insulin resistance and obesity, or it may reflect the presence of insulin resistance due to the obese state (26). Hence, it is difficult to compare studies

without controlling for such factors as initial body mass and composition, glucose tolerance, and measures of insulin secretion and sensitivity.

In conclusion, this study was conducted among 48 normoglycemic, postmenopausal Caucasian females. Within this relatively small and homogeneous population there was a striking difference in the 4-yr weight gain patterns of the post-obese normal-weight women compared to the control women who were not predisposed to obesity. Weight regain occurred in most of the post-obese women despite the fact that they had patterns of resting and postprandial energy expenditure and fuel utilization that were similar to those of matched, never-obese control subjects. Physical inactivity, on the other hand, was predictive of greater weight regain. It is interesting to compare these findings of induced weight loss–spontaneous regain with those of other investigators who demonstrated that normal-weight subjects also tend to spontaneously return to their starting body weights following a period of either chronic semi-starvation (27) or overfeeding (28). Those findings underscore the tendency for individuals to respond to temporary perturbations in energy balance by restabilizing at a predetermined body composition. At first observation, these patterns seem to support the theory that weight is determined by an inherent set-point. However, among our subjects, even though the average weight regain was similar to the weight loss, there was large variability in the amount of weight regain. Over the four years, some women regained as little as 2 kg and others as much as 26 kg, with the standard deviation being 50% of the mean weight regain. This variability suggests that exogenous factors may contribute to the weight gain rather than an inherent set-point. Overall, our data suggest that this tendency to weight regain among obesity-prone women is more likely to be due to maladaptive responses to the environment in terms of physical inactivity or excess energy intake than to reduced energy requirements.

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