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CHANGES IN ENERGY EXPENDITURE RESULTING FROM ALTERED BODY WEIGHT

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Abstract Background. No current treatment for obesity reliably sustains weight loss, perhaps because compensatory metabolic processes resist the maintenance of the altered body weight. We examined the effects of experimental perturbations of body weight on energy expenditure to determine whether they lead to metabolic changes and whether obese subjects and those who have never been obese respond similarly.

Methods. We repeatedly measured 24-hour total energy expenditure, resting and nonresting energy expenditure, and the thermic effect of feeding in 18 obese subjects and 23 subjects who had never been obese. The subjects were studied at their usual body weight and after losing 10 to 20 percent of their body weight by underfeeding or gaining 10 percent by overfeeding.

Results. Maintenance of a body weight at a level 10 percent or more below the initial weight was associated with a mean (\pm SD) reduction in total energy expenditure of 6 ± 3 kcal per kilogram of fat-free mass per day in the subjects who had never been obese ($P<0.001$) and 8 ± 5 kcal per kilogram per day in the obese subjects

($P<0.001$). Resting energy expenditure and nonresting energy expenditure each decreased 3 to 4 kcal per kilogram of fat-free mass per day in both groups of subjects. Maintenance of body weight at a level 10 percent above the usual weight was associated with an increase in total energy expenditure of 9 ± 7 kcal per kilogram of fat-free mass per day in the subjects who had never been obese ($P<0.001$) and 8 ± 4 kcal per kilogram per day in the obese subjects ($P<0.001$). The thermic effect of feeding and nonresting energy expenditure increased by approximately 1 to 2 and 8 to 9 kcal per kilogram of fat-free mass per day, respectively, after weight gain. These changes in energy expenditure were not related to the degree of adiposity or the sex of the subjects.

Conclusions. Maintenance of a reduced or elevated body weight is associated with compensatory changes in energy expenditure, which oppose the maintenance of a body weight that is different from the usual weight. These compensatory changes may account for the poor long-term efficacy of treatments for obesity. (N Engl J Med 1995;332:621-8.)

OBESITY is a common and intractable problem in some modern societies. Body weight is normally regulated by integrated, coordinate effects on food intake and energy expenditure.¹ The high rate of recidivism among obese people who lose weight may reflect the operation of such regulatory processes.²⁻⁴

In humans, total energy expenditure is accounted for by resting energy expenditure (approximately 60 percent of total energy expenditure), which is the metabolic cost of processes such as the maintenance of transmembrane ion gradients and resting cardiopulmonary activity; the thermic effect of feeding (approximately 10 percent of total energy expenditure), which is the energy expended in the digestion, transport, and deposition of nutrients; and nonresting energy expenditure (approximately 30 percent of total energy expenditure), which is all the remaining expenditure of energy, mainly in the form of physical activity.⁵ In an earlier

study, we found a persistent 28 percent decrease in the energy expended per unit of body-surface area in formerly obese patients with a stable reduced weight,⁶ suggesting a metabolic resistance to the maintenance of a reduced body weight. The present study was designed to examine the components of energy expenditure during the maintenance of usual and altered body weight in obese subjects and subjects who had never been obese.

METHODS

Subjects

Eighteen obese subjects (11 women and 7 men; mean [\pm SD] age, 29 ± 10 years [range, 21 to 45]) and 23 subjects who had never been obese (7 women and 16 men; mean age, 26 ± 10 years [range, 19 to 41]) were recruited through physicians' referrals or advertisements (Table 1). All subjects were at their maximal lifetime weight and had maintained this weight within a range of 2 kg for at least six months. None were taking medications or on special diets. Subjects whose body-mass index (expressed as the weight in kilograms divided by the square of the height in meters) was higher than 28.0 were classified as obese.⁷ All subjects had normal findings on physical examination and laboratory evaluations, including thyroid-function tests, complete blood count, tests for hepatitis A and B and human immunodeficiency virus infection, biochemical tests, and urinalysis. Six of the obese subjects and two of those who had never been obese

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smoked 2 to 10 cigarettes daily throughout the study. The protocol was approved by the Rockefeller University Hospital Institutional Review Board, and written informed consent was obtained from all the subjects.

Study Design

The subjects were admitted to the Clinical Research Center at Rockefeller University and fed a liquid formula (40 percent fat [corn oil], 45 percent carbohydrate [glucose polymer], and 15 percent protein [casein hydrolysate]) supplemented with 5.0 g of iodized sodium chloride, 1.9 g of potassium ions as a potassium salt, and 2.5 g of calcium carbonate per day, 1 mg of folic acid twice weekly, and 36 mg of ferrous iron every other day. The mean caloric content of this formula, measured with a bomb calorimeter, was 1.36 kcal per gram. With the use of standard digestibility quotients, the content of metabolizable calories was 1.25 kcal per gram.⁸ Fecal calorie and urinary nitrogen losses were measured at all weight plateaus to confirm that they did not change (see below). The caloric intake was adjusted until the body weight was constant (slope of the regression line of body weight [grams] vs. time [days], <10 g per day) for at least 14 days. All subjects then underwent studies of energy expenditure and body composition during approximately a 10-day period while continuing to ingest the same quantity of dietary formula. Body composition was analyzed by hydrodensitometry⁹; stool and urine samples, collected for eight days, were analyzed to determine fecal calorie loss (by bomb calorimetry) and urinary nitrogen excretion¹⁰; and resting energy expenditure and the thermic effect of feeding were determined by indirect calorimetry with the use of a Beckman MMC Horizon Metabolic Cart (Beckman Instruments, Fullerton, Calif.) with a ventilated hood fitted snugly around the subject's neck¹¹ (and unpublished data).

Resting energy expenditure at 8 a.m. in the postabsorptive state was calculated from oxygen consumption corrected for the respiratory quotient and the daily rate of nitrogen excretion based on the nitrogen content of the dietary formula and the rate of urinary nitrogen excretion. To measure the thermic effect of feeding, at 9 a.m. the sub-

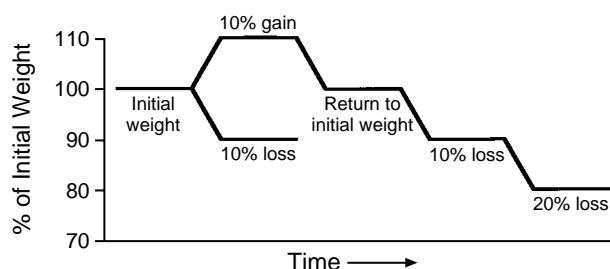


Figure 1. Study Design.

All subjects were studied at their initial weight and after at least one change in weight.

jects were given dietary formula with a caloric content equal to 60 percent of the 24-hour resting energy expenditure measured that morning. Oxygen consumption and carbon dioxide production were measured in the hood calorimeter for 30 minutes 2 and 4 hours after the feeding. The area of the polygon whose base is the prefeeding value of resting energy expenditure and whose other vertices are resting energy expenditure at 9 a.m., 11 a.m., and 1 p.m. represents the increase in energy expenditure during the four hours after ingestion of food; this area was used to calculate the percentage of calories oxidized after ingestion of the formula.

Since no technique is available for the direct measurement of non-resting energy expenditure, we calculated this component of energy expenditure as the difference between total energy expenditure and the sum of the resting components of total energy expenditure: non-resting energy expenditure = total energy expenditure - (resting energy expenditure + thermic effect of feeding). In a subgroup of subjects studied at multiple weight plateaus, total energy expenditure was also determined by the differential excretion rates¹² of two stable isotopes of water (²H₂O and H₂¹⁸O) and by indirect calorimetry performed at the Clinical Diabetes and Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases (Phoenix, Ariz.), in a respiration chamber equipped with wall-mounted radar detectors to monitor physical activity.¹³ These subjects also underwent measurement of body composition by isotope dilution¹² and by dual-photon absorptiometry¹⁴ to validate the caloric titration and hydrodensitometric methods used in the study (unpublished data).

After the completion of studies at their initial weight, 11 of the obese subjects and 13 of the subjects who had never been obese (hereafter referred to as nonobese) were given the maximally tolerated amount of self-selected foods (generally 5000 to 8000 kcal per day) until they had gained 10 percent of their initial body weight (Fig. 1). No formula was ingested during the period of weight gain, which ranged from 4 to 6 weeks in the nonobese subjects and from 6 to 10 weeks in the obese subjects. At the new weight plateau, the dietary formula was reinstated, and the quantity of formula was titrated to maintain the weight. When the weight had been stable for at least 14 days, the studies of energy expenditure and body composition, described above, were repeated. Eight obese women who had undergone and maintained a 10 percent weight gain were then fed 800 kcal per day of the formula until they had returned to their initial weight. They were given the same number of kilocalories of formula that had been required to maintain their initial weight, and the studies

Table 1. Characteristics and Body Composition of Subjects at Initial and Altered Weights.*

SUBJECTS	AGE	WEIGHT	FAT-FREE MASS	FAT MASS	% WEIGHT CHANGE AS FAT MASS
	yr		kilograms		
Nonobese (n = 13)					
Initial weight	27 ± 7	66.5 ± 11.8	54.5 ± 12.1	12.0 ± 4.5	—
10% gain		73.2 ± 13.3†	56 ± 12.6‡	17.1 ± 4.7§	80.1 ± 25.2
Obese (n = 11)					
Initial weight	28 ± 8	131.2 ± 25.3¶	62.8 ± 10.8¶	68.4 ± 18.6¶	—
10% gain		143.1 ± 25.6¶¶	65.6 ± 13.0¶¶	74.9 ± 18.6¶¶*	57.9 ± 34.8
Obese (n = 8)					
Initial weight	29 ± 9	129.7 ± 36.8	60.8 ± 11.9	68.9 ± 38.8	—
Return to initial weight		129.1 ± 36.4	61.6 ± 15.5	67.5 ± 30.0	—
Nonobese (n = 11)					
Initial weight	25 ± 7	70.5 ± 11.7	53.0 ± 10.4	17.5 ± 12.6	—
10% loss		63.7 ± 10.1	50.6 ± 9.5	13.1 ± 3.5	63.7 ± 27.5
Obese (n = 9)					
Initial weight	32 ± 8	132.1 ± 26.9¶	64.1 ± 11.3¶	68.0 ± 19.8¶	—
10% loss		114.3 ± 21.5†¶	59.7 ± 9.1¶††	54.6 ± 14.7¶‡‡	83.6 ± 23.8
Obese (n = 10)					
Initial weight	31 ± 8	124.8 ± 29.6	60.8 ± 11.2	64.4 ± 24.8	—
20% loss		95.6 ± 22.5†	57.5 ± 10.5†	39.0 ± 17.2†	82.1 ± 25.5

*Values are means ± SD.

†P < 0.001 for the comparison with the initial weight.

‡P = 0.022 for the comparison with the initial weight.

§P = 0.003 for the comparison with the initial weight.

¶P < 0.001 for the comparison with nonobese subjects at the same weight plateau.

¶¶P = 0.004 for the comparison with the initial weight.

**P = 0.002 for the comparison with the initial weight.

††P = 0.047 for the comparison with the initial weight.

‡‡P = 0.021 for the comparison with the initial weight.

of energy metabolism were repeated once their weight had been stabilized.

After the initial-weight studies described above, 9 obese subjects and 11 nonobese subjects were fed 800 kcal of the dietary formula per day until their body weight had been reduced to a level that was 10 percent below their initial weight (Fig. 1). (Eight of the obese and one of the nonobese subjects had previously undergone studies after a 10 percent gain in weight.) The period of weight loss ranged from 4 to 7 weeks for the nonobese subjects and from 6 to 14 weeks for the obese subjects. When the subjects had lost 10 percent of their initial weight, the formula was reinstated and adjusted to maintain the weight for at least 14 days; the studies described above were then repeated. Ten obese subjects who had undergone initial-weight studies (seven of whom were also studied after a 10 percent weight loss) were fed 800 kcal of dietary formula per day until they had lost 20 percent of their initial weight. The studies described above were performed after their weight had stabilized at the lower level.

Resting energy expenditure was determined in some subjects at the end of each period of weight gain or loss, when the intended level of weight had been achieved (10 percent higher or lower than the initial weight or after a return to the initial weight) but the subjects were still gaining or losing weight. These studies were performed to assess the degree to which the metabolic status was carried over from a period of changing weight to a period of stable weight.

Statistical Analysis

The results are presented as means \pm SD. Energy expenditure at each weight plateau is expressed as the absolute number of kilocalories per day, as well as the number per kilogram of fat-free mass, to allow comparisons among different groups of subjects at the same weight plateau and among different weight plateaus for the same subject. The thermic effect of feeding and fecal calorie loss are ex-

pressed as percentages of ingested calories that were oxidized and lost in stool, respectively. Comparisons of energy expenditure in the same subjects at different weight plateaus were made by a one-way analysis of variance with repeated measures.¹⁵ The effects of sex and adiposity on measures of energy expenditure at different weight plateaus were determined by a multivariate analysis of variance with repeated measures¹⁵ in which sex and adiposity were treated as dichotomous variables (male vs. female and nonobese vs. obese).

At the usual body weight, resting energy expenditure is closely correlated with measures of metabolic mass (e.g., fat-free mass).¹³ Regression lines relating energy expenditure to metabolic mass do not have zero intercepts.³ Thus, subjects with values on the same regression line can have different values for the ratio of energy expenditure to metabolic mass. To correct for this possibility, regression equations relating measures of energy expenditure to fat-free mass and fat mass at the initial weight were calculated at that weight and used to determine the predicted value of energy expenditure in the same subject at each new weight plateau. The observed-minus-predicted values were then tested against the null hypothesis that the observed-minus-predicted value was 0, to determine whether the observed values differed significantly from the predicted values for each subject. All statistical tests were two-tailed.

RESULTS

Energy Expenditure

The rates of energy expenditure changed in both the obese and the nonobese subjects after changes in body weight (Table 2 and Fig. 2 and 3). A 10 percent increase or decrease in the usual weight was accompanied by a 16 percent increase or 15 percent decrease,

Table 2. Measures of 24-Hour Energy Expenditure.*

SUBJECTS	TOTAL ENERGY EXPENDITURE			RESTING ENERGY EXPENDITURE			NONRESTING ENERGY EXPENDITURE			FECAL CALORIE LOSS	THERMIC EFFECT OF FEEDING
		<i>kcal/kg fat-free mass</i>	<i>observed minus predicted kcal</i>		<i>kcal/kg fat-free mass</i>	<i>observed minus predicted kcal</i>		<i>kcal/kg fat-free mass</i>	<i>observed minus predicted kcal</i>		
	<i>kcal</i>			<i>kcal</i>			<i>kcal</i>		<i>% kcal ingested</i>		
Nonobese (n = 13)											
Initial weight	2481±412	47±7	—	1463±270	28±5	—	976±239	18±7	—	2±2	3±1
10% gain	3110±527†	54±18†	368±246‡	1610±267	30±5	27±163	1496±381†	28±8†	360±288§	2±2	5±1¶
Obese (n = 11)											
Initial weight	3162±712	51±7**	—	2127±427	35±7	—	1075±481	16±6	—	2±2	2±3
10% gain	4034±746†	59±6†††	534±278‡	2261±446	33±5	6±348	1764±468†**	26±4†	524±262‡	2±3	4±2§§
Obese (n = 8)											
Initial weight	3079±627	51±8	—	2015±402	33±8	—	1030±545	16±7	—	2±1	3±1
Return to initial weight	3079±627	50±9	-35±347	2021±386	30±3	-79±307	1109±452	17±7	37±579	2±1	4±1
Nonobese (n = 11)											
Initial weight	2380±528	45±6	—	1511±304	29±3	—	864±278	16±4	—	2±2	6±2
10% loss	1952±402†	39±3§§	-218±123§	1290±228¶	26±3¶¶	-54±98	658±240¶	13±3	-158±183***	3±2	4±3
Obese (n = 9)											
Initial weight	3100±648	50±8	—	2068±359	34±7	—	1030±509	13±3§§	—	2±1	3±3
10% loss	2549±554†	42±5†	-244±198†††	1778±416¶	30±4‡‡‡§§§	-137±305¶¶¶	768±246†	16±7	-165±194	2±2	3±2
Obese (n = 10)											
Initial weight	3129±735	51±7	—	1984±342	32±5	—	1089±456	17±6	—	2±2	3±2
20% loss	2243±504	39±4†	-301±252†††	1581±348†	28±3****	-79±294	589±357†	10±5†	-273±336***	3±2	3±2

*Values are means \pm SD. The thermic effect of feeding is expressed as the percentage of metabolizable calories ingested (metabolizable caloric density of formula, 1.25 kcal per gram); fecal calorie loss is expressed as the percentage of total calories ingested (caloric density of formula by bomb calorimetry, 1.36 kcal per gram).

†P<0.001 for the comparison with the same subjects at their initial weight.

‡P=0.003 for the comparison with 0.

||P<0.001 for the comparison with nonobese subjects.

††P=0.067 for the comparison with nonobese subjects.

¶¶P=0.042 for the comparison with the same subjects at their initial weight.

***P=0.025 for the comparison with 0.

‡‡‡P=0.037 for the comparison with the same subjects at their initial weight.

¶¶¶P=0.058 for the comparison with 0.

****P=0.023 for the comparison with the same subjects at their initial weight.

‡‡P<0.001 for the comparison with 0.

¶¶P=0.002 for the comparison with the same subjects at their initial weight.

**P=0.016 for the comparison with nonobese subjects.

§§P=0.004 for the comparison with the same subjects at their initial weight.

|||P=0.003 for the comparison with the same subjects at their initial weight.

†††P=0.004 for the comparison with 0.

§§§P=0.004 for the comparison with nonobese subjects.

||||P=0.023 for the comparison with 0.

respectively, in 24-hour total energy expenditure corrected for body composition. Fat-free mass was significantly related to total energy expenditure, resting and nonresting energy expenditure, and the thermic effect of feeding. Fat mass was significantly related to total and resting energy expenditure.

In agreement with the results of other studies,¹⁶ total energy expenditure and resting energy expenditure, expressed as kilocalories per kilogram of fat-free mass per day, were significantly higher in the obese subjects than in the nonobese subjects, whereas the thermic effect of feeding was lower in the obese subjects than in the nonobese subjects.^{17,18} The higher resting energy expenditure in the obese subjects probably reflects increased cardiorespiratory work related to chest-wall weight and a larger mass of adipose tissue. Smokers did not differ significantly from nonsmokers for any of the measures. Fecal calorie and urinary nitrogen losses, expressed as percentages of ingested calories and protein, respectively, were not significantly affected by changes in body weight and did not differ significantly according to sex or prior adiposity.

Effects of Weight Gain

Total energy expenditure, nonresting energy expenditure, and the thermic effect of feeding were significantly higher after a 10 percent gain in weight than at the initial weight. Stabilization of body weight after a 10 percent gain resulted in significant increases in observed-minus-predicted values for total energy expenditure, nonresting energy expenditure, and the thermic effect of feeding (Table 2). The magnitude of these changes was not affected by sex or initial adiposity. In 14 subjects (7 obese and 7 nonobese), the percentage of time spent in motion during a 23-hour period, measured in a respiration chamber, did not differ significantly between the initial weight (9.1 ± 2.0 percent) and the 10 percent higher weight (8.6 ± 2.1 percent, $P = 0.47$).

Return to Initial Weight

Eight obese women were studied at their initial weight, at a weight 10 percent higher than their initial weight, and after a return to their initial weight. No significant differences in body composition or in any aspect of energy expenditure were noted between the time of the initial-weight study and the return to the initial weight (Tables 1 and 2).

Effects of Weight Loss

Total energy expenditure and nonresting and resting energy expenditure were significantly lower at weights 10 and 20 percent below the initial weight than at the initial weight (Table 2). Stabilization of body weight at a level 10 percent below the initial weight was associated with negative observed-minus-predicted values for total energy expenditure and nonresting and resting energy expenditure. Stabilization of body weight at a level 20 percent below the initial weight was associated

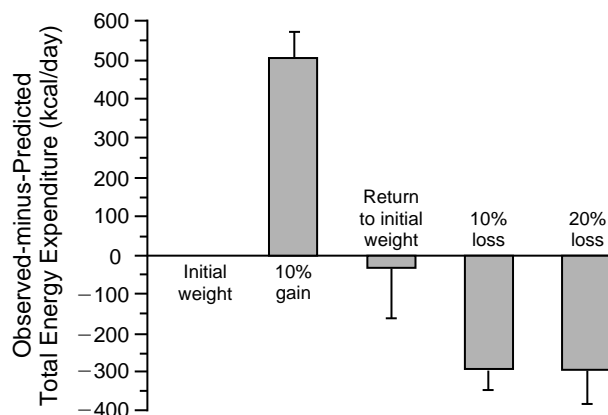


Figure 2. Mean (\pm SD) Observed-minus-Predicted Total Energy Expenditure (Shaded Bars) Based on the Regression of Total Energy Expenditure in a Model with a Variable Combining Fat-free Mass and Fat Mass in the Same Subjects at Their Initial Weight.

The components of total energy expenditure are given in Table 2.

with negative observed-minus-predicted values for total energy expenditure and nonresting energy expenditure. The magnitude of these changes was not significantly related to sex or initial adiposity. There were no significant differences in energy expenditure at weights 10 and 20 percent below the initial weight, suggesting that the maximal adaptation to the maintenance of a reduced body weight was already attained at the 10 percent level. Among eight subjects (six nonobese and two obese) the mean percentage of time spent in motion in the respiratory chamber was 9.2 ± 2.0 percent at the initial weight and 9.4 ± 1.8 percent after a 10 percent loss in weight ($P = 0.52$).

Static Weight Maintenance versus Dynamic Weight Change

The high degree of weight stability among the subjects (mean rate of weight change during the 10-day testing periods, -1.2 g per day) suggests that body composition was constant during weight maintenance. When weight and body composition are stable, the respiratory quotient reflects mainly the composition of the diet. As expected, the processes of weight gain and loss resulted in increases and decreases, respectively, in the respiratory quotient. However, the respiratory quotient did not differ significantly from the quotient for the dietary formula (0.85) at any of the weight plateaus, indicating that the subjects were in caloric balance at each plateau, without a carryover effect of weight loss or gain on caloric requirements or substrate use.

The effects of weight gain and loss on energy metabolism were also assessed by comparing resting energy expenditure at the end of the dynamic phase of weight change with that at the end of the period of maintenance of the same weight (Table 3). The process of increasing weight by overfeeding was accompanied by approximately 12 percent more resting energy expenditure than a 10 percent weight gain maintained for 14

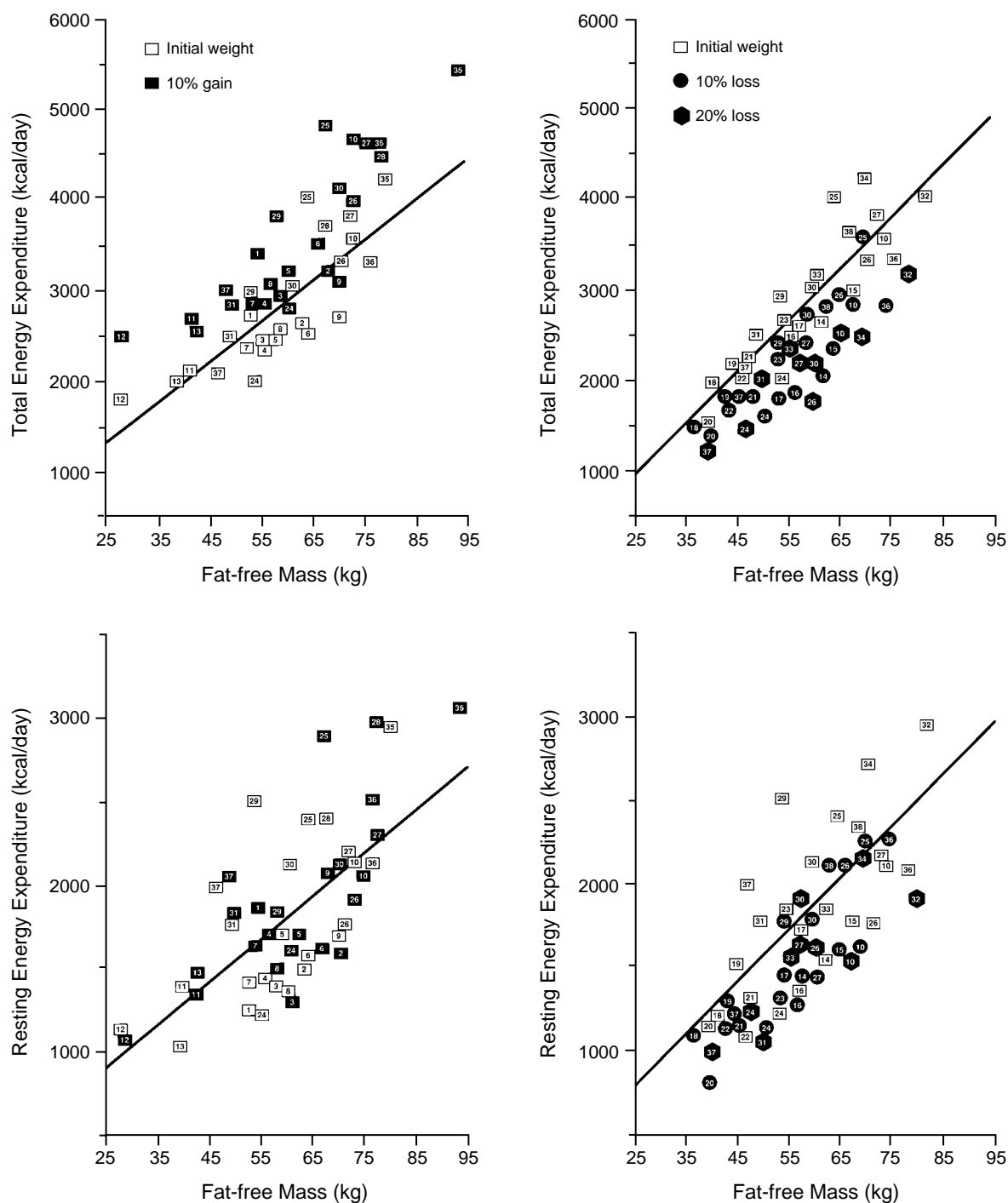


Figure 3. Total and Resting Energy Expenditure According to Fat-free Mass at the Initial Weight and after a Gain or Loss in Weight. The results are presented in terms of fat-free mass to facilitate comparisons among subjects studied at different weights. The diagonal lines represent regression equations for energy expenditure as compared with fat-free mass at the initial weight and at an altered weight in the same subjects. For subjects studied at their initial weight and after a 10 percent gain in weight (left-hand graphs), total energy expenditure equaled 39.7 kg of fat-free mass plus 348.8 ($r^2=0.72$, $P<0.001$), and resting energy expenditure equaled 13.1 kg of fat-free mass plus 670.1 ($r^2=0.42$, $P=0.004$). For subjects studied at their initial weight and after a weight loss (right-hand graphs), total energy expenditure equaled 56.8 kg of fat-free mass minus 496.1 ($r^2=0.74$, $P<0.001$), and resting energy expenditure equaled 27.5 kg of fat-free mass plus 220.2 ($r^2=0.44$, $P=0.004$).

Plotted numbers denote individual subjects. Subjects 1 through 23 were not obese; subjects 24 through 38 were obese. Six women and two men studied after a 10 percent weight loss had previously been studied after a 10 percent weight gain; six women studied after a 20 percent weight loss had previously been studied after a 10 percent gain and a 10 percent loss. The number and direction of previous weight changes did not significantly affect any measures of energy expenditure at a given weight plateau.

days. Conversely, the process of losing weight on a diet of 800 kcal per day resulted in 10 to 15 percent less resting energy expenditure than a stabilized weight loss of 10 percent.

Body Composition

A 10 percent gain in weight resulted in increases in adipose tissue and fat-free body mass, and a weight loss of 10 percent resulted in significant decreases in both these measures. These changes in body composition, expressed as the change in the percentage of body fat, were statistically significant within all subgroups of subjects. There was no evidence that sex or prior adiposity affected the distribution of weight gained or lost between fat mass and fat-free mass (Table 1). There was a trend for the obese subjects to gain a lower percentage of weight as fat than the nonobese subjects ($P=0.11$) and to lose a higher percentage of weight as fat ($P=0.13$).

DISCUSSION

We found that energy expenditure adjusted for metabolic mass increased with a weight gain and decreased with a weight loss. These changes in energy expenditure were evident during periods of stable altered body weight and were in a direction tending to return the subject to his or her initial weight; their magnitude was similar in nonobese and obese subjects. After a 10 percent gain in weight, the increase in total energy expenditure reflected a large increase in the absolute number of kilocalories of nonresting energy expenditure per day and a small increase in the absolute number of kilocalories per day attributed to the thermic effect of feeding. After a 10 or 20 percent loss in weight, the decline in total energy expenditure reflected similar decreases in both nonresting and resting energy expenditure.

In some studies, energy expenditure has been higher than that predicted for metabolic mass during weight

gain or maintenance of a higher body weight in non-obese subjects.¹⁹ In other studies,^{20,21} such an increase has not occurred. Resting energy expenditure declines during a period of weight loss,²² but whether a similar decline occurs when weight loss has stabilized is the subject of considerable debate.²³⁻²⁶ Likewise, there is a lack of agreement concerning the effect of weight reduction on total energy expenditure; both decreases (of 8 to 22 percent) and no change or increases (of approximately 9 percent, as compared with the values for weight-matched nonobese controls) have been reported.²⁷⁻²⁹

Several considerations are important in drawing conclusions from our findings. The alterations in energy expenditure do not reflect carryovers from the dynamic periods of weight change, since the measures of energy expenditure at the initial weight and after a return to that weight were similar, the anticipated changes in resting energy expenditure occurred during periods of weight change, and respiratory quotients at the various weight plateaus equaled that predicted for a stable weight while subjects were ingesting the dietary formula. Subtle shifts in body composition during periods of stable weight could have masked differences in energy expenditure among the weight plateaus. Such changes are unlikely, since they would have led to discrepancies between total energy expenditure as measured by formula titration and total energy expenditure as measured by elimination rates for $^2\text{H}_2\text{O}$ and H_2^{18}O . Yet these two measures were highly correlated and did not differ significantly at any weight plateau (unpublished data). In addition, respiratory quotients during all periods of stable weight equaled that predicted on the basis of the nutrient composition of the formula diet, suggesting that there was no net storage or catabolism of fat.

Although we did not examine the permanence of these changes in rates of energy expenditure, a reduced level of energy expenditure has been reported to persist in subjects who have maintained a reduced body weight for periods ranging from six months to more than four years.⁶ The aspect of body composition that mediates or signals these changes in energy expenditure is not known. In our study, the largest changes in body composition with weight alteration occurred in fat mass. A substantial body of literature suggests that the mass of adipose tissue or the size of adipocytes is the aspect of body composition that is regulated,³⁰ but the feedback mechanism for the effect of fat mass on energy metabolism is not known. A candidate gene for such a signal from fat has recently been cloned.³¹

The metabolic variable most affected by weight change was nonresting energy expenditure. Since it was not measured directly, the nature of the changes in this variable cannot be identified. Differences in the energy needed to move a larger or smaller body mass account for only some of the differences in energy expenditure, as suggested by Weigle and Brunzell, in whose study lost weight was replaced with backpack loads.³² This cannot be the entire explanation, however, since obese and lean subjects at their usual body

Table 3. Comparison of Resting Energy Expenditure and Respiratory Quotient at the End of a Period of Weight Gain or Loss and during Maintenance of the Altered Weight.*

PERIOD	NO. OF SUBJECTS	WEIGHT	RESTING ENERGY EXPENDITURE	RESPIRATORY QUOTIENT
		kg	kcal/day	
Weight gain	14	136.2±41.1	2391±750†	0.92±0.07‡
Weight maintenance (10% gain)		136.5±41.5	2102±573	0.86±0.07
Weight loss	8	127.9±25.4	1704±450§	0.78±0.08
Weight maintenance (return to initial weight)		129.1±26.5	2059±384	0.85±0.08
Weight loss	9	112.8±20.6	1598±385	0.73±0.06**
Weight maintenance (10% loss)		114.2±21.5	1747±416	0.83±0.08

*Results are means ±SD. All P values are for the comparison between weight gain or loss and weight maintenance.

† $P<0.001$.

§ $P=0.009$.

|| $P=0.043$.

‡ $P=0.03$.

¶ $P=0.029$.

** $P=0.014$.

weight have nearly equal nonresting energy expenditure, corrected for both fat-free mass and fat mass. One possibility is that the efficiency with which skeletal muscle performs mechanical work is different at different weight plateaus (decreased with a 10 percent gain in weight and increased with a 10 percent loss). The efficiency of muscular work before and after weight gain does not change, nor does the energy expenditure associated with moderate exercise.^{33,34} The effect of a change in weight on the energy expended during mild physical exertion, however, has not been systematically studied, and this minimal level of exertion may be most representative of the physical activity of sedentary adults. The possibility that changes in skeletal muscle have a role in mediating the alterations in energy expenditure that occur with weight loss may be the reason exercise is helpful in maintaining a reduced body weight.

Body weight in adults is remarkably stable for long periods of time. In the Framingham Study the body weight of the average adult increased by only 10 percent over a 20-year period.³⁵ Such a fine balance is evidence of the presence of regulatory systems for body weight.^{4,36} Whatever the mechanism (or mechanisms), the weight at which regulation occurs differs from one person to another, and these differences are almost certainly due in part to genetic^{37,38} and developmental³⁹ influences.

Our results have immediate implications for the clinical management of obesity. Many obese people who lose weight have metabolic alterations similar to those observed in our subjects. The reduction in energy expenditure to a level 15 percent below that predicted for body composition, as a result of a 10 percent (or larger) decrease in body weight, is large when one considers that an average daily intake of 2500 kcal would be associated with a positive energy balance of approximately 375 kcal per day. In addition, the sense of hunger or dysphoria that may accompany this state of reduced energy expenditure will promote increased food intake, further widening the gap between energy output and intake.³ Physicians should be aware that for some obese patients the achievement of what is considered to be a more healthful body weight may be accompanied by metabolic alterations that make it difficult to maintain the lower weight. Nevertheless, the beneficial effect of even a modest weight loss on lipid and carbohydrate metabolism in obese patients^{40,41} justifies persistent efforts at weight reduction and maintenance of a reduced body weight for the treatment of obesity.

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REFERENCES

1. Keesey RE, Corbett SW. Metabolic defense of the body weight set-point. In: Stunkard AJ, Stellar E, eds. *Eating and its disorders*. Vol. 62 of Research publications: association for research in nervous and mental disease. New York: Raven Press, 1984:87-96.
2. Leibel RL. A biologic radar system for the assessment of body mass: the model of a geometry sensitive endocrine system is presented. *J Theor Biol* 1977;66:297-306.
3. Weigle DS. Appetite and the regulation of body composition. *FASEB J* 1994;8:302-10.
4. Leibel RL. Is obesity due to a heritable difference in 'set point' for adiposity? *West J Med* 1990;153:429-31.
5. Ravussin E, Bogardus C. Relationship of genetics, age and physical fitness to daily energy expenditure and fuel utilization. *Am J Clin Nutr* 1989;49:968-75.
6. Leibel RL, Hirsch J. Diminished energy requirements in reduced-obese patients. *Metabolism* 1984;33:164-70.
7. Epstein FH, Higgins M. Epidemiology of obesity. In: Bjorntorp P, Brodoff BN, eds. *Obesity*. Philadelphia: J.B. Lippincott, 1992:330-42.
8. Department of Agriculture. Composition of foods: raw, processed, prepared. Agricultural handbook no. 8 series. Washington, D.C.: Government Printing Office, 1963:159-69.
9. Heymsfield SB, Wang J, Kehayias JJ, Heshka S, Lichtman S, Pierson RN Jr. Chemical determination of human body density in vivo: relevance to hydrodensitometry. *Am J Clin Nutr* 1989;50:1282-9.
10. Benedict FG, Fox EL. A method for determination of the energy values of foods and excreta. *J Biol Chem* 1925;66:783-99.
11. Ferrannini E. The theoretical bases of indirect calorimetry: a review. *Metabolism* 1988;37:287-301.
12. Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol* 1982;53:955-9.
13. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man: methods and results using a respiratory chamber. *J Clin Invest* 1986;78:1568-78.
14. Mazess RB, Peppler WW, Gibbons M. Total body composition by dual-photon (^{153}Gd) absorptiometry. *Am J Clin Nutr* 1984;40:834-9.
15. SAS/STAT user's guide: version 6. 4th ed. Cary, N.C.: SAS Institute, 1990.
16. Ravussin E, Burnand B, Schutz Y, Jequier E. Twenty-four-hour energy expenditure and resting metabolic rate in obese, moderately obese, and control subjects. *Am J Clin Nutr* 1982;35:566-73.
17. Blondheim SH, Mendelson B. Dietary thermogenesis: why the conflicting results? In: Berry EM, Blondheim H, Eliahou HE, Shafir E, eds. *Recent advances in obesity research*. London: John Libbey, 1987:151-4.
18. Ravussin E, Swinburn BA. Energy metabolism. In: Stunkard AJ, Wadden TA, eds. *Obesity: theory and therapy*. 2nd ed. New York: Raven Press, 1993:97-123.
19. Sims EAH, Danforth E Jr, Horton ES, Bray GA, Glennon JA, Salans LB. Endocrine and metabolic effects of experimental obesity in man. *Recent Prog Horm Res* 1973;29:457-96.
20. Norgan NG, Durbin JVGA. The effect of 6 weeks of overfeeding on the body weight, body composition, and energy metabolism of young men. *Am J Clin Nutr* 1980;33:978-88.
21. Tremblay A, Despres JP, Theriault G, Fournier G, Bouchard C. Overfeeding and energy expenditure in humans. *Am J Clin Nutr* 1992;56:857-62.
22. Forbes GB, Welle SL. Lean body mass in obesity. *Int J Obes* 1983;7:99-107.
23. Elliot DL, Goldberg L, Kuehl KS, Bennett WM. Sustained depression of the resting metabolic rate after massive weight loss. *Am J Clin Nutr* 1989;49:93-6.
24. Doré C, Hesp R, Wilkins D, Garrow JS. Prediction of energy requirements of obese patients after massive weight loss. *Hum Nutr Clin Nutr* 1982;36C:41-8.
25. Froidevaux F, Schutz Y, Christin L, Jequier E. Energy expenditure in obese women before and during weight loss, after refeeding, and in the weight-relapse period. *Am J Clin Nutr* 1993;57:35-42.
26. Amatruda JM, Statt MC, Welle SL. Total and resting energy expenditure in obese women reduced to ideal body weight. *J Clin Invest* 1993;92:1236-42.
27. deBoer JO, van Es AJH, Roovers LCA, van Raaij JM, Hautvast JG. Adaptation of energy metabolism of overweight women to low-energy intake, studied with whole-body calorimeters. *Am J Clin Nutr* 1986;44:585-95.
28. Weigle DS, Sande KJ, Iversius PH, Monsen ER, Brunzell JD. Weight loss leads to a marked decrease in nonresting energy expenditure in ambulatory human subjects. *Metabolism* 1988;37:930-6.
29. Astrup A, Buemann B, Christensen NJ, Madsen J. 24-Hour energy expenditure and sympathetic activity in postobese women consuming a high-carbohydrate diet. *Am J Physiol* 1992;262:E282-E288.
30. Faust IM. Role of the fat cell in energy balance physiology. In: Stunkard AJ, Stellar E, eds. *Eating and its disorders*. Vol. 62 of Research publications: association for research in nervous and mental disease. New York: Raven Press, 1984:97-107.

31. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425-32.
32. Weigle DS, Brunzell JD. Assessment of energy expenditure in ambulatory reduced-obese subjects by the techniques of weight stabilization and exogenous weight replacement. *Int J Obes* 1990;14:Suppl 1:69-77.
33. Weigle DS. Contribution of decreased body mass to diminished thermic effect of exercise in reduced-obese men. *Int J Obes* 1988;12:567-78.
34. Geissler CA, Miller DS, Shah M. The daily metabolic rate of the post-obese and the lean. *Am J Clin Nutr* 1987;45:914-20.
35. Belanger AJ, Cupples LA, D'Agostino RB. Means at each examination and inter-examination consistency of specified characteristics: Framingham Heart Study, 30-year followup. In: Kannel WB, Wolf PA, Garrison RJ, eds. *The Framingham Study: an epidemiological investigation of cardiovascular disease*. Sect. 36. Washington, D.C.: Government Printing Office, 1988. (NIH publication no. 88-2970.)
36. Harris RB. Role of set-point theory in regulation of body weight. *FASEB J* 1990;4:3310-8.
37. Bogardus C, Lillioja S, Ravussin E, et al. Familial dependence of the resting metabolic rate. *N Engl J Med* 1986;315:96-100.
38. Bouchard C, Perusse L. Genetics of obesity. *Annu Rev Nutr* 1993;13:337-54.
39. Knittle JL, Timmers K, Ginsberg-Fellner F, Brown RE, Katz DP. The growth of adipose tissue in children and adolescents: cross-sectional and longitudinal studies of adipose cell number and size. *J Clin Invest* 1979;63:239-46.
40. Olefsky J, Reaven GM, Farquhar JW. Effects of weight reduction on obesity: studies of lipid and carbohydrate metabolism in normal and hyperlipoproteinemic subjects. *J Clin Invest* 1974;53:64-76.
41. Jimenez J, Zuniga-Guajardo S, Zinman B, Angel A. Effects of weight loss in massive obesity on insulin and C-peptide dynamics: sequential changes in insulin production, clearance, and sensitivity. *J Clin Endocrinol Metab* 1987;64:661-8.