Energy Metabolism in Response to Overfeeding in Young Adult Men

Samuel Klein and Michael Goran

The effect of overfeeding on energy metabolism was evaluated in four young adult men of normal weight. Subjects were fed a hypocaloric diet for 8 days followed by an 8-day hypercaloric diet to maximize differences in the metabolic response to the two diets. Energy intake during the hypocaloric and hypercaloric phases was 1.32 and 2.26 times resting metabolic rate (RMR), respectively. Additional calories during hypercaloric feeding were provided as 1,659 ± 40 kcal/d carbohydrate and lipid. Total daily energy expenditure (TDEE) was measured by the doubly labeled water technique and RMR by indirect calorimetry. Nonresting energy expenditure (NREE) was calculated as the difference between TDEE and RMR. During the 8-day hypocaloric diet period, energy intake was approximately 340 kcal/d less than the measured rate of TDEE (2,384 ± 219 kcal/d) and the subjects lost 0.8 ± 0.3 kg body weight. During the 8-day hypercaloric diet period, TDEE increased by 425 ± 103 kcal/d ($P = .03$), which dissipated 25% ± 5% of the increased energy intake. One fourth of the increase in TDEE was caused by an increase in RMR (110 ± 24 kcal/d, $P = .02$) and the remainder by an increase in NREE (316 ± 103 kcal/d, $P = .05$). These results demonstrate that only a small portion of excess energy intake is dissipated by an increase in energy expenditure. NREE can be an important component of the increase in energy metabolism during overfeeding.

BODY WEIGHT STABILITY over long periods of time reflects an extraordinary relationship between energy intake and energy expenditure. Most adult humans in Western civilizations ingest approximately 900,000 kcal/yr without large changes in body weight.[1] Even small differences in daily energy balance over long periods of time could have dramatic effects on body weight. For example, ingesting only 25 kcal/d more than expended, a 1% error in energy balance, would theoretically cause an accumulation of about 1 kg body fat in 1 year. Therefore, it is remarkable that without conscious effort most persons match energy intake so closely with energy expenditure and can maintain a constant weight.

The effect of overfeeding on energy metabolism has important public health and clinical implications because the accumulation of fat in obese persons is caused by long-term excessive caloric intake. It has been proposed that energy expenditure increases during overfeeding because weight gain has often been found to be less than that theoretically predicted by the amount of excess calories ingested.[2-5] However, studies that have actually measured total energy expenditure during overfeeding have been confusing because of conflicting results. Total energy expenditure has been reported to decrease,[6] remain the same,[7,8] or increase[9-11] after increasing caloric intake.

In evaluating the adaptative response of energy metabolism to overfeeding, it is important to take into account the various components of total daily energy expenditure (TDEE)—resting metabolic rate (RMR), thermic effect of food (TEF), and thermic effect of physical activity (TEPA).[12] Most studies have reported a small increase in RMR after overfeeding.[6,11,13-14] The absolute TEF is also increased because TEF is a direct function of the amount of calories ingested.[15] The effect of overfeeding on physical activity is difficult to examine because of practical limitations in its measurement. The daily energy costs associated with physical activity include the energy cost required for the activities of daily living, exercise, spontaneous physical activity, and fidgeting. Energy expended by physical activity should increase during overfeeding if body mass increases and activity is maintained.[10]

It seems logical that TDEE would increase during overfeeding because of increases in the individual components of energy expenditure. TDEE measured by whole-body chamber calorimetry has been shown to increase by 21%, representing one third of the excess caloric intake.[11] However, these measurements were made under conditions that restrict physical activity and thereby could have attenuated the full thermogenic response. Surprisingly, Roberts et al,[8] using the doubly labeled water technique to measure TDEE in free-living subjects, found that TDEE did not increase during overfeeding compared with values obtained during a maintenance diet period. However, their subjects were very active during maintenance feeding and required 185% of measured RMR to maintain stable body weight. The high energy cost of physical activity during maintenance feeding could have blunted the ability to increase TDEE during overfeeding by reducing the capacity to increase RMR[16] and physical activity during overfeeding.

In the present study, we evaluated energy metabolism in response to overfeeding in healthy young adult men. TDEE was measured by the doubly labeled water technique[17] and RMR by indirect calorimetry during an 8-day basal diet period (kcal intake = 132% of RMR) and an 8-day high-calorie diet period (kcal intake = 226% of RMR). In contrast to earlier studies, a mildly hypocaloric diet rather than a maintenance diet was provided before overfeeding

From the Department of Internal Medicine and the Department of Preventive Medicine and Community Health, The University of Texas Medical Branch, Galveston, TX.

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Current address: M.G., Department of Medicine, Division of Endocrinology, Metabolism and Nutrition, University of Vermont, Burlington, VT.

Address reprint requests to Samuel Klein, MD, The University of Texas Medical Branch, Division of Gastroenterology, G-64, Galveston, TX 77555-0764.

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to reduce energy flux and thereby maximize the differences in thermogenic response to the two diets.

SUBJECTS AND METHODS

Subjects

Four male volunteers of normal weight participated in the study (Table 1). They were considered to be in good health after a comprehensive medical evaluation that included a complete history, physical examination, routine blood tests, and electrocardiogram. All subjects ingested their regular diet and were weight-stable for at least 10 days before initiation of the study. The study was approved by the Institutional Review Board and the Clinical Research Center of The University of Texas Medical Branch at Galveston, and all subjects gave written informed consent before their participation.

Experimental Protocol

Subjects were admitted to the Clinical Research Center of The University of Texas Medical Branch at Galveston for 17 days. They were free to move around within the Clinical Research Center during the study and had access to a stationary bicycle ergometer; however, physical activity was not directly monitored. Each subject ingested a regular hospital meal at 6:00 PM on the day of admission. Indirect calorimetry, using a metabolic cart with face mask system (SensorMedics, Anaheim, CA), was performed the following morning (day 1) after subjects had fasted for 12 to 14 hours to determine carbon dioxide production, oxygen consumption, and RMR. Measurements were taken every 30 seconds for 15 to 20 minutes while subjects were lying comfortably in a darkened and quiet room. Indirect calorimetry was subsequently performed every morning during the study after subjects had fasted for 12 to 14 hours overnight.

After baseline indirect calorimetry measurements were obtained on day 1, subjects were started on a liquid formula diet composed of chocolate-flavored Ensure (Ross Laboratories, Columbus, OH) plus additional carbohydrate and lipid calories as Polycose (Ross Laboratories) and Lipomul (Upjohn, Kalamazoo, MI), respectively, as needed to achieve the targeted intake of energy, protein, carbohydrate, and fat. A single manufacturer's lot of each product was used for all subjects to reduce potential nutrient variability; all nutrient intake was restricted to the liquid formula diet. A hypocaloric diet was consumed during the first 8 days of the study followed by a hypercaloric diet during the last 8 days. The amount of Ensure given daily during both the low- and high-calorie diet periods was the same and provided 1 g protein/kg initial body weight/d. Energy intake during the low-calorie diet was targeted to equal 130% of the RMR measured on day 1. Polycose and Lipomul were added to the diet formula so that approximately 60% of nonprotein calories were provided as carbohydrate and 40% as lipid. Daily energy intake was increased by approximately 1,650 kcal during the high-calorie diet period, with Polycose and Lipomul each providing half (825 kcal) of the increase in calories. The total liquid diet consumed each day was prepared in the morning, divided into four identical servings, and given to the subjects at 8:00 AM and 12:00, 4:00, and 8:00 PM. Complete ingestion of the entire liquid formula diet was ensured by observing the subjects during every meal.

Table 1. Characteristics of Study Subjects

Subject No.	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)
1	24	179	74	23.1
2	29	178	69	21.8
3	35	167	65	23.3
4	32	168	66	23.4
Mean ± SE	30 ± 2	173 ± 3	69 ± 2	22.9 ± 0.4

TDEE was measured during each 8-day dietary period using the doubly labeled water technique.[17] At 7:00 AM on day 1, a urine sample was obtained to determine background enrichment of ^2H and ^{18}O. At 7:30 AM, subjects ingested a mixture of ^2H_2O (0.1 g ^2H/kg) and $H_2{}^{18}O$ (0.2 g ^{18}O/kg) followed by two 75-mL vial rinses with tap water; blood was collected 4 hours later for analysis of total body water. Subsequently, subjects voided each morning at 6:00 and 7:30 AM. The second voided specimen was collected daily to measure ^2H and ^{18}O enrichment. The 8-day period from the morning of day 1 to the morning of day 9 and the 8-day period from the morning of day 9 to the morning of day 17 were used to evaluate TDEE while the subjects ingested low- and high-calorie diets, respectively. The possibility that significant de novo lipogenesis occurred during overfeeding was reduced by supplying dietary fat in a quantity that was almost twice the amount of estimated fat deposition.

Analysis of Samples

Urine samples were stored in sealed Vacutainer tubes (Terhumo Medical, Elkton, MD) at −70°C until analysis by isotope ratio mass spectrometry. Samples were analyzed in duplicate for $H_2{}^{18}O$ and ^2H_2O using the carbon dioxide equilibration technique[18] and the off-line zinc reduction method,[19] respectively, as previously described.[20] Briefly, the carbon dioxide equilibration technique involved dispensing 1.5 mL of sample into a 10-mL Vacutainer tube and filling it with 99.9% pure carbon dioxide. The sample was shaken overnight to achieve equilibration of ^{18}O in water and carbon dioxide. The carbon dioxide was introduced into a VG Sira II isotope ratio mass spectrometer through an automated carousel sample system (VG, Middlewhich, Cheshire, UK) and analyzed for the ratio of mass 46:44. With this method, the average standard deviation for 91 sets of triplicate samples analyzed for $H_2{}^{18}O$ enrichment with average enrichment of 93.8% was ±0.4%.[20] The zinc reduction method used the quartz reduction vessels described by Wong and Klein[21] and a ratio of 3 μL sample (undistilled) with 100 mg zinc (Biogeochemical Laboratories, Bloomington, IN). Reduction was achieved by heating at 500°C for 30 minutes in an aluminum block (Biogeochemical). The ratio of mass/charge 3 to mass/charge 2 in the hydrogen gas produced was analyzed with a VG Sira II isotope ratio mass spectrometer equipped with a 20-port automated inlet system. We have previously found that with this method, the average standard deviation for 65 sets of triplicate ^2H_2O samples with mean sample enrichment of 334.0% was ±2.8%.[20]

Calculations

Urine samples from the first and last 2 days of each study period were used to calculate turnover rates of $H_2{}^{18}O$ and ^2H_2O based on the slope and intercept of the semilogarithmic plot of isotope enrichment in urine versus time after dosing. This 2-point approach was used in favor of the multipoint approach because it is more robust to physiologic variation in water and energy flux.[22,23]

Total body water was calculated by measuring the increase in enrichment of ^{18}O in plasma 4 hours after ingestion of $H_2{}^{18}O$.[24] Carbon dioxide production rates were calculated using equation A6 of Schoeller et al,[17] as follows:

$$rCO_2 = \frac{N}{2.078}(1.01\,K_0 - 1.04\,Kh),$$

where rCO_2 is the rate of carbon dioxide production, N is total

body water, K_0 is the turnover rate of $H_2{}^{18}O$, and K_h is the turnover rate of ^2H_2O. Oxygen consumption was derived by dividing the rate of carbon dioxide production by a modified food quotient.[25] The dietary food quotient was adjusted to account for negative and positive energy balances during hypocaloric and hypercaloric feeding periods. During underfeeding, it was assumed that endogenous adipose tissue triglycerides were oxidized to compensate for the deficit in energy intake. During overfeeding, it was assumed that 87% of energy intake not metabolized as fuel was deposited as fat[5]; 10% of fat accretion was considered to come from de novo lipogenesis and 90% from dietary lipid deposition. TDEE was calculated using equation 12 of de Weir.[26]

Nonresting energy expenditure (NREE) during each 8-day dietary period was calculated as the difference between TDEE and the average daily RMR measured during that period. During the low-calorie diet period, NREE represented contributions from TEF and TEPA. During the high-calorie diet period, NREE represented contributions from TEF, TEPA, and the energy cost of fat accretion.

Statistical Analysis

All data are presented as means ± standard error. The statistical significance of differences between measurements obtained during the basal and high-calorie diet periods was evaluated using a two-tailed Student's *t* test for paired samples.

RESULTS

Dietary intakes during the low- and high-calorie diet periods are shown in Table 2. Daily total caloric intake increased by 1,659 ± 40 kcal during the high-calorie diet period. Protein intake was the same during both dietary periods so that the percentage contribution of dietary protein to total calories decreased in proportion to the increase in total calorie ingestion. Each subject experienced mild hunger during the basal diet period, but complained of fullness and satiety during the high-calorie diet period.

Daily changes in body weight during the study period are shown in Fig 1. At the end of the mildly hypocaloric basal diet period, subjects had lost 0.80 ± 0.34 kg body weight. Initial weight loss during the first 4 days of the basal diet was more rapid than during the last 4 days when body weight plateaued. Increasing caloric intake during the 8-day high-calorie diet period caused a total positive energy balance of 7,144 ± 1,750 kcal and a mean increase in weight of 1.49 ± 0.43 kg. Subjects' mean final weight was 0.70 ± 0.54 kg greater than the prestudy body weight.

Table 2. Dietary Intake During Basal and High-Calorie Diet Periods

Nutrient Intake	Basal Diet	High-Calorie Diet
Energy		
kcal/d	2,044 ± 66	3,703 ± 106
% RMR	132 ± 1	226 ± 5
Protein		
g/d	68.3 ± 1.9	68.3 ± 1.9
% Total energy	13.3 ± 0.1	7.4 ± 0.1
Carbohydrate		
kcal/d	1,088 ± 24	1,914 ± 55
% Total energy	53.2 ± 0.3	51.7 ± 0.03
Fat		
kcal/d	690 ± 28	1,512 ± 43
% Total energy	33.7 ± 0.2	40.8 ± 0.04

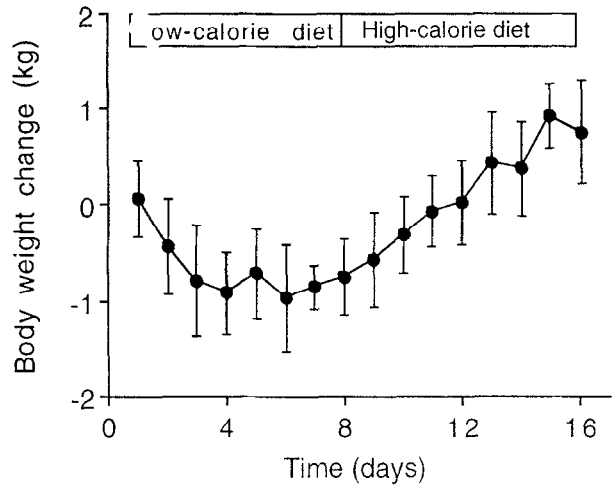

Fig 1. Change in body weight (mean ± SE) during ingestion of a hypocaloric diet for 8 days followed by a hypercaloric diet for 8 days in four young adult men of normal weight. The low-calorie diet provided approximately 130% of resting energy requirements, and the high-calorie diet consisted of the basal diet plus 1,659 ± 40 mixed carbohydrate and fat calories providing approximately 225% of resting energy requirements.

Table 3 summarizes data used in calculating TDEE, and Table 4 summarizes changes in energy metabolism during the two diet periods. There was an 18% ± 3% (425 ± 103 kcal/d) increase in TDEE during overfeeding ($P = .015$), which accounted for 25% ± 5% of the increased energy intake. Both resting and nonresting components of energy expenditure increased in each subject during the high-calorie diet period. At the end of the high-calorie diet period, RMR increased by 110 ± 24 kcal/d ($P = .02$), which was 8% ± 2% greater than the baseline value. The increase in RMR during overfeeding accounted for about 26% of the increase in TDEE and represented about 6% of the increased caloric intake. NREE increased by 316 ± 103 kcal/d during overfeeding ($P = .05$), which was 42% ± 15% greater than NREE during the basal diet period and accounted for about 74% of the increase in TDEE and about 19% of the increased energy intake.

DISCUSSION

In the present study, we evaluated the effect of mixed-diet overfeeding on energy expenditure in young adult men. Increasing energy intake by 1,660 kcal/d for 8 days after short-term hypocaloric feeding in our subjects caused an 18% increase in the rate of TDEE. The increase in energy expenditure accounted for approximately one fourth of the increased caloric intake, whereas approximately three

Table 3. Doubly Labeled Water Data

	Low-Calorie Diet	High-Calorie Diet
Total body water (mol)	2,050 ± 131	2,070 ± 127
Rate of ^2H disappearance (d^{-1})	0.11803 ± 0.02748	0.11204 ± 0.01050
Rate of ^{18}O disappearance (d^{-1})	0.14247 ± .02975	0.14112 ± 0.01218
Modified food quotient	0.85 ± 0.01	0.92 ± 0.01

Table 4. Energy Intake, Expenditure, and Balance During Low- and High-Calorie Diet Periods

	Low-Calorie Diet	High-Calorie Diet	Difference	P
Energy intake	2,044 ± 66	3,703 ± 106	1,659 ± 40	.0001
Energy expenditure				
TDEE	2,384 ± 219	2,809 ± 291	425 ± 103	.03
RMR	1,529 ± 53	1,639 ± 40	110 ± 24	.02
NREE	855 ± 190	1,171 ± 262	316 ± 103	.05
Energy balance*	−340 ± 167	893 ± 219	1,233 ± 95	.001

NOTE. Values are kcal/d (means ± SE).
*Daily intake minus TDEE.

fourths of the increased calories were stored. Both resting and nonresting components of energy expenditure increased during overfeeding.

Our study differs from earlier studies of overfeeding in that a mildly hypocaloric diet providing approximately 130% of resting energy requirements was given before overfeeding in an attempt to enhance differences in the metabolic response to the two diets. During overfeeding, an additional 1,660 kcal/d composed of an equicaloric mixture of carbohydrate and fat was given in conjunction with the basal diet. Nutrient intake was precisely measured by providing all food as a defined liquid formula under close observation in a metabolic ward. Despite differences in study design, our results agree with most other overfeeding studies[7-11] in demonstrating that the thermogenic adaptation to short-term overfeeding is small.

The results from our study underscore the importance of NREE (TEF, TEPA, and energy cost of fat accretion) in regulating energy metabolism during overfeeding. Approximately two thirds of the increase in TDEE during high-calorie feeding was caused by an increase in NREE. Assuming that TEF was equal to 8% to 10% of energy intake,[7,11,15] the increase in TEF would account for approximately 50% of the increase in NREE and 40% of the increase in TDEE observed during overfeeding. The energy cost of fat accretion during overfeeding can be estimated by assuming that 10% of the lipid originated from de novo lipogenesis and 90% from dietary fat. Because the energy requirement of de novo lipogenesis is estimated to be about 23% of carbohydrate calories and lipid deposition about 3% of lipid calories,[27] the energy cost of fat accretion represented approximately 12% of the increase in NREE and 9% of the increase in TDEE. The remaining component of NREE, TEPA, would therefore account for about 35% of the increase in NREE and about 25% of the increase in TDEE.

Differences in the energy cost of physical activity may explain the differences in TDEE observed during mixed overfeeding among studies.[6,8-11] Ravussin et al[11] also found that TEPA was an important factor for increasing energy expenditure in response to overfeeding. In their study, the increase in TEPA during overfeeding accounted for approximately 40% of the increase in TDEE even though their subjects were restricted to a respiratory chamber. In contrast, in the only other study to use the doubly labeled water technique to examine the effect of mixed-diet overfeeding, Roberts et al[8] found that TEPA did not change during overfeeding in free-living subjects. The subjects studied by Roberts et al[8] were extremely active during the maintenance diet period and required 1.85 times the RMR in energy intake to maintain a constant body weight. This high level of activity might have reduced their capacity to further increase physical activity energy expenditure during overfeeding. In contrast to the differences reported regarding TEPA, the increase in RMR relative to the excess caloric intake was similar among studies. Therefore, the results of our study taken in the context of results from earlier studies suggest that the alterations in involuntary energy metabolism such as RMR during overfeeding are minimal and predictable, whereas voluntary alterations such as changes in physical activity can vary widely. In addition, the small number of subjects evaluated in each study could have contributed to the variability observed between studies. Our study involved only four subjects, whereas Roberts et al[8] and Ravussin et al[11] included only seven and five subjects, respectively.

Adaptive changes in physical activity have also been described in response to other external stimuli. Semistarvation is associated with a reduction in physical activity[28] that serves to reduce energy expenditure when fuel supply is limited. Recent data suggest that strenuous exercise may reduce postexercise physical activity. Rigorous training in elderly persons caused a 60% reduction in physical activity during the remainder of the day.[29] These observations in conjunction with the results of the present study and those of Ravussin et al,[11] suggest that alterations in physical activity provide a potential mechanism for dissipating excess energy intake during overfeeding and preserving fuel economy during periods of negative energy balance.

In summary, results of the present study suggest that both resting and nonresting components of energy expenditure can increase during short-term overfeeding. However, the alterations in total energy expenditure were small and only a portion of the excess energy ingested was dissipated. These data provide further support to the notion that humans are limited in their capacity to increase TDEE in response to changes in energy intake.

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