Fat and carbohydrate overfeeding in humans: Different effects on energy storage

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Fat and carbohydrate overfeeding in humans: different effects on energy storage[1–3]

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ABSTRACT Both the amount and composition of food eaten influence body-weight regulation. The purpose of this study was to determine whether and by what mechanism excess dietary fat leads to greater fat accumulation than does excess dietary carbohydrate. We overfed isoenergetic amounts (50% above energy requirements) of fat and carbohydrate (for 14 d each) to nine lean and seven obese men. A whole-room calorimeter was used to measure energy expenditure and nutrient oxidation on days 0, 1, 7, and 14 of each overfeeding period. From energy and nutrient balances (intake−expenditure) we estimated the amount and composition of energy stored. Carbohydrate overfeeding produced progressive increases in carbohydrate oxidation and total energy expenditure resulting in 75–85% of excess energy being stored. Alternatively, fat overfeeding had minimal effects on fat oxidation and total energy expenditure, leading to storage of 90–95% of excess energy. Excess dietary fat leads to greater fat accumulation than does excess dietary carbohydrate, and the difference was greatest early in the overfeeding period. *Am J Clin Nutr* 1995;62:19–29.

KEY WORDS Obesity, nutrient partitioning, nutrient balance, energy balance, diet composition

INTRODUCTION

Obesity is a major health problem affecting more than 34 million Americans (1). An understanding of how obesity develops is necessary to develop strategies for its prevention and treatment. This could be facilitated by a better ability to identify individuals who are at risk of developing obesity. Such individuals may be characterized by a metabolic and/or a behavioral susceptibility to weight gain (2). Hill et al (2) proposed that behavioral susceptibility to obesity creates the opportunity for positive energy balance to occur (eg, overeating and underexercising), whereas metabolic susceptibility to obesity determines the metabolic fate of the excess energy when positive energy balance occurs. For example, an individual with a high metabolic susceptibility to obesity would be inclined to accumulate more body fat but less glycogen during periods of positive energy balance than would an individual with a lesser metabolic susceptibility to obesity.

There are substantial data to suggest that individuals differ in their behavioral response to different environmental conditions. For example, many human subjects consume more total energy on a high- than on a low-fat diet (3–6). Similarly, it is unlikely that all subjects will show the same gain in body weight and body fat when subjected to positive energy balance. This was demonstrated in the overfeeding studies of Sims et al (7) and Bouchard et al (8). Contrary to the concept of "luxuskonsumption", many recent studies have demonstrated that the majority of excess energy is stored and not expended as heat during overfeeding (9–11). However, differences between energy stored and energy expended and differences in the composition of the fuel mixture oxidized may lead to important individual differences in the metabolic fate of excess energy under conditions of positive energy balance. These differences could stem from differences in partitioning of excess energy into *1*) storage compared with expenditure, *2*) storage in adipose tissue compared with storage in lean body mass, and *3*) storage in visceral compared with peripheral adipose tissue.

Diet composition clearly has an important influence on body-weight regulation. The strongest evidence for this comes from rodent studies in which high-fat diets have been shown to produce obesity independently of total energy intake (12, 13). In human subjects, diet composition can influence total energy intake (3–6) and can alter nutrient balance without changing total energy expenditure (14, 15). In response to acute changes in diet composition, it has been shown that human subjects increase carbohydrate oxidation and total energy expenditure in response to excess carbohydrate (16), but fail to increase fat oxidation or energy expenditure in response to excess fat (17–19). This suggests that under conditions of excess, dietary fat leads to greater fat accumulation than does dietary carbohydrate.

Energy and nutrient balances can be assessed during dietary challenges by combining indirect calorimetry with dietary control. A major advantage of this technique is that changes in body nutrient stores can be detected well before they could be measured with available techniques for assessing body composition. In this study we used this approach to determine how lean and obese men partitioned excess energy provided as carbohydrate or fat.

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SUBJECTS AND METHODS

Subjects

Male subjects aged 18–46 y were recruited for the study. Subjects were excluded if they smoked or if they had a history of diabetes, cardiovascular disease, or major health problems other than obesity. Highly trained individuals and subjects habitually consuming a very-low- or very-high-fat diet were excluded. Nine lean (90–110% of ideal body weight as determined by the 1983 Metropolitan Life Insurance Tables; 20) and seven obese (130–180% of ideal body weight) subjects completed the study. The protocol was approved by the Committee for the Protection of Human Subjects of Vanderbilt University.

Table 1 shows the descriptive characteristics of study participants and their estimated baseline energy requirements. Lean subjects had a significantly greater maximum oxygen consumption ($\dot{V}O_2max$) than obese subjects. Initial body weight, percent body fat, fat-free mass (FFM), fat mass (FM), and age were all significantly greater in the obese group than in the lean group. Similarly, obese subjects had higher baseline energy requirements and lower levels of physical activity. The percent fat in the baseline diet did not differ between lean and obese subjects.

Experimental design

Each subject completed two separate 14-d periods of overfeeding. Each overfeeding period was preceded by 1 wk of consuming a baseline (maintenance) diet. Excess energy was set at 50% above baseline energy intake and was provided entirely as fat during one period and as carbohydrate during the other. Subjects spent 24-h in a whole-room indirect calorimeter to determine energy and nutrient balances on day 7 of baseline (which corresponds to day 0 of the protocol) and on days 1, 7, and 14 of each overfeeding period. This allowed us to estimate how much excess energy was expended compared with stored, as well as the form of stored energy in the body. Physical activity was held constant throughout the study as described below. Sample diets are shown in **Appendix A**.

TABLE 1
Subject characteristics[1]

	Lean subjects (n = 9)	Obese subjects (n = 7)
Age (y)	28.6 ± 5.4	37.6 ± 5.3[2]
Height (m)	1.79 ± 0.07	1.79 ± 0.03
Weight (kg)	68.4 ± 9.9	103.9 ± 10.9[2]
$\dot{V}O_2$ max ($mL \cdot kg^{-1} \cdot min^{-1}$)	41.7 ± 4.7	31.5 ± 3.8
Percent body fat (%)	21.4 ± 3.2	35.4 ± 5.2[2]
Fat mass (kg)	14.7 ± 3.2	37.0 ± 8.2[2]
Fat-free mass (kg)	53.8 ± 7.8	66.9 ± 6.2[2]
Body mass index (kg/m^2)	21.3 ± 1.5	32.3 ± 2.7[2]
Baseline energy requirements (kJ/d)	11 123 ± 961	13 965 ± 836[2]
Percent fat in baseline diet (%)	36 ± 3	33 ± 2.5
Baseline activity (Caltrac units)[3]	345 ± 33	237 ± 10[2]

[1] $\bar{x}$ ± SEM.
[2] Significantly different from lean, $P < 0.01$.
[3] One caltrac unit = 0.5 METS (one MET is equal to the oxygen consumption of a seated individual at rest, ≈3.5 $mL \cdot kg^{-1} \cdot min^{-1}$).

Determination of baseline energy requirements

We took great care to accurately assess usual energy intake during baseline to ensure that the degree of overfeeding was similar for each subject. After recruitment, each subject completed a 14-d weighed diet diary to estimate their usual food intake. Subjects met with a dietitian and were provided with a set of weighing scales and given detailed instructions of how to accurately complete the diet record by describing types of food consumed and to record appropriate weights. Periodic checks were made to ensure that subjects were completing the record in the required manner.

One week after completing the diet records, subjects began the first dietary control phase. For 1 wk, subjects were fed a baseline diet reflecting their self-reported habitual intake of energy, fat, carbohydrate, and protein, as assessed from their diet records. The diets consisted, as much as possible, of the foods usually consumed by the subjects and were delivered in a pattern approximating the subject's usual pattern. Additional food modules (838 kJ), of the same nutrient composition as the diet, were available on request. Use of these modules was previously described (3). This approximated ad libitum feeding. All food was provided and prepared by the Clinical Research Center (CRC) metabolic kitchen, and subjects were required to consume at least one meal at the CRC each day. All other food was packaged to be taken away and eaten in the subject's home or workplace. Body weight was measured daily during the baseline diet to confirm weight stability. In response to trends to decrease body weight (there were no trends to increase body weight), the dietitian met with the subject to alter the diet plan as needed to reachieve weight stability.

Each subject's usual level of physical activity was estimated by using Caltrac accelerometers (Hemokinetics Inc, Madison, WI). Each subject wore an accelerometer for 7 d before beginning the overfeeding period. The accelerometer clips to the waistband or pocket at the front of the body and measures whole-body acceleration. It can be programmed to measure movement in units, where 1 unit = 2.0 METS. One MET is equal to the oxygen consumption of a seated individual at rest, which is ≈3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (21). Other activities that the accelerometer cannot monitor (swimming, cycling, calisthenics, weight training, etc) were recorded separately in terms of type of activity, intensity, and duration. The Caltrac values were averaged over the initial 7-d period, including estimates of the unit equivalent of other activity [(METS/min activity × duration) × 0.5]. This value was used to design an appropriate activity routine while the subject stayed in the whole-room calorimeter and to check for possible changes in activity during the overfeeding periods. Each subject spent the last baseline day in the whole-room calorimeter eating at his usual energy intake and undergoing a usual physical activity routine. It is obviously not possible to exactly reproduce usual physical activity in a room calorimeter, but for each subject, activity in the calorimeter was constant during each stay and in the range of usual activity.

Overfeeding: phase 1

Immediately after the baseline week, subjects began the first overfeeding period, which lasted for 14 d. Subjects were fed a diet providing 150% of their energy intake during the baseline week. The additional 50% of energy was given as either all fat or all carbohydrate. All food was provided by the CRC. Daily energy expenditure and nutrient oxidation were measured in the whole-room calorimeter on days 1, 7, and 14 of overfeeding. Subjects did not have access to food modules during the overfeeding periods. Activity was monitored (with Caltrac accelerometers) during the last 7 d of overfeeding.

Overfeeding: phase 2

A 4-wk washout period separated the first and second phases of the experimental period. During the first 3 wk subjects were free to consume whatever food they chose. In the fourth week subjects were fed the diet reflecting their habitual intake. The second overfeeding phase mirrored the first exactly except that the form of the excess energy (fat or carbohydrate) was switched. The diets were administered in a randomized crossover design.

Dependent measures

A treadmill test to exhaustion, using the protocol of Bruce et al (21), was used to estimate maximal oxygen uptake of subjects. Body weight and height were measured on a Platform Detecto scale (Webb City, MO) and graduated wall meter, respectively. Body composition was estimated from body density by using underwater weighing to determine body volume, with simultaneous measurement of residual lung volume with the closed-circuit, nitrogen-dilution technique (22). Percent body fat was estimated from body density by using the revised equation of Brozek et al (23). Body weight was measured on each morning before entering the metabolic chamber and body composition was determined immediately before and after each overfeeding period.

Blood was taken from each subject to determine circulating concentrations of free fatty acids, insulin, and glucose. Samples were taken after an overnight fast during the week before beginning each overfeeding period and at the end of each overfeeding period.

Total daily energy expenditure and substrate oxidation were measured in a whole-room indirect calorimeter, located in the CRC, as described previously (3, 14, 24). Subjects entered the chamber at 0800 and left the following day at 0700. Results were extrapolated to 24 h. Oxygen consumption and carbon dioxide production were determined from the flow rate and differences in gas concentrations between entering and exiting air. Values were corrected for temperature, barometric pressure, and humidity. Energy expenditure was calculated from oxygen consumption and respiratory quotient (RQ). The operation of the chamber was controlled by a personal computer by using a software program written in TURBO C. The program was based on calculations described by Jequier et al (25). Values for all indexes were averaged over 2-min intervals and recorded in a data file. An activity button system was linked to the computer. This was used to mark events (eg, sleep, meals, exercise) and the appropriate button was pressed before commencing and on completion of an event.

Energy expenditure due to activity was estimated by using a mechanical-force platform serving as the chamber floor. The platform detects vertical and horizontal displacement of the center of gravity and is capable of detecting displacements as small as 50 g. This system was described in detail elsewhere and has been shown to be accurate to within 1% (26). The accelerometer was worn during each chamber stay and subjects performed a prescribed amount of walking and stepping exercises, aimed at mimicking the total amount of activity usually performed outside the chamber. Walking was performed at a rate of 8 m/10 s and stepping at 4 steps/10 s. The number and duration of exercise bouts was individually adjusted to achieve a value similar to the average accelerometer reading. Activity was scheduled at 1030, 0130, 1600, and 1900 when necessary. Subjects collected all of their urine while in the calorimeter. Aliquots were analyzed for total nitrogen content (27).

Data analysis

Results were analyzed by using repeated-measures analysis of variance (ANOVA) with obesity status as a grouping factor (lean compared with obese). Diet (overfeeding fat compared with overfeeding carbohydrate) and time (measures at baseline and days 1, 7, and 14 for each diet) were repeated-measures factors. A nonparametric Mann-Whitney U test was used to establish any differences in initial subject characteristics. SAS statistical software (SAS Institute, Cary, NC) was used for the analysis.

RESULTS

Body weight and body composition

Body weight increased significantly after both fat and carbohydrate overfeeding ($P < 0.001$), with the greatest increase occurring between days 1 and 7 (**Figure 1**). Baseline body weight was significantly positively correlated with weight gain during the carbohydrate ($r = 0.55$, $P < 0.05$) but not the high-fat ($r = 0.34$, NS) overfeeding. At the end of the washout period, body weight had declined to near prestudy values. The body weights for lean subjects before the first and second

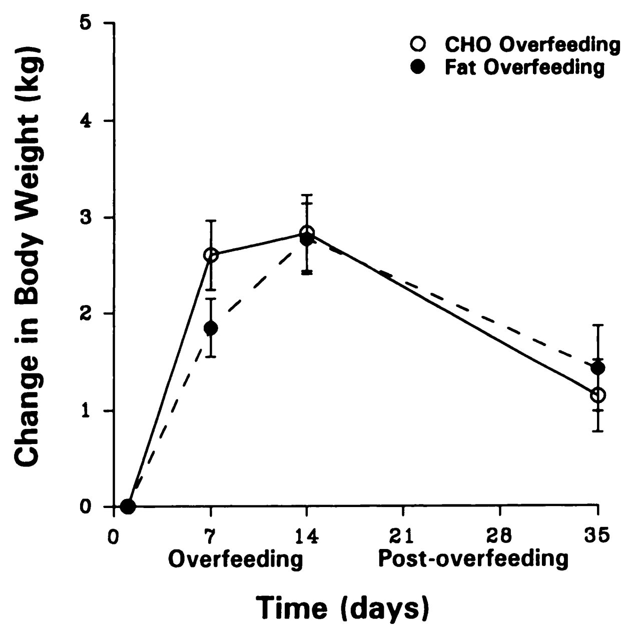

FIGURE 1. Changes in body weight during and for 21 d after fat and carbohydrate (CHO) overfeeding in 16 male subjects.

overfeeding periods were 68.1 ± 3.3 and 68.8 ± 7.3 kg, respectively. For obese subjects the weights before the first and second overfeeding periods were 103.7 ± 9.1 and 105.1 ± 9.1 kg, respectively.

Body-composition changes, as determined by underwater weighing, are shown in **Table 2**. FM and FFM increased significantly with carbohydrate overfeeding ($P < 0.02$) and fat overfeeding ($P < 0.001$). There were no significant differences between diets and/or groups in body weight or body-composition changes. The percentage of weight gained as FM (54–56%) or FFM (44–46%) was similar between diets and groups. Note, however, that the changes in body composition were very small and near the detection limits of our technique. The study was not designed to produce significant alterations in body composition, but rather to predict changes in body stores of protein, carbohydrate, and fat from measures of intake and oxidation of each.

Energy balance

The increase in energy expenditure caused by fat overfeeding was not statistically significant. With carbohydrate overfeeding there was a significant increase in energy expenditure on days 7 and 14 (**Figure 2**). We assumed that excess energy not expended was stored in the body. **Figure 3** shows the estimated energy stored as a proportion of excess ingested energy. This allows for differences between groups and individuals in the absolute excess energy consumed. Overall, a greater proportion of the excess energy was stored when the excess was given as fat compared with carbohydrate ($P < 0.002$). However, there was a significant day × diet interaction ($P < 0.05$) so that energy storage remained constant over time with fat but not carbohydrate overfeeding. With fat overfeeding 91–95% of the excess energy was stored throughout the study. Although ≈90% of the excess energy was stored on the first day of carbohydrate overfeeding, it declined significantly on days 7 and 14, with 77% and 83% of the excess being stored, respectively ($P < 0.04$).

Nutrient balance

Nutrient oxidation

The observed changes in nutrient oxidation were very different between carbohydrate and fat overfeeding. **Figures 4** and **5** show changes in daily oxidation rates of protein, carbohydrate, and fat during each overfeeding period. Protein oxidation decreased over time during both overfeeding periods ($P < 0.05$), with a trend for this to be greater with carbohydrate than fat overfeeding ($P < 0.08$). Fat overfeeding produced only minimal changes in fat and carbohydrate oxidation whereas carbohydrate overfeeding produced significant changes in both ($P < 0.001$). During carbohydrate overfeeding there was a rapid increase in carbohydrate oxidation and a significant decline in fat oxidation.

TABLE 2
Changes in body composition[1]

	Lean subjects (n = 9)	Obese subjects (n = 7)	All subjects (n = 16)
Carbohydrate overfeeding			
ΔBody fat (%)	0.69 ± 0.62	0.77 ± 0.31	0.72 ± 0.37
ΔFat mass (kg)	1.09 ± 0.49	2.06 ± 0.23[2]	1.48 ± 0.32[2]
ΔFat-free mass (kg)	1.38 ± 0.52	1.41 ± 56	1.40 ± 0.37[2]
Fat overfeeding			
ΔBody fat (%)	0.93 ± 0.28	0.80 ± 0.22	0.88 ± 0.18[2]
ΔFat mass (kg)	1.21 ± 0.29	1.90 ± 0.39[2]	1.51 ± 0.24[2]
ΔFat-free mass (kg)	1.10 ± 0.25	1.08 ± 0.19[2]	1.09 ± 0.16[2]

[1] $\bar{x}$ ± SEM.
[2] Significantly different from zero.

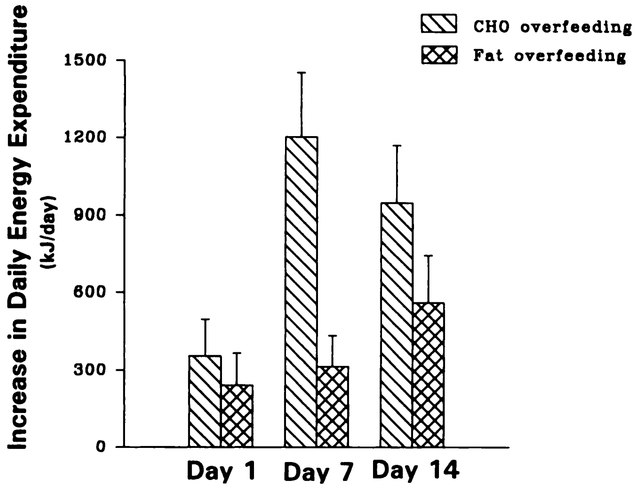

FIGURE 2. The increase in total daily energy expenditure above baseline (day 0) is shown for each overfeeding period in 16 male subjects.

Nutrient storage

The accumulation of energy, protein, fat, and carbohydrate was estimated from the balance of each (**Figure 6**). Energy balance was near zero at baseline and became positive during both overfeeding periods. Carbohydrate balance was positive and fat balance was negative at baseline. This was likely due to the inability to exactly reproduce amount and type of usual

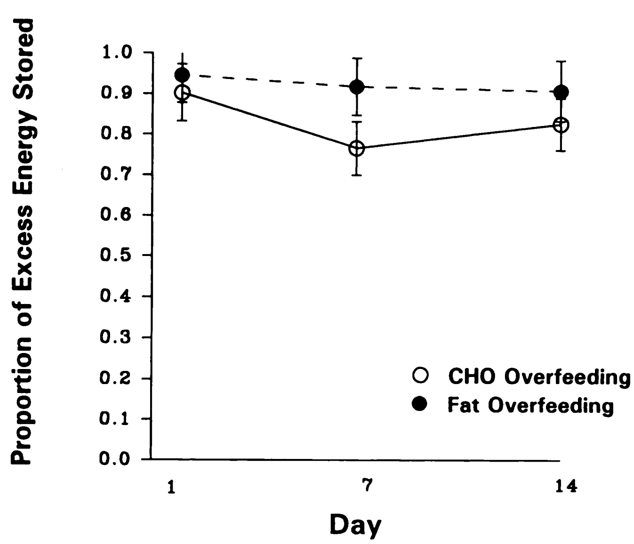

FIGURE 3. The proportion of excess energy stored in the body is shown for fat and carbohydrate (CHO) overfeeding in 16 male subjects. The proportion of excess stored is calculated as (total excess minus the measured increase in daily energy expenditure)/total excess.

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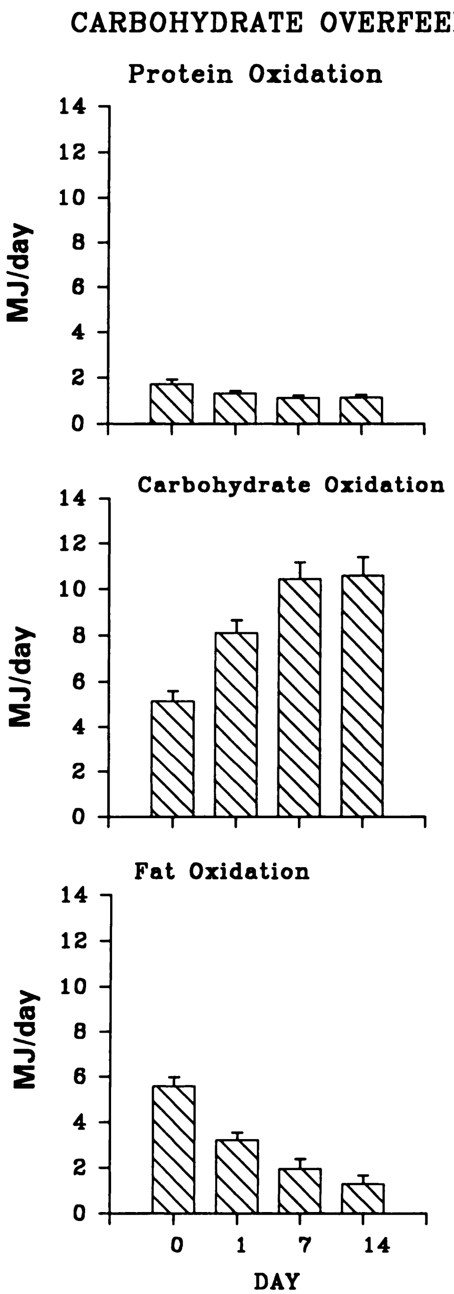

FIGURE 4. Total daily oxidation rates of protein, carbohydrate, and fat at baseline and during the carbohydrate overfeeding period for 16 male subjects.

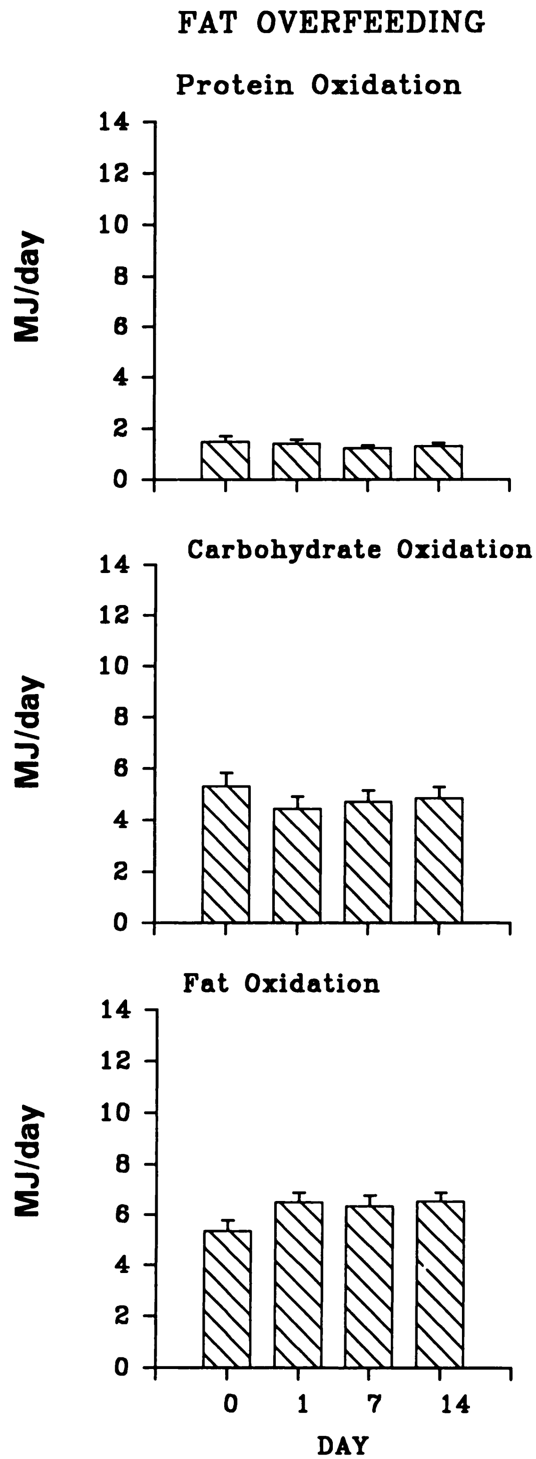

FIGURE 5. Total daily oxidation rates of protein, carbohydrate, and fat at baseline and during the fat overfeeding period for 16 male subjects.

physical activity in the calorimeter. Protein balance increased over time with both overfeeding diets (day effect, $P < 0.03$). Because fat overfeeding had minimal effects on fat and carbohydrate oxidation, the majority of the excess dietary fat was stored as body fat. This remained constant throughout the overfeeding period. Fat accumulation was initially lower and carbohydrate accumulation higher with carbohydrate than with fat overfeeding ($P < 0.001$). However, with the progressive decline in fat oxidation, fat storage increased so that on day 14 there was no difference between diets in fat or carbohydrate storage.

Figure 7 shows nutrient storage expressed relative to the total excess energy. This takes into account the different absolute amounts of excess energy fed to subjects and groups. Relative fat balance was significantly greater and carbohydrate balance less during fat than during carbohydrate overfeeding ($P < 0.001$). However, relative fat balance during carbohydrate overfeeding increased significantly over time ($P < 0.05$),

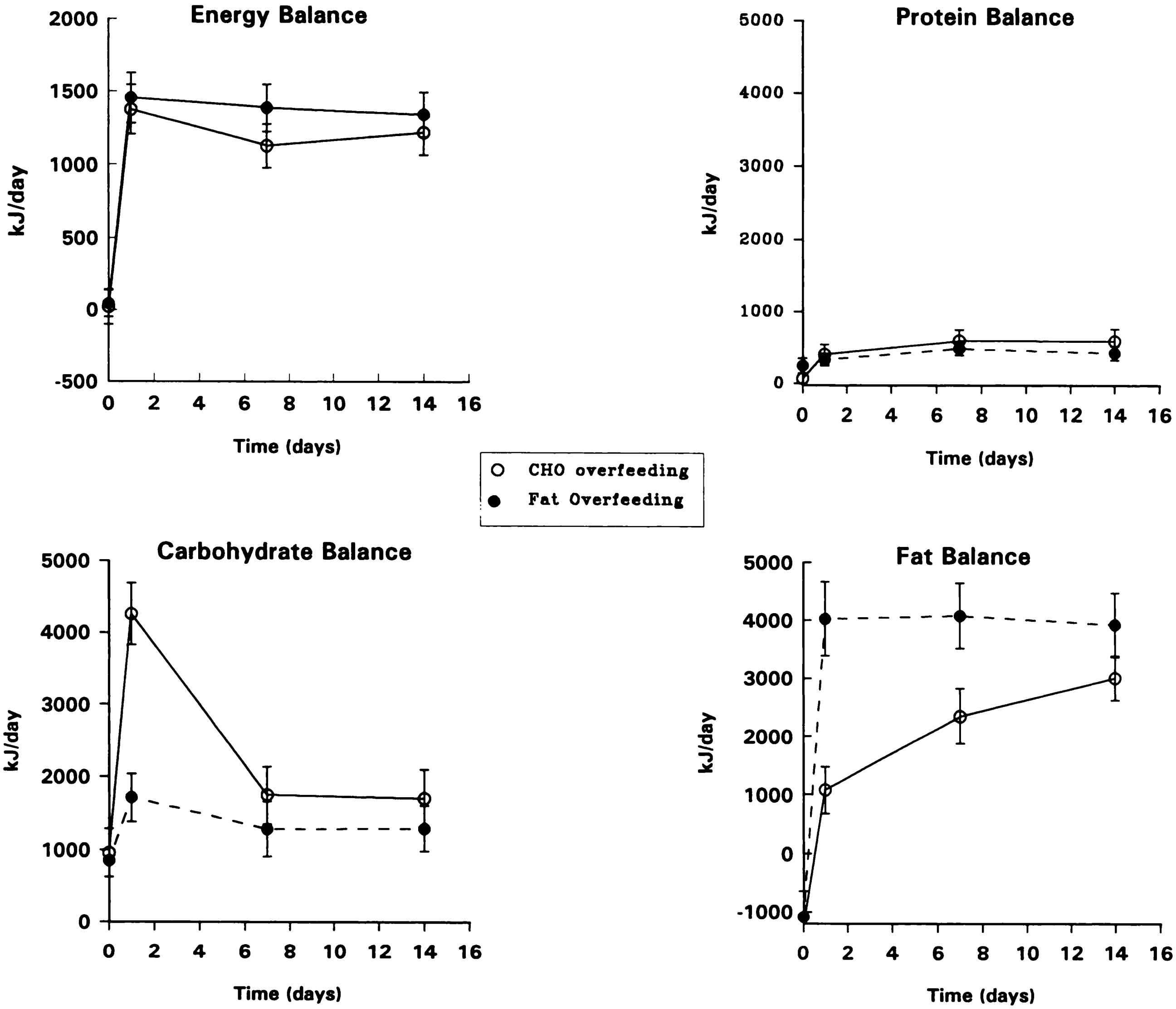

FIGURE 6. Daily balances of energy, protein, carbohydrate (CHO), and fat are shown for fat and CHO overfeeding for 16 male subjects. Daily balances were calculated as total intake minus total oxidation of each nutrient.

achieving a similar amount of fat storage by day 14 as with fat overfeeding day 14.

Lean-obese differences

We examined differences in the response to overfeeding between lean and obese subjects. In general, both groups responded similarly to overfeeding, keeping in mind that overfeeding was based on energy requirements, so that obese subjects received more total energy during overfeeding than lean subjects. There were no significant differences between groups in energy or nutrient balance, although the individual differences in these measures were large. Obese subjects, however, had a higher average RQ and oxidized proportionally more carbohydrate than lean subjects during both overfeeding periods ($P < 0.007$).

Fasting concentrations of insulin, glucose, and free fatty acids

Table 3 shows the fasting concentrations of insulin, glucose, and free fatty acids on day 0 and on the morning of day 15 of each overfeeding period. Values are shown separately for lean and obese subjects. In general, insulin concentrations were higher and free fatty acid concentrations were lower on the morning of day 15 after carbohydrate overfeeding than on day 15 after fat overfeeding. Glucose concentrations did not vary significantly with either diet.

DISCUSSION

Results of this study demonstrate that diet composition can have important effects on energy expenditure and body energy storage when subjects are in positive energy balance. Greater than 75% of the excess energy consumed by our subjects was stored in the body, not expended, regardless of the composition of the excess. Other recent overfeeding studies have reached the same conclusion (9–11). However, our results demonstrate that excess carbohydrate affects energy and nutrient balances differently than does excess fat. We found that for equivalent amounts of excess energy, fat leads to more body fat accumulation than does carbohydrate.

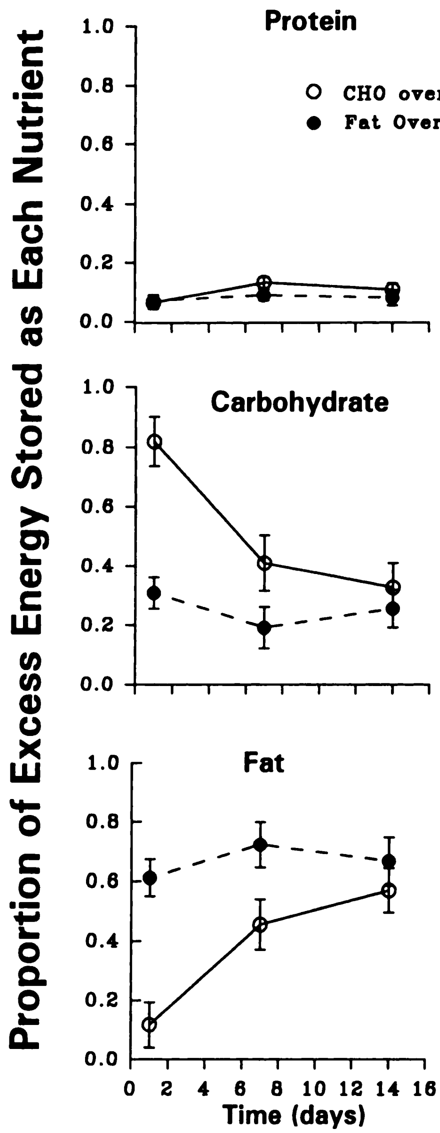

FIGURE 7. Storage of each nutrient during fat and carbohydrate (CHO) overfeeding is expressed as a percent of total excess energy stored in each of 16 male subjects. This accounts for differences in intake of each nutrient between subjects.

Using our whole-room calorimeter, we were able to demonstrate different effects of excess fat compared with excess carbohydrate on energy expenditure, substrate oxidation, and nutrient balance. It is generally accepted that dietary carbohydrate promotes its own oxidation, whereas dietary fat does not (16–19). This was clearly the case in the present study. Fourteen days of fat overfeeding produced no significant changes in fat oxidation or total daily energy expenditure. The small increase in energy expenditure with fat overfeeding can be explained by an increased thermic effect of food (TEF) and a slight increase in body mass. By comparing fat intake with fat oxidation, we found that the degree of positive fat balance during fat overfeeding was equal to 90–95% of the total excess energy consumed. Moreover, because fat overfeeding hardly increased substrate oxidation, this high storage efficiency continued throughout the study.

Carbohydrate overfeeding produced a very different picture. Progressive increases in both carbohydrate oxidation and total energy expenditure were seen with carbohydrate overfeeding. Both were evident on the first day of overfeeding and reached maximum by day 7. The increased energy expenditure seen with carbohydrate overfeeding was approximately double that which could be explained by the combination of increased TEF and increased body mass. Thus with carbohydrate overfeeding, more of the excess energy was oxidized and less stored in the body than was seen during fat overfeeding.

We anticipated that sustained carbohydrate overfeeding would lead to accumulation of body fat due to de novo lipogenesis. Although the issue of whether carbohydrate overfeeding led to de novo lipogenesis in tissues such as the liver cannot be definitively determined in this study, the calorimetry data indicate that net lipogenesis from carbohydrate did not occur. There were short periods during some carbohydrate overfeeding days in which the nonprotein RQ was >1.0, suggesting that some de novo lipogenesis occurred. It is impossible under conditions of this study to accurately quantify this de novo lipogenesis. Other investigators using isotopic techniques have reported that de novo lipogenesis in human subjects is not a major way to accumulate body fat stores (28). It may, however, be slightly higher in hyperinsulinemic obese subjects than in lean subjects and may depend on the type of carbohydrate in the diet (29). From these results, however, we conclude that positive fat balance was due to a decrease in fat oxidation accompanying the increase in carbohydrate oxidation. By day 14 of the overfeeding period, the proportion of total stored energy that was stored as body fat did not differ between the two diets.

When the total 14-d overfeeding period is considered (ie, areas under the curve for total energy and fat), substantially more total energy and more total fat is stored when the excess is fat compared with carbohydrate. Even on day 14, when the portion of the excess stored as fat was not significantly different between the two diets, total energy expenditure was higher with carbohydrate overfeeding so that the total stored energy was less than with fat overfeeding.

Other investigators have demonstrated in a single meal (18, 19) and over an entire day (17) that excess fat does not increase fat oxidation. These results extend that work to show that fat has only a slight effect on fat oxidation over the course of a 2-wk overfeeding period. This is consistent with the notion that increases in fat oxidation occur secondary to increases in the body fat mass (30). The change in body fat mass in the present study was small. The effects of excess carbohydrate on energy and nutrient balance require further explanation. In particular, the extent of fat storage during carbohydrate overfeeding depended on the extent to which fat oxidation was inhibited.

As might be expected, carbohydrate overfeeding was associated with a small increase in overnight fasting plasma insulin and a decrease in nonesterified fatty acids, whereas fat overfeeding did not affect these measures. These responses are consistent with the observed pattern of changes in substrate oxidation in which carbohydrate overfeeding stimulated carbohydrate utilization while suppressing fat oxidation. Fat overfeeding did not noticeably alter fuel metabolism. The lack of a more substantial change in these measures, especially with carbohydrate overfeeding, is not surprising.

TABLE 3
Fasting plasma insulin and free fatty acid (FFA) concentrations[1]

	Lean subjects				Obese subjects			
	CHO overfeeding		Fat overfeeding		CHO overfeeding		Fat overfeeding	
	Day 0	Day 15	Day 0	Day 15	Day 0	Day 15	Day 0	Day 15
Insulin (pmol/L)	132 ± 50	207 ± 110[2]	228 ± 120	108 ± 31[2]	199 ± 42	332 ± 109[2,3]	172 ± 77	278 ± 70[2,3]
Glucose (mmol/L)	4.9 ± 0.2	4.8 ± 0.1	4.6 ± 0.2	5.0 ± 0.2[2]	5.0 ± 0.2	4.9 ± 0.3	4.9 ± 0.1[3]	5.0 ± 0.1
FFA (mg/L)	90 ± 13	43 ± 7[2]	88 ± 15	58 ± 11[2]	86 ± 15	54 ± 7	80 ± 20	74 ± 16

[1] $\bar{x}$ ± SEM.
[2] Significantly different from day 0, $P < 0.05$.
[3] Significantly different from lean subjects, $P < 0.05$.

Whereas lean and obese subjects responded similarly, in general, to the overfeeding periods, there was one important difference. Regardless of the composition of the overfeeding diet, obese subjects oxidized proportionally more carbohydrate and less fat than did lean subjects. We have proposed that subjects who show the greatest reliance on carbohydrate oxidation during perturbations to energy balance may be most at risk to develop obesity (2, 3). Others have also suggested that a high RQ may be associated with susceptibility to obesity (31). Because the obese subjects in this study were already obese, it is impossible to determine whether a high reliance on carbohydrate oxidation in response to overfeeding contributed to obesity development. It could clearly contribute to maintenance of the obese state. It may be hypothesized that individual differences in RQ after overfeeding predict susceptibility to obesity. This has been demonstrated in rats, in whom a high RQ in response to a high-fat diet predicts subsequent weight gain (32).

We believe it is important to consider individual differences in the influence of diet composition on body-weight regulation. Individual differences in fat compared with carbohydrate oxidation may underlie differences in fat storage during overfeeding. Much longer periods of overfeeding may be necessary to see such individual differences during fat overfeeding, because such differences may occur secondary to substantial changes in body fat mass (30). However, a 14-d period appears to provide a good opportunity to study individual differences in response to carbohydrate overfeeding. For example, it would be interesting in future studies to assess whether the lean subjects who showed the greatest reduction in fat oxidation during carbohydrate overfeeding would be more metabolically susceptible to develop obesity than those with a lesser decline. In support of this speculation, Bouchard et al (8) reported large differences in the amount and composition of weight gained during experimental overfeeding of mixed diets. Those subjects with the highest oxidative capacity of skeletal muscle (as assessed by citrate synthase activity) had the lowest ratio of fat to lean mass in weight gain (33). Similar, we (34) and others (35) have demonstrated that the fiber composition of skeletal muscle may predict development of obesity.

In evaluating the role of diet composition on body-weight regulation, the plane of energy balance (ie, positive, negative, or zero) must be considered. Whereas fat and carbohydrate clearly differ in effects on energy expenditure and substrate oxidation during overfeeding, such differences may not be as apparent when overfeeding is not present. For example, when fed high- compared with low-fat diets containing a fixed amount of energy estimated to provide maintenance energy requirements, human subjects rapidly adjust substrate oxidation to substrate intake, with no significant differences in total energy expenditure (14). Leibel et al (36) found no difference in body weight when subjects were fed maintenance levels of diets differing in fat content. Similarly, differences in diet composition during energy restriction would be expected to have only slight effects on energy and nutrient balance (37). This illustrates that obesity cannot develop without an initial period in which energy intake exceeds energy expenditure and that overfeeding is an important tool for studying obesity development.

There are several reasons in general to be concerned about high-fat diets. Such diets are much more likely to be associated with overeating than are diets high in carbohydrate (3–6). Second, excess energy as fat is stored more efficiently than is excess energy as carbohydrate (12). Finally, diets high in fat may have a negative impact on health independently of obesity (38–40).

We found the greatest differences between fat and carbohydrate overfeeding early in the overfeeding period, before carbohydrate overeating produced substantial decreases in fat oxidation. From these results we can speculate that if obesity arises as a result of long periods of sustained overeating, the composition of excess energy would have relatively small effects on fat storage, with slightly more fat stored if the excess is high in fat rather than in carbohydrate. However, if obesity arises as a result of multiple periods of overeating over a single day or over a few days, the difference in fat storage would be greater with excess fat than with excess carbohydrate. Future work will be necessary to determine whether the same pattern of differences seen in this study would be seen during a second or third bout of overfeeding.

It is important to note that in this study we required subjects to eat all excess food during periods of overfeeding. There are data suggesting that diets high in carbohydrate are more satiating than are diets high in fat (3–5), and that voluntary intake is likely to be lower with high-carbohydrate than with high-fat diets. However, some people may be poor regulators of food intake, and these individuals should be aware that intake of low-fat foods also needs to be regulated because body fat accumulation can result from overconsumption of these foods.

In summary, this study provides important information about the potential impact of diet composition on body-weight regulation and obesity development. First, all overeating will eventually lead to obesity. Regardless of diet composition, most excess energy is stored in the body and not expended as heat. Although we demonstrated differences between carbohydrate and fat overfeeding, which we believe are important, the fact remains that obesity can develop from overeating carbohydrate. Advising people that they can eat an unlimited amount of a high-carbohydrate diet is not appropriate. Second, excess dietary fat is stored with a very high efficiency and the body does not acutely adjust to increased fat intake. If overeating occurs, more of the excess will end up as body fat if the excess is fat compared with carbohydrate. This may be particularly important if obesity develops in some people from cumulative acute periods of overeating. Third, whereas fat overeating would be predicted to lead to efficient storage of excess energy in all subjects, some differences might be seen with carbohydrate overfeeding. In particular, those subjects who show the greatest inhibition of fat oxidation during carbohydrate overfeeding would be expected to show the greatest accumulation of body fat. A major goal for weight maintenance should be avoidance of a positive fat balance. This can be accomplished by both reducing dietary intake of fat and increasing physical activity.

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APPENDIX A

	Food item	Weight
Maintenance: diet example		
		g
Breakfast	Plain bagel	85
	Cream cheese	35
	Milk (2% fat)	310
	White sugar	9
	Brewed coffee	440
Lunch	White bread	50
	Round steak (lean, broiled)	55
	Lettuce	30
	Mayonnaise	12
	Mustard	5
	Potato chips	35
	Brewed tea	480
	White sugar	10
Snack	Peanut butter cup	51
Dinner	Sirloin steak (lean, broiled)	86
	Boiled potatoes	126
	Butter	8
	Sour cream	35
	Tomato soup, canned	200
	Soda, lemon and lime	336
Evening	Graham crackers	27
	Peanut butter	22
	Milk (2% fat)	260
Carbohydrate overfeeding: diet example		
Breakfast	Honey nut cheerios[1]	45
	Whole milk	180
	Half and half cream	110
	White sugar	9
	Brewed coffee	440
	Apple juice	165
	Plain bagel	85
	Jelly	20
	Butter	10
Lunch	Steak round (lean, broiled)	65
	Hamburger roll	55
	Mayonnaise	12
	Lettuce	25
	American cheese (processed)	23
	Pineapple juice	147
	Pretzels	75
	Cream of mushroom soup (canned)	200
	Soda, lemon and lime	336
Snack	Jelly beans	85
	Grape juice	230
Dinner	Roast pork tenderloin, lean	75
	French green beans	100
	Boiled potatoes	120
	White bread	50
	Butter	22
	Pears, canned in juice	200
	Soda, ginger ale	567
Snack	Milk chocolate, plain	43
	Pound cake	55

APPENDIX—*Continued*

	Food item	Weight
Fat overfeeding: diet example		
Breakfast	Cream of wheat, dry weight	35
	Whipping cream	202
	White sugar	11
	Butter	9
	Banana, peeled	70
	Orange juice	120
Lunch	Plain bagel	80
	Roast turkey breast, no skin	50
	Cheddar cheese	21
	Lettuce	25
	Mayonnaise	17
	Chocolate milk (1% fat)	200
	Whipping cream	120
	Vanilla ice cream (16% fat)	140
	Chocolate syrup	34
Snack	Peanut butter cup	51
Dinner	Round steak (lean, broiled)	81
	Boiled potatoes	130
	Whipping cream	30
	White bread	25
	Broccoli, boiled	90
	Butter	30
Snack	Saltine crackers	11
	Cheddar cheese	20
Example of food module (only offered during baseline diet)[2]		
	Banana, peeled	65
	Peanut butter	13
	Milk (2% fat)	120

[1] General Mills, Minneapolis.
[2] This food module was offered as milk shakes.