Ability to Adjust Nocturnal Fat Oxidation in Response to Overfeeding Predicts 5-Year Weight Gain in Adults

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Objective: To determine whether metabolic responses to short-term overfeeding predict longitudinal changes in body weight.

Methods: Twenty-four-hour energy expenditure (EE) and substrate utilization were measured at baseline in a room calorimeter following 3 days of eucaloric and hypercaloric feeding (40% excess) in a sample of lean adults (n: 34; age: 28 ± 2 y; BMI: 22 ± 3 kg/m²). Body mass and fat mass (dual-energy x-ray absorptiometry) were measured annually for 5 years. Regression analyses examined whether changes in EE and fuel use with overfeeding predicted body weight and composition changes over 5 years.

Results: Overfeeding increased EE and reduced fat oxidation when examined over the 24-hour, waking, and nocturnal periods. Absolute change in body mass over 5 years was 3.0 ± 0.6 kg (average rate of change = 0.7 ± 0.1 kg/y, P < 0.001). Lower nocturnal (but not 24-hour or waking) fat oxidation (r = −0.42, P = 0.01) and EE (r = −0.33, P = 0.05) with overfeeding were the strongest predictors of 5-year weight gain. When adjusted for covariates, changes in nocturnal fat oxidation and EE with overfeeding predicted 41% of the variance in weight change (P = 0.02).

Conclusions: Failure to maintain fat oxidation at night following a period of overfeeding appears to be associated with a metabolic phenotype favoring weight gain.

Introduction

Obesity affects millions of adults in the United States, and the prevention of weight gain and problem of weight maintenance have become a serious public health challenge (1). Although two-thirds of the US population has overweight or obesity (2), some people appear to be more resistant to weight gain than others despite living in a similar obesogenic environment (3,4). Individuals can be susceptible to weight gain because of factors such as a low metabolic rate, reduced activity thermogenesis, decreased fat oxidation, insulin resistance, low leptin, and reduced sympathetic nervous system activity (5-8). Behavioral and genetic factors also play an important role in the susceptibility to weight gain (6). A better understanding of the factors that predispose to or protect from weight gain will be useful in developing strategies to prevent obesity.

Our group has focused on the variability in substrate oxidation as a potential mechanism underlying predisposition to weight gain (3,4). Specifically, our Energy Adaptations over Time Study (EATS) explored the idea that exposing persons to a short period of positive energy balance (EB) might reveal metabolic differences in the propensity for weight gain. EATS enrolled subjects from families in which obesity was a problem (obesity prone; OP) and who self-identified as prone to weight gain. Others were from families in which obesity was not a problem and self-identified as constitutively thin or resistant to weight gain (obesity resistant; OR). A surprising finding from EATS was that short-term overfeeding (compared to a eucaloric control condition) had the most pronounced influence on nocturnal, not 24-hour or daytime, substrate utilization (3). The results showed that the nocturnal nonprotein respiratory quotient (nRQ) did not change with overfeeding in the OR subjects but
increased significantly in OP subjects. The results further suggested that fat oxidation during the night was downregulated in the OP subjects following a brief period of overfeeding, whereas the obesity-resistant subjects appeared to maintain their usual rate of fat oxidation.

Our previous cross-sectional study was limited by the fact that our subjects were selected as OP or OR on clinical features. We did not know at the time whether they would be predisposed to weight gain or not. To address this limitation, we present results of our 5-year follow-up on these subjects. To our knowledge, no previous studies have tested whether the ability to maintain fat oxidation at night when faced with brief periods of overeating (e.g., 1-3 days) predicts weight maintenance or weight gain. This is an important question because transient periods of overfeeding are common in modern society with vacations, holidays, and celebrations (9). Here, we wondered whether the changes in nocturnal energy metabolism with overfeeding observed in our previous studies of OP and OR predict weight or adipose tissue gain over 5 years. For the present analysis, we combined OP and OR subjects because we hypothesize that the two groups originally selected are simply enriched in individuals likely or not to gain weight over time.

Methods

Participants
Participants were a subset (n = 34) of men and women aged between 25 and 35 years who participated in our previous studies examining the effects of overfeeding on nutrient oxidation (3,10). Additional details on the participants are provided in the Supporting Information. Participants provided written informed consent prior to enrolling and received a stipend upon completing the study, per the principles expressed in the Declaration of Helsinki. The study was approved by the Colorado Multiple Institutional Review Board.

Preliminary assessments
At baseline, subjects underwent a physical examination, had body composition measured by dual-energy x-ray absorptiometry (DXA; Hologic Discovery W, Bedford, Massachusetts), resting energy expenditure (EE) measured by hood indirect calorimetry (Parvo Medics TrueOne® 2400, Sandy, Utah), and a 24-hour EE measurement by whole-room calorimetry (3,10). Physical activity was assessed for 1 week using a pedometer (Digi-Walker™, New Lifestyles, Inc., Lee’s Summit, Missouri).

Design
Subjects were studied at the Clinical Translational Research Center (CTRC) at the University of Colorado—Anschutz Medical Campus on two occasions separated by at least 1 month. Two days prior to CTRC study (free-living conditions), subjects consumed either a controlled eucaloric (11) or hypercaloric diet (1.4 times estimated baseline energy needs) in a randomized order. On the third day of each controlled diet period, subjects spent 23 hours in the whole-room calorimeter to measure substrate oxidation and EE (3). Additional details on the study design are in the Supporting Information.

Whole-room calorimeter and study day
Participants entered the calorimeter at 0800 hours after a standardized breakfast (25% of daily energy). Lunch and dinner were given at 1200 hours and 1700 hours (both contained 30% of daily energy), with a snack (15% of daily energy) given at 2000 hours. The subjects went to bed at 2200 hours and exited the chamber at 0700 hours the following morning (3). Oxygen (O₂) consumption and carbon dioxide (CO₂) production were determined from the air flow rates and differences in gas concentrations between air entering and air exiting the calorimeter, as previously described (12). Twenty-three-hour urine output was collected to measure nitrogen excretion. EE and substrate oxidation were calculated from O₂ consumption, RQ, and urinary nitrogen excretion based on published equations (Supporting Information) (13).

Body composition measurements at baseline and follow-up visits
Whole-body fat mass (FM), fat-free mass (FFM), and body weight were measured at baseline by DXA. Subjects reported back to the University of Colorado Hospital every year for 5 years to have repeat DXA measurements. Only subjects completing ≥3 years of follow-up were included in the present analysis.

Statistical analysis
The primary goal of the analysis was to determine the degree to which nocturnal responses to 3 days of being overfed a mixed diet predicted the rate of change in outcomes of body weight and FM measured over a 5-year follow-up period. Candidate predictor variables included changes in 24-hour, daytime, and nocturnal EE, npRQ, fat oxidation, and carbohydrate oxidation in response to the feeding conditions measured during the baseline chamber stay (overfed minus eucaloric). The daytime period began at ~0800 hours and
end at ~2200 hours (lights out), and the nocturnal period ended at ~0700 hours. Fat and carbohydrate oxidation values were expressed as a percentage of energy expended over 24 hours, or over the day and night segments. The exact duration of the day and night (nocturnal) periods were individually determined and normalized to 16 hours and 8 hours, respectively, as described in the Supporting Information. Given that sleep was not specifically measured, we also report data from a 90-minute time segment between 0300 hours and 0530 hours that is representative of sleeping metabolic rate (labeled sleep in results).

The rate of change in body mass and FM was calculated as the difference between the last follow-up time point minus baseline divided by the number of follow-up years. A flow diagram showing study numbers from the parent study (3) and reasons for exclusion from the present statistical data analysis are shown in Figure 1. Associations of candidate variables with the body composition outcomes were first examined individually with Pearson correlations. Significant correlates were placed in multivariate linear regression analyses along with age, sex, baseline FFM, and baseline FM to adjust for these characteristics.

Repeated measures mixed models adjusted for sex, FM, and FFM were used to compare the room calorimeter data between feeding conditions at baseline. Paired t tests were used to test for significant changes in the body composition outcomes. \( P \leq 0.05 \) was considered statistically significant. Subject characteristics are presented as mean ± standard deviation (SD). Metabolic and body composition parameters are presented as mean ± standard error of the mean (SEM). Data were analyzed using SPSS® Statistics version 23.0 (IBM Corp., Armonk, New York).

### Results

The present analysis includes 34 subjects (n = 15 male/19 female) who completed annual body composition follow-up visits for ≥ 3 years after the initial overfeeding study (mean follow-up time: 4.6 ± 0.6 years). Baseline characteristics are shown in Table 1. Body weight was not significantly different between the baseline eucaloric and overfed study periods (\( P > 0.05 \)).

#### TABLE 1 Subject characteristics

|                     | Combined | Males | Females |
|---------------------|----------|-------|---------|
| \( N \)             | 34       | 15    | 19      |
| Baseline            |          |       |         |
| Age, y              | 27.9 ± 2.4 | 27.8 ± 2.4 | 28.0 ± 2.4 |
| Height, m           | 1.73 ± 0.1 | 1.8 ± 0.08 | 1.67 ± 0.07* |
| Weight, kg          | 65.9 ± 11.7 | 73.8 ± 9.6 | 59.7 ± 9.4* |
| BMI, kg/m^2         | 21.9 ± 2.9 | 22.6 ± 2.4 | 21.3 ± 3.1 |
| Fat mass, kg        | 14.4 ± 6.0 | 11.7 ± 4.5 | 16.6 ± 6.3 |
| Fat-free mass, kg   | 51.0 ± 11.1 | 61.6 ± 6.9 | 42.7 ± 5.0 |
| Body fat %          | 22.2 ± 8.1 | 15.6 ± 4.6 | 27.4 ± 6.3* |
| Follow-up           |          |       |         |
| Years of follow-up  | 4.7 ± 0.6 | 4.7 ± 0.6 | 4.6 ± 0.7 |
| \( \Delta \) Body mass, kg | 3.0 ± 3.4 | 3.0 ± 3.4 | 3.0 ± 4.4 |
| Rate of weight change, kg/y | 0.70 ± 0.8 | 0.64 ± 0.4 | 0.73 ± 1.1 |
| \( \Delta \) Fat mass, kg | 2.1 ± 2.7 | 2.6 ± 1.7 | 1.8 ± 3.3 |
| Rate of fat mass change, kg/y | 0.47 ± 0.6 | 0.55 ± 0.3 | 0.41 ± 0.8 |
| \( \Delta \) Fat-free mass, kg | 0.8 ± 2.3 | 0.22 ± 1.8 | 0.69 ± 1.5 |
| Rate of fat-free mass change, kg/y | 0.11 ± 0.4 | 0.04 ± 0.4 | 0.16 ± 0.3 |

Demographic data are presented as mean ± SD.

*Significantly different from males, \( P < 0.05 \).

#### TABLE 2 Energy metabolism measured in the room calorimeter after 3 days of a eucaloric diet and after 3 days of overfeeding

|                     | Eucaloric       | Overfeeding      | \( P \) value |
|---------------------|-----------------|------------------|--------------|
| 24-h                |                 |                  |              |
| Energy intake (kcal/d) | 2097.5 ± 67.4 | 2945.6 ± 94.0 | <0.001       |
| Energy balance (kcal/d) | \(-207.6 ± 51.3\) | 523.5 ± 45.6 | <0.001       |
| EE adj (kcal/min)*  | 1.60 ± 0.03 | 1.68 ± 0.02 | 0.003        |
| npRQ adj  | 0.86 ± 0.01 | 0.90 ± 0.01 | 0.002        |
| Nocturnal           |                 |                  |              |
| EE adj (kcal/min)*  | \(0.94 ± 0.03\) | 1.0 ± 0.02 | 0.05         |
| npRQ adj  | \(0.82 ± 0.02\) | 0.85 ± 0.02 | 0.06         |
| Sleep (0330-0500)   |                 |                  |              |
| EE adj (kcal/min)  | 0.86 ± 0.02 | 0.90 ± 0.03 | 0.19         |
| npRQ adj  | 0.82 ± 0.02 | 0.85 ± 0.02 | 0.19         |

Variables are mean ± SEM.

*Adjusted for sex, fat-free mass, and fat mass.

EE, total (24-h) energy expenditure; npRQ, nonprotein respiratory quotient.

\( VOLUME 25 | NUMBER 5 | MAY 2017 \)

Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity
Changes in energy intake, expenditure, and balance in response to overfeeding

Table 2 reports energy intake, balance, and expenditure for all subjects during the two diet phases. By design, net energy intake was increased by 40% in the overfeeding condition, resulting in an average 24-hour positive EB of 523.5 ± 45.6 kcal (P < 0.001). Short-term overfeeding led to a significant increase in 24-hour EE (5% increase, P = 0.003) and nocturnal EE (6% increase, P = 0.05). EE measures calculated between 0330 hours and 0500 hours (the time when EE was at its lowest level of the 24 hours) were significantly lower than those calculated during the entire sleep opportunity for both feeding conditions (P < 0.001). However, EE averaged over 0330 hours to 0500 hours did not significantly change with overfeeding (P = 0.19).

Changes in nonprotein respiratory quotient in response to overfeeding

Table 2 also displays changes in the npRQ for the two diet phases. Short-term overfeeding led to a significant increase in the 24-hour npRQ, indicating higher carbohydrate oxidation (5% increase, P = 0.003). Nocturnal npRQ tended to increase by 4% with overfeeding, but this change did not reach significance (P = 0.06). The npRQ between 0330 hours and 0500 hours was not different between eucaloric and overfed conditions (P = 0.19).

Changes in nutrient balance and oxidation in response to overfeeding

Table 3 presents the macronutrient intake, balance, and oxidation data over 24 hours and for the nocturnal and sleep segments. Overfeeding resulted in positive nutrient balance for all three macronutrients (P < 0.001). Twenty-four-hour carbohydrate and protein oxidation increased and fat oxidation significantly decreased with overfeeding. Nocturnal and sleep responses mirrored the 24-hour changes, indicating that more carbohydrate, more protein, and less fat were oxidized at night when subjects were overfed compared to the eucaloric condition. We note high variability in the nocturnal fat oxidation responses, with some individuals showing an ability to match (or increase) nocturnal fat oxidation to increased fat intake and others showing a large decrease in nocturnal fat oxidation with overfeeding (range +21% increase to −64% decrease in nocturnal fat oxidation).

Five-year body composition changes

Follow-up body composition data (absolute and rate of change) are presented in Table 1. Over the follow-up period, the absolute change in body mass was 3.0 ± 0.6 kg (range −4.1 to 11.8 kg) with an average rate of change of 0.7 ± 0.1 kg/y (P < 0.001). The absolute change in FM was 2.1 ± 0.5 kg (range −2.3 to 10.9 kg) with an average rate of change of 0.5 ± 0.1 kg/y (P < 0.001). The rate of change in body mass and FM was similar between sexes (P > 0.05).

Relationship between metabolic adaptations to short-term overfeeding and 5-year body composition changes

Changes in 24-hour npRQ, EE, fat oxidation, and carbohydrate oxidation with overfeeding were not significantly correlated with changes in body composition (r values ranged from −0.19 to 0.19, P values from 0.27 to 0.96). Similar nonsignificant relationships were observed when correlating changes in daytime chamber measurements to body composition changes (r values ranged from −0.24 to 0.16, with P values from 0.17 to 0.99). Only when examined over the nocturnal period was the rate of change in body weight significantly related to baseline changes in npRQ (r = 0.48, P = 0.004, Figure 2A), fat oxidation (r = −0.42, P = 0.01, Figure 2B), and EE (r = −0.33, P = 0.056, Figure 2C). Change in FM was not related to the change in npRQ (r = 0.26, P = 0.14, Figure 2D) but was correlated with changes in fat oxidation expressed as a percentage of nocturnal EE (r = −0.34, P = 0.05, Figure 2E). Change in FM tended to be correlated with the baseline change in nocturnal EE (r = −0.32, P = 0.07 for body, Figure 2F). Together, in a multivariate model including age, sex, FFM (baseline), and FM (baseline), changes in npRQ and EE at night explained 41% of the variance in the rate of weight change (Table 4). After adjustment for baseline covariates (age, sex, FFM, and FM), changes in the nocturnal npRQ independently predicted 18% of the variance in 5-year weight change such that a 0.1-unit increase in nocturnal npRQ (increased carbohydrate oxidation) in response to a period of short-term overfeeding predicted a 0.28 kg/y increase in body weight. Multivariate models predicting the change in FM from the baseline changes in npRQ and EE did not reach statistical significance (Table 4). However, the change in EE tended to remain as a significant predictor of the change in FM (Table 4).

Discussion

We correlated the metabolic responses to short-term overfeeding with measured changes in weight over 5 years of follow-up in a group of subjects who varied in their predisposition to weight gain. Our working hypothesis based on findings of the original cross-sectional study (3,10) was that the ability of some individuals to maintain fat oxidation in the face of overfeeding would correlate with resistance to weight gain over time. The novel observation is that individual differences in nocturnal but not 24-hour or waking fat oxidation in response to overfeeding predicted 5-year weight gain in a sample of lean subjects.

Our group has previously examined fat metabolism in subjects who are prone to gaining weight as compared to those who are relatively protected from weight gain (3,10). These studies were motivated by our previous work in animal models of obesity, which led us to the idea that reductions in the oxidation of dietary fat following a period of passive overfeeding predispose to weight gain (4,14). To determine whether these findings were relevant in humans, we measured 24-hour fat metabolism in situations in which the systems regulating EB are challenged by various states of energy imbalance (e.g., overfeeding and exercise). The findings from these independent studies unexpectedly showed differences in nocturnal but not daytime fat oxidation following acute metabolic challenges (3,15). The present study provides compelling evidence in support of the idea that failure to maintain or even increase fat oxidation at night following a period of overfeeding may be associated with a metabolic phenotype favoring fat storage. Specifically, we observed that a shift in the nocturnal npRQ in favor of decreased fat oxidation with overfeeding independently predicted 18% of the variance in 5-year weight change (0.3 kg/y; range −0.8 to +3.0 kg/y). While the average rate of weight gain may appear modest, the magnitude of change agrees with other reports in the literature (16).
When examined over 24 hours, differences in fat oxidation under both eucaloric and overfed conditions at baseline did not predict 5-year weight changes. This is in contrast with studies that have suggested differences in 24-hour fat oxidation predispose to weight gain (5,7,8,16-20). For example, Zurlo et al. reported in a sample of non-diabetic Pima Indians fed a weight-maintenance diet that individuals in the highest decile of 24-hour npRQ had a 2.5-fold increased risk of at least a 5-kg weight gain compared to those in the lowest decile.
Also, elevated 24-hour npRQ under EB conditions was positively associated with ad libitum food intake (16,18), and a higher waking (postprandial) npRQ is linked to weight gain (16). The fact that changes in 24-hour npRQ with overfeeding did not predict weight gain in the present study may be related to the fact that subjects were lean at baseline and the overall change in weight was relatively small. It may be that 24-hour fat oxidation responses to overfeeding in relevant populations (e.g., persons with obesity, known increased genetic risk) will be significant predictors of future weight gain.

Fatty acids are the primary energy source during the overnight-fasted period (8,21), and impaired nocturnal fatty acid oxidation has been observed in insulin-resistant and type 2 diabetic adults with obesity (22,23). Here we provide evidence that the inability to increase the oxidation of fatty acids during an overnight fast when challenged with a positive EB may be related to a greater propensity for weight gain. Our data are particularly relevant in light of accumulating evidence showing that sleep plays an important role in the regulation of EB and metabolic health (24-27). Controlled in-laboratory sleep studies in normal-weight subjects have

![Figure 2 Scatterplots showing the relationship between the changes in nocturnal nonprotein respiratory quotient (npRQ), fat oxidation (as a percentage of nocturnal energy expenditure), and energy expenditure (EE) with overfeeding and longitudinal changes in body mass and fat mass (FM). The changes in nocturnal npRQ, fat oxidation (as a percentage of nocturnal energy expenditure), and EE were calculated as the overfed minus eucaloric condition. Pearson correlation coefficients and P values displayed for the combined group; ⋄ males, ⋄ females.](image-url)
TABLE 4 Multiple regression results predicting the rate of change in body mass and fat mass from baseline to follow-up

|                     | Change in weight (kg/y) | Change in fat mass (kg/y) |
|---------------------|-------------------------|---------------------------|
| Age                 | 0.06 ± 0.05 (P = 0.25)  | 0.04 ± 0.05 (P = 0.43)    |
| Sex (female)        | -0.61 ± 0.55 (P = 0.28) | -0.51 ± 0.49 (P = 0.60)   |
| Baseline FM         | 0.04 ± 0.03 (P = 0.12)  | 0.02 ± 0.02 (P = 0.43)    |
| Baseline FFM        | -0.02 ± 0.02 (P = 0.52) | -0.009 ± 0.02 (P = 0.67)  |
| Change in nocturnal npRQ | 0.28 ± 0.12 (P = 0.02)  | 0.12 ± 0.10 (P = 0.25)    |
| Change in nocturnal EE | -0.28 ± 0.15 (P = 0.07) | -0.25 ± 0.13 (P = 0.08)   |
| Intercept           | -0.56 ± 2.0 (P = 0.019) | 0.004 ± 1.8 (P = 0.27)    |

The prediction of fat mass from changes in nocturnal physiology might become more prominent with age or in studies of relevant populations such as reduced obesity.

Changes in EE with overfeeding were negatively correlated with the change in fat mass and tended to be negatively correlated with the rate of change in body mass. These findings corroborate with previous studies showing that reduced 24-hour EE and sleeping metabolic rate are predictors of weight gain (3,7,16,20,34-36). Previous studies have observed that the decrease in 24-hour EE with short-term overfeeding might be related to changes in spontaneous physical activity (10). However, in a prior analysis of spontaneous physical activity from this same group of subjects, we found only modest changes in activity with overfeeding (10). Given that periods of overfeeding are episodic during periods of weight gain, it may be that changes in activity over a single episode of overfeeding are minimal but significant when compounded over multiple overfeeding episodes.

A strength of the study is that we measured metabolic responses to overfeeding in nonobese individuals who had a propensity to gain weight or remain thin. A main limitation to the study is the lack of an objective measure of sleep quality, as we cannot rule out individual differences in sleep duration on the nocturnal responses used in the regression analysis to predict changes in body composition. Sleep restriction (extended wakefulness) increases 24-hour EE, and we cannot rule out the possibility that some of the changes in EE were due to differences in sleep duration and not overfeeding. Finally, the increased npRQ in response to overfeeding may reflect individual differences in autonomic nervous system, hormonal activity, and/or cardiorespiratory fitness. Unfortunately, detailed nocturnal profiles of sympathetic nervous system activity and hormones (e.g., growth hormone) were not measured. Other limitations include that we did not specifically measure nighttime protein oxidation and sleep was not specifically controlled because subjects were awakened for a blood draw and breath sample in the middle of the night.

**Conclusion**

Taken together, the present results suggest that metabolic responses to daytime energy imbalances manifest overnight while people sleep, and this period may play an important role in the regulation of body weight. Sleep has been linked to metabolic health and obesity in
several studies, but it is still unclear what the normal function of sleep is for metabolism. It may be that sleep is a critical window when regulatory systems respond to periods of overfeeding in a manner that restores EB, and these regulatory mechanisms are blunted in people with obesity or those who are at risk of developing obesity.

Acknowledgments

We thank the Nursing, Clinical Lab, and Bionutrition Staffs of the University of Colorado CTRC. We also thank the volunteers who participated in this study.

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