Associations Among Dietary Fat Oxidation Responses to Overfeeding and Weight Gain in Obesity-Prone and Resistant Adults

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Objective: This study tested the hypothesis that 3 days of overfeeding (OF) decreases dietary fat oxidation and predicts longitudinal weight change in adults classified as obesity prone (OP) and obesity resistant (OR) based on self-identification and personal and family weight history. Changes in diurnal profiles of plasma metabolites and hormones were measured to probe mechanisms.

Methods: Adults identified as OP (n=22; BMI: 23.9 ± 2.4 kg/m²) and OR (n=30; BMI: 20.5 ± 2.2 kg/m²) completed 3 days of eucaloric (EU) feeding and 3 days of OF. On day 3, the 24-hour total and dietary fat oxidation was measured using room calorimetry and an oral ¹⁴C tracer. Plasma glucose, insulin, triglycerides, and nonesterified fatty acid (NEFA) concentrations were frequently sampled over 24 hours. Body composition was measured annually for 4.0 ± 1.4 years in a subsample (n=19 OP and 23 OR).

Results: Dietary fat oxidation over 24 hours was not altered by OF versus EU (P=0.54). Weight gain in OP correlated with lower nocturnal NEFA concentrations during OF (r=−0.60; P=0.006) and impaired fuel selection over 24 hours (metabolic inflexibility, wake respiratory quotient-sleep respiratory quotient) (r=−0.48; P=0.04).

Conclusions: Short-term OF did not alter dietary fat oxidation. Lower nocturnal NEFA availability and metabolic inflexibility to overfeeding may be factors contributing to weight gain.

Obesity (2018) 26, 1758-1766. doi:10.1002/oby.22321

Introduction

Obesity is major health problem in the United States and around the world (1). The problem of obesity involves complex interactions among environmental, biological, and social pressures (2,3). However, there is marked heterogeneity in the biological systems regulating body weight, and even in the current obesogenic environment, not all individuals develop obesity. While some individuals have a predisposition toward excess weight gain (obesity prone [OP]), other individuals seem to be able to respond to the obesogenic environment in a way that resists weight gain (obesity resistant [OR]).

One environmental stressor believed to promote obesity is overfeeding (OF) because of the broad availability of high-calorie foods (4). The variability in the metabolic response to OF has been used by several investigators to explore candidate mechanisms that predispose or protect against weight gain (5-12). Using rats selectively bred to be OP or OR on a high-fat diet (HFD) (13), we showed that dietary fat oxidation was reduced in OP rats following a HFD. This reduction in dietary fat oxidation was associated with a shunting of dietary fat away from oxidation in tissues such as skeletal muscle and toward storage in adipose tissue (14,15). Our group also studied humans classified as OP and OR based on self-identification, BMI, and family weight history (6). These
Previous studies in human participants have largely utilized indirect calorimetry to investigate the effects of OF on fat oxidation (16). A limitation of this method is the inability to identity the source of the fat being oxidized (e.g., meal-derived triglycerides [TG] vs. adipose-tissue-derived nonesterified fatty acids [NEFA] vs. intracellular lipid). In the present study, we used a dietary fat tracer to compare meal fat oxidation in EU and OF states between adults classified as OP or OR who participated in our Energy Adaptations Over Time Study (EATS) (6). We hypothesized that OF in OP adults (compared with OR) would result in a reduction in dietary fat oxidation expressed either as a fraction of meal fat or grams of fat, as had been observed in our OP rodent model following a HFD. Diurnal profiles of plasma NEFA, glucose, insulin, and TG were measured to gain insight into mechanisms related to changes in fat metabolism with OF. Changes in dietary fat oxidation and diurnal plasma profiles were explored as potential predictors of longitudinal weight gain in OP and OR adults.

Methods
Participants
Participants were healthy men and women who were 25 to 35 years of age and classified as either OP or OR based on personal and family weight history (6). OP had BMI of 23 to 27 kg/m² and at least one first-degree relative with BMI > 30 kg/m², reported having to work to maintain their weight by being conscientious about their food intake and/or activity, were not actively attempting to lose weight, and were weight stable for at least 3 months prior to study. OR had BMI of 19 to 22.9 kg/m² and no first-degree relative with BMI > 30 kg/m², reported no history of ever having overweight (weight stable ±10 lb over the previous 2 years), and described themselves as “constitutively thin,” expending little effort to maintain weight.

Participants were excluded if they had a significant medical illness, took medications known to affect weight or metabolism, or had history or evidence of significant psychological dysfunction. All study-related procedures were followed in accordance with the ethical standards of the Colorado Multiple Institutional Review Board and in accordance with the Helsinki Declaration.

Study design and experimental diet
Assessments of body composition, resting energy expenditure (REE), and total energy expenditure (TEE) were collected on all participants at baseline. Participants were then studied for two 7-day periods (6 days free-living and 1 inpatient day), separated by at least 1 month. During study periods, participants were instructed to consume only food and beverages provided by the Colorado Clinical and Translational Research Center (CTRC) kitchen. For the first 4 days of each study period, participants consumed a controlled EU “run-in” diet to ensure energy balance (percent of total energy intake: 20% protein, 30% fat, 50% carbohydrate). For the next 3 days, participants consumed in random order either a controlled EU or a hypercaloric diet containing 140% of estimated energy needs (OF). The macronutrient composition of the EU and OF diets were the same as the run-in diet and only differed in energy content. The last day of each feeding condition (day 7) was spent in a room calorimeter.

Preliminary assessments and determination of basal energy requirements
Body composition was measured by dual-energy x-ray absorptiometry (Hologic Discovery W, Bedford, Massachusetts) and REE by hood indirect calorimetry (TrueOne 2400; Parvo Medics, Sandy, Utah). The energy requirements for free-living EU feeding were based on measured REE and body composition as previously reported (6). To determine energy requirements for the chamber stays, TEE was measured during an independent “baseline” stay in the room calorimeter as previously described (6).

Room calorimeter and tracer studies
Participants were admitted to the CTRC on the morning of the first day of each feeding condition. At 7:30 AM, participants consumed a test meal consisting of 25% of daily energy intake (based on the EU or OF diet) and 20 μCi of [1-14C] oleic acid (≥97% enrichment; Moravek, Inc., Brea, California). Participants entered the room calorimeter after the test meal at 8 AM for measurement of energy expenditure and nutrient oxidation over the next 23 hours. Lunch, dinner, and a snack were administered in the chamber at 12 PM (30% of daily energy), 5 PM (30% of daily energy intake), and 8 PM (15% of daily energy intake), respectively. To approximate daily activity levels, participants performed two 20-minute bouts of stepping at 2:30 and 4:30 PM. Breath samples were obtained hourly during waking hours, once during the night (2 AM) and 24 hours after administration of the test meal for measurement of tracer oxidation. Breath samples were obtained by having participants exhale into a scintillation vial containing hyamine hydroxide and phenolphthalein in methanol. The 14C content of these samples was then measured by scintillation counting (LS6500; Beckman Coulter, Brea, California). Background activity, determined by counting a sample containing only scintillation fluid and hyamine hydroxide, was subtracted from experimental values. Disintegrations per minute were converted to μCi/MCO2 expired per hour over 24 hours, and then the specific activity of 14C/g fat in the test meal was used to convert this value to grams of fat oxidized.

Oxygen (O2) consumption and carbon dioxide (CO2) production were determined from differences in gas concentrations between air entering and exiting the calorimeter as previously described (12). Twenty-four-hour urine output was collected to measure nitrogen excretion. Fat oxidation was calculated from O2 consumption, respiratory quotient (RQ), and nitrogen excretion based on published equations (17). An index of metabolic flexibility (i.e., the tendency to switch from carbohydrate fuels during the day in the fed state to fat at night in the fasted state) was calculated from the chamber data, defined as the difference between the awake RQ (8 AM to 10 PM) and sleep RQ (10 PM to 6 AM).

Hormone and metabolite measurements
A fasting blood sample was obtained at 7 AM prior to administration of the test meal and entering the room calorimeter. In the room calorimeter, blood sampling for insulin and metabolites (NEFA, TG, glucose) was performed at the following times beginning at 8:30 AM: every 30 minutes for 210 minutes and then at clock times of 1 PM, 3 PM, 5 PM, 6 PM, 8 PM, 10 PM, 2 AM, and 7 AM the following day. Plasma was separated from whole blood after centrifugation and stored at −80°C until samples were analyzed in batch by the CTRC Core Lab. The homeostasis model assessment of insulin resistance index was calculated.
as fasting plasma glucose (milligrams per deciliter) × fasting insulin (μIU/milliliter)/405 (18).

**Longitudinal assessments of body weight and composition**

Repeated weights and whole-body dual-energy x-ray absorptiometry measurements were obtained on participants annually for up to 5 years (mean follow-up = 4.0 ± 1.4 years). Participants completing ≥ 1 year of follow-up were included in the present analysis (n = 19 OP and 23 OR). Of the total number participating in the follow-up program, twenty-six participants completed 5 years of measurements, six completed 4 years, three completed 3 years, four completed 2 years, and three completed 1 year.

**Statistical analyses**

Data are expressed as means ± SEM unless otherwise stated and analyzed with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All outcomes were analyzed using separate linear mixed models (SAS PROC MIXED procedure). Each linear mixed model consisted of group (OP, OR), diet (EU, OF), and the interaction of group and diet as fixed effects and participants as random effects. Analyses were performed for the entire 24-hour study period as well as for the daytime (8 AM to 10 PM) and nighttime (10 PM to 6 AM) separately. Areas under the curve (AUC) were calculated for each variable using the trapezoidal rule. Total AUC was calculated for plasma NEFA concentrations, and incremental AUCs (i.e., AUC above baseline) were calculated for plasma glucose, insulin, and TG concentrations. Pearson correlation coefficients (r) examined relationships between parameters of interest and longitudinal body weight and composition changes. Longitudinal data were expressed as rate of body weight change (RoWC) and fat mass (FM) change (RoFMC) calculated as the difference between the last follow-up time point minus baseline, divided by the number of follow-up years. Baseline body composition (FM and fat-free mass) and BMI were explored as covariates in all analyses, although these statistical adjustments did not alter the results and are not reported. Statistical significance was assumed when \( P < 0.05 \).

**Results**

**Participants**

Fifty-two participants (22 OP, 30 OR) completed both EU and OF study periods. For the dietary fat oxidation analyses (primary outcome), eight individuals were excluded because of either invalid tracer (one OP, three OR) or chamber data (four OR). For the plasma analyses, four additional participants (two OP, two OR) were excluded because of missing or invalid samples for one or more of the assays. Correlational analyses were performed on all individuals with valid metabolic data under both feeding conditions and ≥ 1 year of follow-up body composition data. Baseline characteristics of the study participants are shown in Table 1.

**24-hour total fat oxidation and fuel selection**

Total 24-hour fat oxidation was lower following OF in both OP and OR (\( P < 0.04 \) for both; Figure 1A and Figure 2A). As previously reported (6), fat oxidation at night tended to be reduced to a greater extent in OP (\( P = 0.09 \)) compared with OR, who appeared to maintain their baseline rate of fat oxidation (\( P = 0.42 \); Figure 1A and Figure 2A).

**Dietary fat oxidation**

Under the EU condition, 24-hour oxidation of a dietary fat tracer consumed as part of the breakfast meal did not differ between OP and OR (\( P = 0.81 \); Figure 1B and Figure 2B). OF had no effect on absolute dietary fat oxidation (grams over 24 hours) in either group (\( P = 0.54 \) for feeding condition; Figure 1B and Figure 2B). The lack of change in absolute dietary fat oxidation with OF despite higher fat intake at breakfast resulted in a reduction in the fraction of meal fat oxidized over 24 hours in both groups (\( P = 0.002 \) for feeding condition; Figure 1C and Figure 2B). The contribution of meal fat to total fat oxidation is depicted in Figure 2C, but differences were not significant.

| TABLE 1 Participant characteristics at baseline |
|------------------------------------------------|
| **Obesity prone (OP), \( n = 22 \)** | **Obesity resistant (OR), \( n = 30 \)** | **P** |
| **Female \( (n, \%) \)** | 14, 64 | 14, 47 | 0.23 |
| **Age, y** | 28.5 ± 2.6 | 28.0 ± 2.6 | 0.53 |
| **BMI, kg/m²** | 23.9 ± 2.4 | 20.5 ± 2.2 | <0.001 |
| **Weight, kg** | 70.0 ± 9.4 | 63.5 ± 11.3 | 0.03 |
| **Fat mass, kg** | 18.4 ± 6.0 | 11.9 ± 3.0 | <0.001 |
| **Fat-free mass, kg** | 51.2 ± 9.7 | 51.3 ± 11.2 | 0.98 |
| **EU energy intake, kcal** | 2,332.0 ± 340.1 | 2,361.4 ± 437.4 | 0.75 |
| **OF energy intake, kcal** | 3,247.3 ± 509.8 | 3,243.6 ± 596.0 | 0.98 |
| **Energy intake, % above EU condition** | 39.1 ± 5.0 | 37.1 ± 6.2 | 0.23 |
| **Test meal EU fat intake, g** | 20.7 ± 3.3 | 20.2 ± 3.9 | 0.62 |
| **Test meal OF fat intake, g** | 29.0 ± 4.7 | 28.2 ± 5.3 | 0.59 |
| **Test meal, % above EU condition** | 40.2 ± 2.6 | 40.0 ± 7.1 | 0.94 |
| **EU 24-hour total fat oxidation (g/d)** | 92.8 ± 10.9 | 90.7 ± 10.7 | 0.88 |
| **OF 24-hour total fat oxidation (g/d)** | 64.5 ± 10.3 | 69.9 ± 8.9 | 0.71 |
| **EU 24-hour dietary fat oxidation (g/d)** | 8.8 ± 0.6 | 9.1 ± 0.7 | 0.81 |
| **OF 24-hour dietary fat oxidation (g/d)** | 9.3 ± 1.2 | 9.5 ± 1.0 | 0.87 |

Data are means ± SD.
Metabolic flexibility
There was a significant group × diet interaction ($P=0.02$), such that OR tended to be more metabolically flexible to the OF challenge compared with OP (Figure 3). The interaction remained significant after adjusting each participant’s OF measurement according to the EU measurement and after adjusting for FM and fat-free mass.

Diurnal plasma metabolic profiles
In both groups, plasma glucose concentrations were lowest at 7 AM and increased following each meal, although there was a time of day effect with postprandial glucose responses being lower in the morning versus evening ($P<0.05$ for time; Figure 4A). Surprisingly, daytime plasma glucose AUC was lower with OF in both OP ($P=0.02$) and OR ($P=0.006$; Figure 5A). At night, plasma glucose concentrations decreased and reached values similar to baseline in both conditions.

With OF, plasma glucose concentrations at the 2 AM time point were increased in both OP (87.2±1.7 vs. 91.3±1.9 mg/dL; $P=0.002$) and OR (86.8±1.2±90.7±1.1 mg/dL; $P=0.002$) compared with the EU condition.

Plasma insulin concentrations were lowest at 7 AM and peaked following each meal, with similar peaks and troughs among OP and OR under the EU condition (Figure 4B). Over 24 hours, plasma insulin AUC increased following OF in both groups ($P<0.007$ for both groups) with no differences between groups ($P=0.14$; Figure 5B). During sleep, plasma insulin concentrations were not different from baseline in the EU condition in either group ($P>0.05$). However, OF significantly increased the nocturnal plasma insulin AUC in OP but not OR ($P=0.007$ for group × condition interaction; Figure 5B). OF increased insulin resistance as measured by homeostasis model assessment of insulin resistance.

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Figure 1 (A) Total fat oxidation, (B) absolute dietary fat oxidation (grams of meal fat oxidized), and (C) relative dietary fat oxidation (percentage of tracer dose) during the eucaloric (EU) and overfed (OF) conditions in OP and OR adults. Data are means ± SEM. Arrows indicate the time of breakfast, lunch, and dinner consumption. The gray area represents nighttime.
Correlates of longitudinal change in body weight and composition

OP and OR gained 3.5±0.8 kg and 2.6±0.6 kg of body weight, respectively, with no differences between groups over 4.0±1.4 years of follow-up. These changes in body weight corresponded to an increase of 2.4±0.7 kg in FM in OP and 1.9±0.4 kg in FM in OR during the follow-up period. A reduction in nocturnal fat oxidation following OF correlated with an increased rate of body weight and FM gain in OP (n=19; RoWC: r=−0.44, P=0.057; RoFMC: r=−0.55, P=0.02) but not OR (n=23; RoWC: r=−0.14, P=0.51; RoFMC: r=0.14, P=0.52; Figure 6A-6B). Decreased metabolic flexibility (awake-sleep nonprotein RQ) during OF was associated with greater weight gain in OP (n=19; r=−0.48; P=0.04) but not OR (n=23; r=−0.27; P=0.21; Figure 6C-6D). The tendency to oxidize a greater proportion of meal fat over 24 hours and at night during periods of OF was linked to greater weight gain in OP (n=18; r=0.50; P=0.03) but not OR (n=21; r=−0.08; P=0.72; Figure 6E-6F). Finally, suppressed nocturnal plasma NEFA under hypercaloric feeding conditions was significantly correlated with the rate of weight gain in OP (n=19; r=−0.60; P=0.006) but not OR (n=22; r=−0.01; P=0.96; Figure 6G-6H). Correlations for the two groups combined are shown in Supporting Information Figure S1.

Discussion

We assessed 24-hour dietary fat oxidation using a dietary fat tracer under EU and OF conditions in adults classified as OP and OR. Our major goal was to determine whether a reduction in dietary fat oxidation in the OF state was a risk factor for weight gain. We found that OF had no effect on absolute dietary fat oxidation over 24 hours in either group, and absolute dietary fat oxidation was not a predictor of longitudinal weight change. Instead, we showed that OF decreased total fat oxidation, primarily because of decreased endogenous and not dietary fat oxidation. We also reported that metabolic inflexibility to OF and reductions in nocturnal fat oxidation and plasma NEFA concentrations following OF correlated with weight gain in OP.

There is a widely held view that defects in fat oxidation predispose to obesity (15). Most previous studies have used indirect calorimetry to measure fat oxidation, but this method cannot identify the source of the fat being oxidized (7,16). Few studies have used tracers to examine the oxidation of dietary fat or have used tracers to examine details of fat metabolism in the context of short-term OF. Studies in rodent models
of obesity have consistently shown a defect in dietary fat oxidation in preobese rats (14,19). We have previously observed lower dietary fat oxidation and higher dietary fat adipose tissue storage in obese compared with lean Zucker rats (14,20) as well as in OP compared with OR rats (14,21). In our studies of rodents, the OR phenotype responded to a brief period of OF by reducing food intake and maintaining dietary fat oxidation, which was associated with modest changes in FM. The results suggested that the OR phenotype was associated with more accurate nutrient sensing and greater delivery of a dietary fat tracer to liver and muscle. In contrast, 24-hour dietary fat oxidation was significantly reduced in OP rats.

To our knowledge, no previous study has compared changes in dietary fat oxidation after OF in OP and OR individuals with normal weight. Our hypothesis in the present study was that OF would reduce dietary fat oxidation and that reductions would be most pronounced in OP

![Figure 4](image-url)
participants. We thought that preferential delivery of dietary fat to adipose tissue would impair nutrient sensing and be related to weight gain in OP participants, whereas OR participants would have a more accurate coupling between dietary fat intake and oxidation. Our results are contrary to our hypothesis and our previous observations in rats (20). Surprisingly, we observed that during periods of OF groups, absolute dietary fat oxidation appears to be clamped at levels similar to EU conditions in both OP and OR groups, whereas the fraction of meal fat oxidized in response to OF decreases, suggesting storage of excess meal fat intake at similar levels in OP and OR. We also showed that the contribution of dietary fat to total fat oxidation increases under OF conditions, suggesting decreased reliance on endogenous lipid stores.

One feature that appears to distinguish OP and OR adults during periods of OF is the ability to maintain total fat oxidation at levels similar to energy-balanced conditions, particularly at night (6,9). In the EATS, we showed that OF of a mixed diet led to an overall increase in daytime carbohydrate oxidation at the expense of fat oxidation in both OP and OR groups (6). However, at night, OR participants were able to maintain fat oxidation during OF compared with OP, who continued to rely more on carbohydrates. Our published longitudinal data showed that the individuals who relied less on lipid as an energy substrate at night had a greater tendency to gain body weight and body fat relative to those who oxidized lipid more readily (9). The ability to switch from carbohydrate to fat oxidation when transitioning from fed to fasted states has been termed metabolic flexibility (22,23). Flexible fuel switching over 24 hours may turn out to explain how some rodents and humans are able to maintain a stable body weight in the face of wide changes in diet composition. The use of OF as a short-term “metabolic stressor” in the present study unmasked differences in metabolic flexibility between OP and OR adults. Specifically, OR participants were better able to adapt fuel use to fuel availability during OF compared with OP, suggesting that OP participants were less metabolically flexible. To our surprise, metabolic flexibility to OF emerged as a correlate of weight gain in our study. The changes in metabolic flexibility in OP and OR participants were largely driven by the sleep RQ, participants which is consistent with a recent study in which lean men were overfed for 8 weeks (5). It will be important for future studies to determine why some individuals are able to maintain metabolic flexibility during periods of OF, while others are metabolically inflexible.

As a secondary aim of the study, we examined diurnal patterns in plasma insulin, glucose, TG, and NEFA to gain insight into how OF alters 24-hour fat oxidation in OP and OR adults. We found that plasma insulin concentrations measured over 24 hours were higher in both groups after OF compared with levels in the EU state, but this difference was greater in the OP group, particularly at night. Higher plasma insulin levels would be expected to result in the suppression of lipolysis and lower oxidation of endogenous fat. Although not a direct measure of lipolysis, plasma NEFA concentrations over 24 hours and at night were decreased in both OP and OR groups. One would expect that OF would result in a prolonged period of nutrient accumulation in the gut, liver, and skeletal muscle throughout the day, and that the body would adapt to this change by increasing lipolysis at night during sleep. Higher plasma insulin levels leading to stronger suppression of lipolysis with overeating therefore appear to be a maladaptive metabolic change favoring fuel storage that is more prominent in OP individuals. Our plasma NEFA data are consistent with other studies in humans showing reduced plasma NEFA availability after short-term HFD, high-carbohydrate diets, and hypercaloric feeding (24–27). Our data contrast studies in dogs, in which high-fat feeding increases nocturnal but not daytime NEFA concentrations (28,29). Initially, it was thought that elevated nocturnal NEFA (not glucose) may be responsible for insulin resistance in the chronic HFD dog model (29). However, more recent evidence...
suggested that increased plasma NEFA at night during a HFD appears to be a signal for hyperinsulinemic compensation during diet-induced insulin resistance in the dog model (28). Interestingly, the present study and a study by Magkos et al. (11) indicate that short-term OF causes impairments in glucose metabolism in the absence of increased nocturnal plasma NEFA concentrations.

The observed plasma insulin response to OF in this study is counterintuitive, and its mechanism remains unclear. This response does not appear to be driven by higher glucose levels. In fact, glucose concentrations in our study tended to be lower after OF in both groups. It is worth speculating that the stimulus for higher insulin was due to higher plasma amino acids, which were likely elevated over 24 hours with the OF challenge (30). It will be important for future studies to characterize 24-hour protein responses to periods of OF and examine relationships to glucose metabolism.

The study has several limitations. We had only one blood draw at night and our study was not designed a priori to characterize nocturnal responses to OF. Along similar lines, the dietary fat tracer was not provided at night but in the breakfast, and we used few time points to calculate dietary fat oxidation over the night. We also did not have
measures of plasma amino acid concentrations or separate measures of protein oxidation during the day and night, which would have provided insight into the hyperinsulinemia despite decreased glucose concentrations. Finally, the OP and OR phenotypes were based on self-report.

Our study demonstrates that 3 days of OF (compared with an EU diet) does not alter dietary fat oxidation expressed as either a fraction of meal fat or grams of fat in OP and OR adults. Our findings suggest subtle differences in total fat oxidation and NEFA metabolism between OP and OR groups, particularly at night. We also show differences in metabolic flexibility between OP and OR unmasked by short-term OF. To our surprise, decreased nocturnal fat oxidation, decreased plasma NEFA, and metabolic inflexibility were significant predictors of weight gain over an average of 4.0 ± 1.4 years in OP but not OR.

Acknowledgments

We wish to thank the staff of the University of Colorado Clinical and Translational Research Centers. We also thank the volunteers who participated in this study.

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