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Title: Does metabolic compensation explain the majority of less-than-expected weight loss in obese adults during a short-term severe diet and exercise intervention?

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Running Head: Compensatory responses with energy restriction

Abstract

Objective: We investigated to what extent changes in metabolic rate and composition of weight loss explained the less-than-expected weight loss in obese men and women during a diet-plus-exercise intervention.

Design: 16 obese men and women (41 ± 9 years; BMI 39 ± 6 kg/m^2) were investigated in energy balance before, after and twice during a 12-week VLED (565–650 kcal/day) plus exercise (aerobic plus resistance training) intervention. The relative energy deficit (EDef) from baseline requirements was severe (74-87%). Body composition was measured by deuterium dilution and DXA and resting metabolic rate (RMR) by indirect calorimetry. Fat mass (FM) and fat-free mass (FFM) were converted into energy equivalents using constants: 9.45 kcal/gFM and 1.13 kcal/gFFM. Predicted weight loss was calculated from the energy deficit using the '7700 kcal/kg rule'.

Results: Changes in weight (-18.6 ± 5.0 kg), FM (-15.5 ± 4.3 kg), and FFM (-3.1 ± 1.9 kg) did not differ between genders. Measured weight loss was on average 67% of the predicted value, but ranged from 39 to 94%. Relative EDef was correlated with the decrease in RMR (R=0.70, P<0.01) and the decrease in RMR correlated with the difference between actual and expected weight loss (R=0.51, P<0.01). Changes in metabolic rate explained on average 67% of the less-than-expected weight loss, and variability in the proportion of weight lost as FM accounted for a further 5%. On average, after adjustment for changes in metabolic rate and body composition of weight lost, actual weight loss reached 90% of predicted values.

Conclusion: Although weight loss was 33% lower than predicted at baseline from standard energy equivalents, the majority of this differential was explained by physiological variables. While lower-than-expected weight loss is often attributed to incomplete adherence to prescribed interventions, the influence of baseline calculation errors and metabolic down-regulation should not be discounted.

Key Words: metabolic compensation, adaptive thermogenesis, predicted weight loss, resting metabolic rate, energy restriction, exercise, metabolic downregulation

Introduction

A common approach to facilitate weight loss is to reduce energy intake. When determining the expected weight loss from a dietary intervention, the method often undertaken is to calculate the energy deficit from weight maintenance requirements at baseline; then multiply by duration of deficit; and then divide the total accumulated deficit by a value such as the Wishnofsky constant (e.g. 7700 kcal/kg) (1). However, baseline energy deficit calculations such as these commonly overestimate the actual weight loss achieved (2, 3). While a lack of adherence is often cited as the primary reason for the shortfall in weight loss (2-4), it is also recognised that biological compensatory responses are elicited when energy restriction is imposed, essentially acting to reduce energy expenditure (5), which in turn reduces the energy deficit and can reduce the weight loss (6-11). Furthermore, the energy density of weight loss is not uniform, and initial body fat, the magnitude of weight loss, and use of resistance exercise or high protein diets may influence the applicability of the Wishnofsky constant (12).

As it is the largest component of total daily energy expenditure, researchers have long been interested in changes to resting metabolic rate (RMR) that accompany energy restriction, and the extent to which variance in RMR may differentiate levels of success in weight loss interventions. Although there is considerable debate as to whether the change in RMR with weight loss is prognostic of successful long-term weight maintenance (13-16), it is well accepted that RMR decreases substantially during energy restriction even before significant weight loss has occurred (16-18). The seminal research undertaken in the Minnesota semi-starvation trials on lean men demonstrated that the decline in RMR was most rapid in the first 2 weeks, indicating that the reduced metabolic activity of the body tissues occurred quickly in response to energy deficiency (19). These adaptive responses are equally evident in obese individuals when energy restricted despite them having substantial energy stores (16).

To accurately predict the amount of weight loss that is physiologically possible requires appropriately accounting for biological compensatory responses that alter the energy deficit trajectory during energy restriction. The extent to which metabolic adjustments may explain the less-than-expected weight loss has been examined using RMR data collected in energy balance before and after the weight loss intervention (2, 3, 20). However, predictions of expected weight loss must account for the reductions in energy expenditure that occur *during* energy restriction, and which are greater than is evident in the weight-reduced energy balance state. Another alteration to daily energy expenditure that accompanies energy restriction is the reduction in dietary-induced thermogenesis (DIT). DIT is the increase in energy expenditure above resting values as a consequence of digestion, absorption and processing of nutrients, as well as the associated sympathetic nervous system response (21). Even without any improved metabolic efficiency in DIT (i.e. reduced thermogenesis per calorie ingested) during energy restriction, a modest to severe reduction in energy intake will result in a meaningful absolute decrease in DIT, particularly for individuals with a large habitual energy intake. Without accounting for this reduction in energy expenditure, the expected weight loss during energy restriction can be miscalculated.

In light of each of these potential sources of error, the current study was undertaken to examine the extent to which changes in metabolic rate and the composition of weight loss explained the less-than-expected weight loss in obese men and women undergoing short-term severe caloric restriction during a diet-plus-exercise intervention.

Subjects and Methods

Study Participants

Sixteen participants (41 ± 9 years; BMI 39 ± 6 kg/m^2) were recruited for the study. Eligibility was dependent upon being euthyroid, non-diabetic, ambulatory, having a BMI >30 kg/m^2, having been weight stable (± 2 kg) for at least 6 months, and being sedentary. Sedentary was defined as no regular physical activity (>60 minutes per week) including work-related physical activity. Respondents were ineligible for inclusion if they were taking medication known to affect body composition or electrolyte balance, pregnant or lactating, planning to fall pregnant in the next 12 months, postmenopausal, or non-ambulatory. The University Human Research Ethics Committee approved the study and signed informed consent was obtained from all participants before enrolment. Participants were required to be available for testing on the same day and time of day each month, and to complete exercise training at the University four times per week.

Study Design

Participants were required to maintain dietary habits and usual level of physical activity for the three weeks between recruitment and baseline testing; the mean weight change during this period was 0.2 ± 0.5 kg (-0.7 to +1.0 kg). Participants undertook two graded exercise treadmill tests during this 3-week period to determine maximal aerobic power and blood lactate thresholds using methods published previously (22). One week preceding the start of the intervention, participants underwent baseline testing of RMR and body composition. Participants were prescribed a 12-week very-low-energy-diet (VLED) plus exercise training program. Body composition and metabolic measures were repeated after the 4th and 8th week of energy restriction, and 7–10 days after completion of the intervention with a weight maintaining (energy balance) diet imposed.

Intervention

Very-Low-Energy Diet (VLED)

The ketogenic VLED incorporated replacement of two meals a day with a liquid formula. Each 40 g supplement provided 640 kJ (15.2 g of protein, 1.8 g fat, and 19.2 g of carbohydrate), with 40% of the energy from protein, 10% from fat, and 50% from carbohydrate. Each 40 g supplement of the formula provided 50% of the recommended daily allowance for essential vitamins and minerals. Participants were instructed in how to prepare the third major meal of the day from lean meat (cooked weight: 120 g for females and 210 g for males) and non-starch vegetables. Additionally, participants were instructed to take two multivitamin supplements per day. The energy intake was 650 kcal/d (2730 kJ/d) for males and 565 kcal/d (2373 kJ/d) for females. Protein intake was 0.94 ± 0.14 g/kg for males and 0.90 ± 0.16 g/kg for females. The diet was medically monitored, and all participants attended a weekly consultation with a medical practitioner. Adherence to the diet was evaluated each week through assessment of urine acetoacetic acid concentration (mmol/L) using Ketostix™ reagent strips (Bayer Corp, USA). Participants with urinary ketone concentrations less than 1.5 mmol/L, indicative of negative or trace values, were educated as to appropriate dietary protocol. No participant recorded low ketone concentrations more than once during the study.

Exercise Training

The training program provided consisted of four aerobic, and two resistance weight training, sessions/ week which were supervised and offered between 0600-2200 hrs six days/week. The aerobic training involved participants walking around a marked grass track at a heart rate 5-10% below the anaerobic threshold, verified using heart rate monitors (Polar 620i, Polar Electro, Oulu, Finland). The aerobic exercise duration began at 30 min/session for the first four weeks, and progressively increased to 60-min during the third month of the intervention. The resistance training sessions involved eight resistance exercises per session: shoulder press, chest press, lat pull down, leg press, bench press, quarter-to-half squats, upright row, and abdominal exercises. In the first month two sets of each exercise were completed per session (set 1 = 10 reps, set 2 = maximal reps to failure while maintaining proper form). The intensity of the exercise was 60% 1-RM week 1, 70% 1-RM week 2 and 3, and 80% 1-RM week 4. The second and third months incorporated three sets/session at 80% 1-RM (set 1/2 = 10 reps, set 3 = maximal reps to failure). All participants completed >95% of the required exercise training sessions.

Anthropometry and Body Composition

Body height (stretch stature) was measured to the nearest tenth of a centimetre using a Harpenden stadiometer, and body weight was measured to the nearest 100 grams recorded on a Wedderburn digital scale (BWB600). Body composition was determined by dual energy x-ray absorptiometry (DXA; Lunar DPX, Lunar, Madison, WI) (23) and from measurements of total body water (TBW) using the stable, non-radioactive, non-toxic isotope deuterium (^2H_2O) as previously published (24).

Resting Metabolic Rate (RMR)

RMR was measured using a ventilated hood system (Deltatrac II, Datex, Helsinki, Finland) calibrated before each measurement with standardised gases. All testing was conducted between 0700-0900 hrs after a 12-hour overnight fast. Participants arrived at the laboratory by car and were instructed to minimise physical activity prior to arrival. Prior to RMR measurement, all participants rested for 45-min during a whole body DXA measurement. Testing was performed in a thermoneutral environment with participants lying supine in a comfortable position, head on a pillow, and a transparent ventilated hood placed over their head. Plastic sheeting attached to the hood was placed around the participant to form a seal between the air inside and outside the hood. During the measurement period participants remained supine, breathed normally, were instructed not to talk or fidget, and listened to quiet music to reduce boredom and remain awake. After a 10-min adaptation to the hood, VO_2 and VCO_2 were measured continuously for 30-min, and the data with the lowest 10-min coefficient of variation was used for analyses as we have previously published (25). RMR was calculated using the Weir equation (26).

Calculations of energy requirements and energy deficit

Baseline weight maintenance energy requirements ($WM_{baseline}$) were calculated as RMR multiplied by a physical activity level (PAL) of 1.5. We have recently presented data from a similar cohort demonstrating that weight stability can be maintained over 4 weeks in obese adults using this approach (27). The baseline energy deficit for each participant was calculated as the baseline WM plus exercise energy expenditure minus intervention energy intake. The energy expenditure of aerobic exercise was determined from an individualised regression equation between HR and the indirect calorimetry-derived energy expenditure developed using steady state data from the GXT. The energy expenditure of the resistance training sessions was calculated using values derived from previous studies using comparable exercises (28-30). The energy equivalence of FM and FFM loss was determined from standard caloric equivalents: 9.45 kcal/gFM and 1.13 kcal/gFFM (31, 32).

Five different approaches were employed to determine predicted weight loss:

Approach 1: Predicted weight loss was initially calculated from the baseline EDef ÷ 7700

$[WM_{baseline}$ + exercise energy expenditure (ExEE) – intervention energy intake (EI)] × 84 days ÷ 7700 kcal/kg; where EI is 650 kcal/d for men and 565 kcal/d for women.

Approach 2: Approach 1 + adjustment for the decrease in dietary-induced thermogenesis (DIT)

$[(WM_{baseline} + ExEE - EI)$ – decrease in dietary-induced thermogenesis (DIT)] × 84 days ÷ 7700 kcal/kg; where the decrease in DIT = $0.1 \times WM_{baseline} - 0.1 \times EI$.

Approach 3: Approach 2 + adjustment for the monthly changes in RMR

$[(RMR_{month2} \times 1.5 + ExEE - EI) \times 28$ days $+ (RMR_{month3} \times 1.5 + ExEE - EI) \times 28$ days $+ (RMR_{month4} \times 1.5 + ExEE - EI) \times 28$ days$] \div 7700$ kcal/kg.

Approach 4: Approach combining changes in DIT and RMR

$\{[(RMR_{month2} \times 1.5 + ExEE - EI) \times 28$ days $+ (RMR_{month3} \times 1.5 + ExEE - EI) \times 28$ days $+ (RMR_{month4} \times 1.5 + ExEE - EI) \times 28$ days$] - [(0.1 \times WM_{baseline} - 0.1 \times EI) \times 84$ days$]\} \div 7700$ kcal/kg.

Approach 5: Approach 4 with individual adjustment for the energy equivalence of the FM and FFM loss rather than using the Wishnofsky constant.

$\{[(RMR_{month2} \times 1.5 + ExEE - EI) \times 28$ days $+ (RMR_{month3} \times 1.5 + ExEE - EI) \times 28$ days $+ (RMR_{month4} \times 1.5 + ExEE - EI) \times 28$ days$] - [(0.1 \times WM_{baseline} - 0.1 \times EI) \times 84$ days$]\} \div$ energy equivalence of the FM and FFM loss for each individual in kcal/kg; where 9.45 kcal/gFM and 1.13 kcal/gFFM.

Statistical Analysis

Differences in metabolic and body composition measures between males and females were examined using independent t-tests. Repeated measures ANOVA were employed to compare if RMR and body composition changed over time. RMR before, during and after the intervention was compared using repeated measures ANCOVA with sex, FFM and FM as covariates. Repeated measures ANOVA were also employed to compare actual weight loss with expected weight loss values determined from the five prediction approaches, and Bonferroni post-hoc tests were performed to locate differences among means. Pearson product correlations were computed to determine potential interrelations between outcome variables, and linear regression analysis was used to explore factors that might explain the less-than-expected weight loss. All statistical calculations were performed using SAS version 9.02 (SAS Institute, Inc, Cary, NC) with $P<0.05$ considered significant. Data are presented as mean ± SD as specified.

Results

Baseline body weight and body composition data are presented in **Table 1** for the whole cohort and for the sexes separately. There was no sex difference in absolute or relative weight loss, FM or FFM loss, or the proportion of weight loss as FM as a result of the 12-week intervention. In terms of the combined cohort, the intervention resulted in a significant weight loss (18.6 ± 5.0 kg; 16.3 ± 3.1%), with a large proportion of the weight lost being FM (84 ± 6%). **Figure 1** displays FM, FFM and RMR before, during and after the intervention. While the change in FFM over the intervention was not statistically significant, FM decreased by ~10% each month. Protein intake was negatively related to the loss of FFM, i.e. lower protein intake resulted in greater loss of FFM ($R = -0.55$; $P<0.05$), but not with loss of FM ($P=0.13$).

Absolute RMR (kcal/day) at week 4 was significantly lower than baseline and, on average, did not change appreciably after this point (**Figure 1**). Repeated measures ANCOVA was undertaken to compare RMR adjusted for sex and body composition in energy balance with measures taken during energy restriction. RMR adjusted for sex, FFM and FM in energy balance (baseline: 1803 ± 122 kcal/d, post-intervention: 1864 ± 128 kcal/d) was significantly higher than during energy restriction (week 4: 1714 ± 122 kcal/d, week 8: 1757 ± 117 kcal/d) ($P<0.01$).

Weight lost each month of the intervention compared with predicted values (Approach 1) is presented in **Figure 2**. There was no significant difference ($P = 0.8$) between actual and predicted values in the first month of the intervention (9.3 ± 3.3 kg and 9.5 ± 2.5 kg, respectively). As much as 1-2 kg of the actual weight loss in the first 2 weeks of the intervention may be attributed to glycogen and associated water losses. However, this is speculative as glycogen was not measured. However the weight losses in the second month (5.1 ± 1.3 kg) and third month (4.2 ± 1.4 kg) of the intervention were significantly ($P < 0.0001$) lower than the predicted values. The differential between actual weight loss and baseline calculations (Approach 1) was significantly correlated with the absolute change in RMR from baseline to the third month of energy restriction, and the relationship remained after adjusting for the magnitude of actual weight loss (**Table 2**). Larger decreases in RMR correlated with a greater discrepancy between predicted and actual weight loss. Furthermore, the differential between actual weight loss and that predicted using baseline values (Approach 1), was significantly correlated with the calculated reduction in DIT over the dietary intervention (R = 0.71, P < 0.01).

Table 3 summarises the energy deficit and predicted weight loss from the five different calculation approaches investigated. Actual weight loss was significantly (P<0.001) lower than the values predicted from baseline measures and using the Wishnofsky constant (e.g. 7700 kcal/kg; Approach 1), with an average discrepancy of 9.9 ± 5.8 kg (1.2–22.2 kg). While there was no sex difference in the magnitude of the discrepancy, the variance in shortfall was in part because the proportional energy restriction provided by the VLED was not the same for all participants. The relative energy restriction ranged between 74 and 87% of baseline weight maintenance requirements, with the magnitude of the restriction being greater for larger participants. Consequently, there was a significant relationship between the energy deficits (using Approach 1) calculated either in absolute or relative terms and the magnitude of decrease in RMR during energy restriction; with larger deficits resulting in greater reductions in RMR (**Table 2**).

After the calculated energy deficit was corrected for the change in DIT (Approach 2), the discrepancy was 7.4 ± 5.4 kg being statistically significant (P<0.01). Similarly, when the calculated energy deficit was corrected for the monthly change in RMR (Approach 3), the discrepancy of 5.8 ± 5.1 kg was statistically significant (P<0.05). However, when energy deficit was calculated with adjustments made for both the change in DIT and monthly change in RMR (Approach 4), the actual weight loss reached, on average, 87% of the predicted value, and the discrepancy of 3.3 ± 4.8 kg was not statistically different from the predicted values (P=0.13). Finally, the energy deficit calculated with adjustments made for both the change in DIT and monthly change in RMR was divided by the energy equivalence of the FM and FFM loss for each individual (Approach 5). Using this approach, the actual weight loss was, on average, 90% of the predicted values, with the shortfall of 2.8 ± 5.0 kg not statistically significant from the predicted values (P=0.20). The comparisons between actual and predicted values are shown graphically in **Figure 3**.

Discussion

Dietary weight loss interventions in obese individuals are often described as being unsuccessful when the weight loss achieved is less than the amount anticipated from baseline energy deficit calculations. The less-than-expected weight loss experienced with energy restriction could be likened to missing the target when hitting a golf ball. The factors contributing to missing the weight loss target may be considered in two categories: [1] ***errors off the tee***: errors from baseline such as miscalculating $WM_{baseline}$, use of the Wishnofsky constant, or not accounting for the immediate reduction in DIT consequent to the reduced energy intake; and [2] ***errors in flight***: deviations from the target that occur as a result of intervening factors once the energy restriction has been imposed such as metabolic depression or behavioural non-compliance. The aims of the current study were to quantify [1] the extent to which actual weight loss matched the baseline predictions, and [2] if variables which can be objectively measured with high precision in the laboratory; i.e. energy expenditure and body composition, explain the less-than-expected weight loss in obese men and women during a diet-plus-exercise intervention.

The primary finding of the current study was that actual weight loss was significantly less than the weight loss expected from baseline calculations, averaging only 67% of the predicted values. This is comparable with the 65% of predicted weight loss seen after 10 weeks of 50% caloric restriction in lean males in the seminal, tightly-controlled, Minnesota weight loss study (33). Physiological compensatory responses acting to increase metabolic efficiencies are likely to have contributed to this less-than-expected weight loss. Such metabolic compensation, particularly during severe energy restriction, was recognised in 1950 by Ancel Keys who noted: *It might seem entirely reasonable that the energetic processes of the body diminish in intensity as the exogenous food supply is reduced. It is reasonable in the sense that a wise man will reduce his expenditure when his income is cut* (19). Research on both lean and obese cohorts has demonstrated that RMR reduces rapidly when individuals are placed in energy restriction, with the magnitude of the decrease being greater than can be accounted for by tissue loss (16, 34). RMR of overweight women has been reported to fall 6%

within 10 days of commencing energy restriction (800 kcal/d; ~40% $WM_{baseline}$) (16), and a comparable (~6%) decrease in resting oxygen consumption was reported after only 4 days of severe energy restriction (450 kcal/day; <25% $WM_{baseline}$) in very obese women (35). In obese women, Bray et al. (35) noted that a weight loss of 1 kg every 4 days would be expected based on the baseline calculated energy deficit. However, the actual weight loss in days 16-20 of restriction was 0.7 kg, and in days 20-24 of restriction the weight loss was only 0.3 kg. The authors proposed that the less-than-expected weight loss could in part be attributed to a 15% reduction in energy expenditure during this period. There was also strong evidence of enhanced efficiency of cellular energy production with energy restriction (35). More recent studies demonstrate rapid alterations in gene expression of processes regulating cellular metabolism, and that these are in response to changes in energy intake *per se* rather than as a consequence of weight loss (7, 36).

In the current study, the average decrease in absolute RMR was 228 kcal/d (11%) within the first month of the intervention. Consequently, from at least this point in time, the EDef estimates derived at baseline were incorrect, leading to an overestimation of the expected weight loss. Previous studies that have considered the influence of changes in RMR on less-than-expected weight loss have relied on measurements taken in energy balance before and after energy restriction (2-4). Consequently the extent to which the reduced RMR during ER may have accounted for the less-than-expected weight loss was likely underestimated. In the study from Del Corral et al. (2), a daily kilocalorie discrepancy was determined from averaging the TEE measured (via doubly-labelled water) in energy balance at baseline and after ~12 kg (15.5%) weight loss, then subtracting the energy intake during energy restriction (800 kcal/d) to get the ‘actual’ energy deficit, and from this the ‘expected’ weight loss was determined. This calculated energy deficit value was compared with the energy equivalent of the FM and FFM loss, or the ‘actual’ kilocalorie loss, and was assumed to be a measure of dietary adherence. While this study has many methodological strengths, given there was no correction made for metabolic compensations that accompany energy restriction, the calculations of dietary adherence may be strongly questioned. The authors propose that any changes in RMR would have been relatively small. However using the same study design, this group has previously reported that the

RMR of comparably sized overweight women fell 6% (~95 kcal/d) within 10 days of commencing energy restriction (800 kcal/d) (16). Furthermore, we can estimate that the DIT may have decreased on average by ~120 kcal/d from consuming the $WM_{baseline}$ diet (~2000 kcal/d) to consuming the energy restricted diet. Collectively, this ~215 kcal/d metabolic conservation during energy restriction would reduce the proposed daily kcal discrepancy by about 60%, and hence suggests a much better dietary adherence than was proposed.

When predicting expected weight loss, few studies have accounted for the reduced DIT that accompanies energy restriction. Any given change in meal size is matched by a corresponding change in postprandial peak metabolism and duration of the thermic response, and thus DIT (21). Due to the severe degree of energy restriction employed in the current study, the calculated decrease in DIT from baseline was on average 236 kcal/d (~80%). Thus, although DIT is a markedly smaller component of total daily energy expenditure than RMR, the absolute energy conservation associated with RMR and DIT during severe energy restriction in this cohort was comparable. Unfortunately, a limitation of the current study is that DIT was not measured, but predicted. However, the energy associated with processing the $WM_{baseline}$ (2958 ± 662 kcal/d) would be expected to have decreased markedly with the change to the energy restricted diet (597 ± 45 kcal/d), and whatever error is incurred by this prediction is likely to be small in absolute terms. It is also important to note that a marked decrease would be experienced whether or not there was improved efficiency in postprandial processing of meals in these underfed participants (37).

Considering both the change in RMR and DIT within the first month of the intervention, the collective metabolic compensation was on average (228 kcal/d + 236 kcal/d) 464 kcal/d, or 16% of $WM_{baseline}$. We investigated the extent to which these efficiencies impacted on the weight loss achieved. After accounting for the change in calculated DIT and measured RMR during the intervention, the actual weight loss was 87% of the predicted value and, on average, was not statistically different to predicted values. Thus 60% of the apparent discrepancy between predicted and actual weight loss could be attributed to overestimation of actual energy needs during energy restriction. Interestingly, this is of the same magnitude as we have estimated in the study by Del Corral et al (2). Accounting for these compensatory metabolic responses, the actual less-than-predicted weight loss in the current study was, on average, only 3.3 kg rather than the 9.9 kg discrepancy indicated from using baseline calculations. Importantly, RMR was measured only twice during energy restriction – additional assessments may enable better quantification of the metabolic compensation.

We also examined if the tissue composition of the weight loss may further explain the weight loss discrepancy. The average loss of FFM over the intervention was modest (3.1 ± 1.9 kg). It is also worth noting that despite the severe EDef, the majority of FFM was lost in the first month, and that even by the end of the intervention the participants were still experiencing consistent FM losses. With the reasonably stable values for RMR in the second and third month of the intervention, this indicates that the energy equivalent of the weight loss was consistent for the majority of the intervention. The Wishnofsky constant (7700 kcal/kg) is based on the assumption that the composition of weight loss is 79% FM and 21% FFM (1). In the current study, FM ranged from 71 – 96% of the weight loss, and so the actual energy deficit per kilogram weight lost ranged 7006 – 9116 kcal/kg. In their study of overweight/obese women undergoing a less energy restrictive diet but without supervised exercise training, Goele et al. (3) reported a much wider range in the energy deficit per kilogram weight lost: 3097 – 16401 kcal/kg. Taking into account the variance in energy equivalence of the weight loss in the current study, a further 0.6 kg of the less-than-expected weight loss was accounted for, leaving the shortfall of 2.8 kg on average, with the actual weight loss not statistically different from this recalculated expected value. The proportion of the less-than-expected weight loss that was accounted for by the body composition of the weight loss in the current study (~5%) was much less than that reported by Goele et al.(3) (14%). However this could be attributed to Goele et al. not having the opportunity to account for changes in RMR during the energy restriction *per se*, and thus overestimating the expected weight loss, particularly in larger individuals who may also have had a larger energy equivalence of the weight lost. After adjusting for the changes in RMR and DIT, and the variance in the composition of the weight loss, actual weight loss averaged approximately 90% of predicted values.

It is worth considering what other biological factors may explain the remaining shortfall of the actual from predicted weight loss, and the variance in this shortfall. Another factor is the possible within-individual changes, and between-individual differences, in activity energy expenditure (AEE). AEE is a function both of the total amount of physical movement and the efficiency, or energy cost, per unit of the movement. We have recently shown in obese pregnant women that, over gestation, the energy cost of movement can decrease, and that this is both due to behavioural (walking more slowly) and biological (improved walking economy) compensations (38). Further, we, and others, have shown reductions in non-exercise activity thermogenesis (NEAT) in overweight and obese individuals in response to exercise training and/or caloric restriction interventions (39-41). Given accurate measurement of daily physical activity and AEE can be challenging in studies of free-living humans, it is useful to consider evidence from highly-controlled animal studies. High inter-animal variability in weight loss was reported in a recent study of MF1 mice which were restricted to 70% of their individual baseline food intake for 28 days. Interestingly, the mice losing more weight had increased, whereas mice losing less weight had decreased, physical activity levels (42). In the current study, we had no measure of NEAT from accelerometry or questionnaires. However, it is possible that reduction in physical movement outside of the exercise training sessions, and reduction in the energy cost of movement *per se* when in severe EDef, may account for some of the less-than-expected weight loss. It is unfortunate that this information is not available to qualify the extent to which variations in physical activity explain the variance in weight loss.

Finally, we must consider that a less-than-expected weight loss may be attributed to non-compliance with the prescribed intervention. Considerable effort was made in the current study to enable and monitor compliance. The low-energy ketogenic diet replaced 2 meals per day with supplements, and participants were provided sample recipes to assist with the preparation of the daily self-prepared meal. Adherence was evaluated through weekly consultations and assessment of urine acetoacetic acid concentration. All participants completed >95% of the required exercise training sessions, and sessions were supervised and workload monitored by the same investigator (NMB). Consequently, we are confident that adherence to the intervention was high.

Future Directions

There are two avenues through which RMR can be reduced during energy restriction: a reduction attributed to the loss of tissues, and a reduction beyond that explained by the loss of tissue – or adaptive thermogenesis. Future studies could consider undertaking frequent serial measures of RMR soon after the imposition of an energy deficit, and continued throughout the phases of weight loss. This will provide the basis to better understand the extent to which energy conservation resulting from the adaptive reduction in thermogenesis contributes to the overall reduction in RMR and to the discrepancy between actual and predicted weight loss.

Conclusions

While less-than-expected weight loss is often attributed to incomplete adherence to prescribed interventions, the influence of baseline calculation errors and compensatory metabolic responses should not be discounted. Strategies to monitor factors that impact energy expenditure are needed during interventions, to enable those trying to lose weight, to stay on course.

Conflict of Interest

None of the authors have any competing financial interests in relation to the work described in this manuscript.

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Figure 1 Fat mass (FM; black bars), fat-free mass (FFM; white bars) and resting metabolic rate (RMR; —▲—) in energy balance before and after the 12-week intervention, and during the intervention at the 4th and 8th week of energy restriction. † RMR significantly different from baseline ($P < 0.05$); FM significantly different from baseline; * $P<0.05$, ** $P<0.01$. FFM did not differ significantly from baseline values.

Figure 2 Actual versus Predicted weight loss after 4 weeks (Month1;◆), 8 weeks (Month2; □) and 12 weeks (Month3; ○) of diet-plus-exercise intervention. Dashed line (- - -) represents the line-of-identity.

Figure 3 Actual versus Predicted weight loss. (A) Predicted weight loss calculated from the baseline energy deficit ÷ 7700; (B) After adjustment for the decrease in dietary-induced thermogenesis (DIT); (C) After adjustment for the monthly changes in resting metabolic rate (RMR); (D) After adjustment for changes in both DIT and RMR; (E) After adjustment for changes in both DIT and RMR, and the energy equivalence of the FM and FFM loss rather than using the Wishnofsky constant.

Table 1 Baseline descriptive data, and changes in body weight and body composition measures with the intervention for the total cohort and by sex.

	Total Cohort (N = 16)	**Males (N = 8)**	**Females (N = 8)**
Age (years)	40.5 ± 9.0	42.2 ± 4.5	39.5 ± 11.0
Height (cm)	168.7 ± 6.7	173.3 ± 2.7	165.9 ± 6.9 [b]
Weight (kg)	114.4 ± 23.7	128.1 ± 21.0	106.2 ± 22.1 [a]
Body mass index (kg.m^{-2})	39.3 ± 6.3	41.2 ± 7.7	38.2 ± 5.5
Fat mass (kg)	58.4 ± 14.2	56.6 ± 14.7	53.7 ± 14.6
Fat-free mass (kg)	59.6 ± 12.0	71.5 ± 6.5	52.5 ± 6.5 [c]
Percent body fat (%)	47.7 ± 4.7	44.9 ± 4.3	50.5 ± 3.3 [b]
Weight loss (kg)	18.6 ± 5.0	20.4 ± 3.5	17.6 ± 5.6
Weight loss (%)	16.3 ± 3.1	16.1 ± 3.2	16.4 ± 3.2
Fat mass loss (kg)	15.5 ± 4.3	17.4 ± 3.1	14.5 ± 4.6
Fat-free mass loss (kg)	3.1 ± 1.9	3.0 ± 2.0	3.1 ± 1.9
Fat mass loss as a proportion of weight loss (%)	83.6 ± 7.8	85.6 ± 8.8	82.4 ± 7.3

Statistically significant differences between males and females: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$

Table 2 Associations between resting metabolic rate and body composition changes and the difference between actual weight loss and the weight loss predicted from baseline calculations.

	Energy Deficit (kcal/d)	Energy Deficit (%)	Predicted – Actual Weight loss (kg)[b]
Change RMR (kcal/d)[a]	**0.64****	**0.70****	**0.51***
Change RMR (kcal/d)[a] adjusted for weight loss	**0.57***	**0.65****	**0.57***
Fat-free mass loss (kg)	0.47	**0.55***	0.12
Fat-free mass loss as a proportion of weight loss (%)	0.20	0.31	0.20
Energy Deficit (kcal/d)	---	---	**0.74****
Energy Deficit (%)	---	---	**0.68****

Abbreviations: RMR, resting metabolic rate. [a] Change from baseline to 3rd month of intervention (i.e. during energy restriction). [b] Weight loss predicted from baseline calculations (Approach 1).

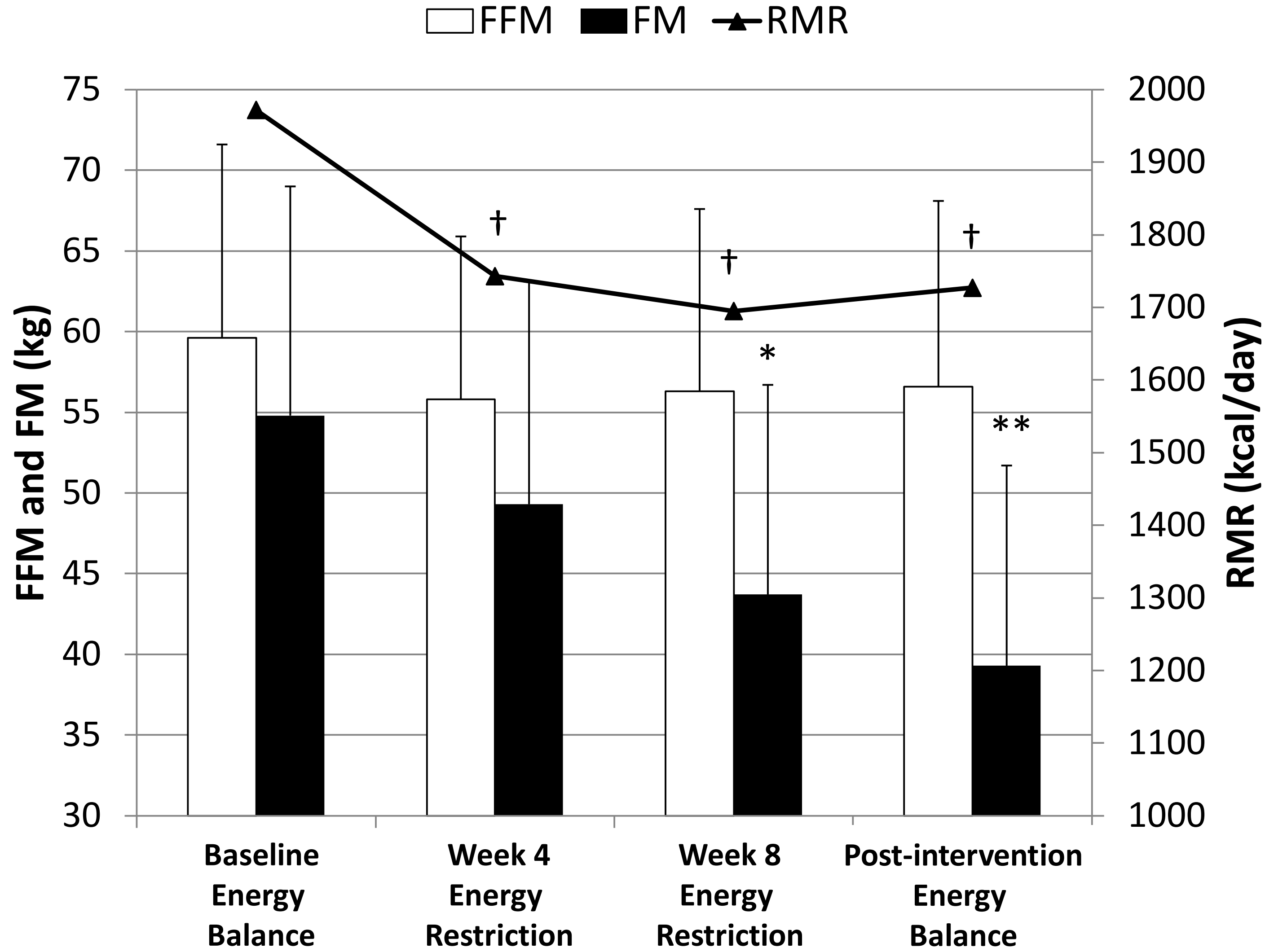
* $P < 0.05$, ** $P < 0.01$. Pearson correlation coefficients and partial correlation analysis (*R* values after adjustment).

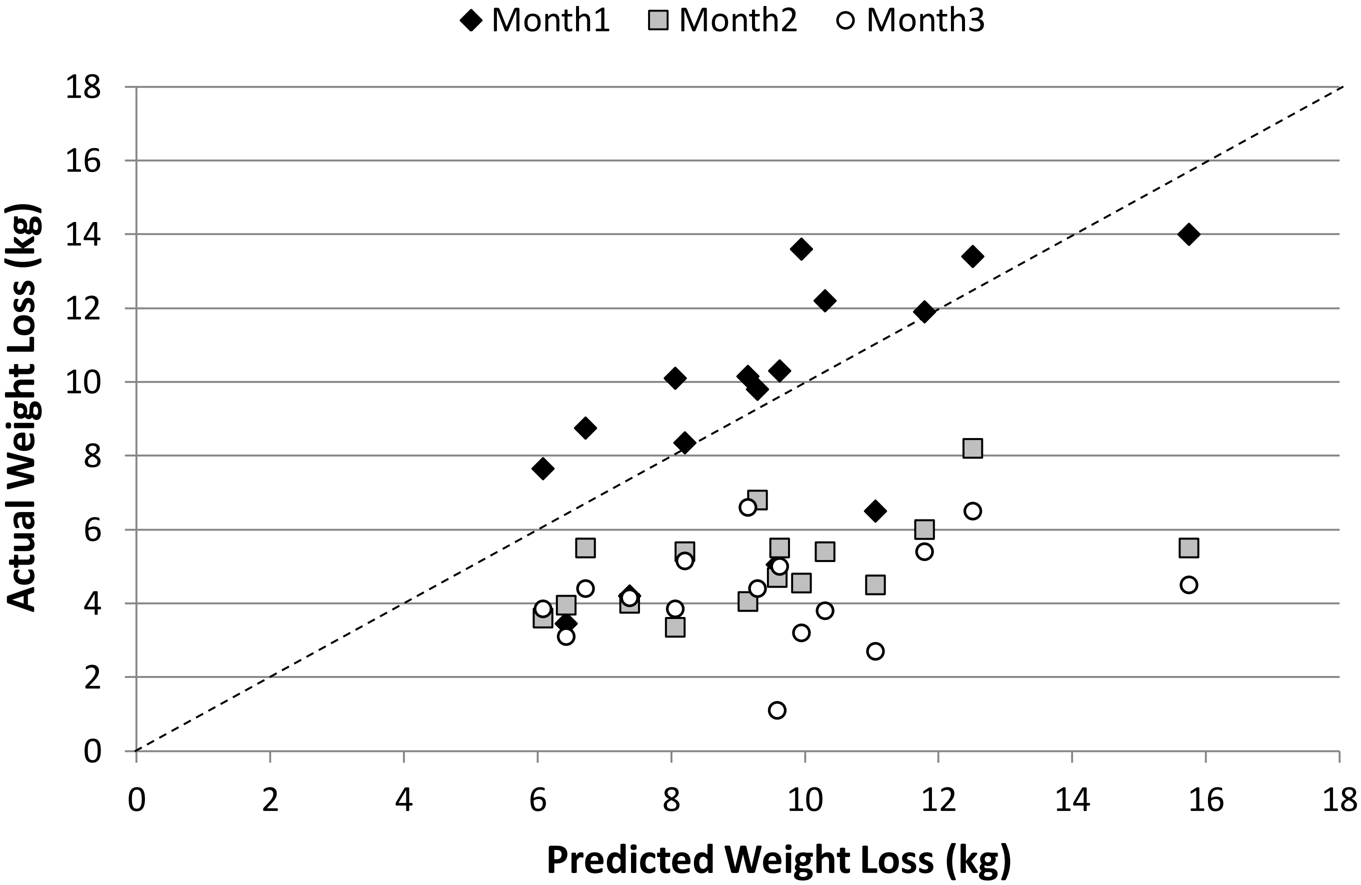
Table 3 Energy deficit and weight loss predicted from baseline calculations, and after adjusting for changes to dietary induced thermogenesis, resting metabolic rate and/or body composition.

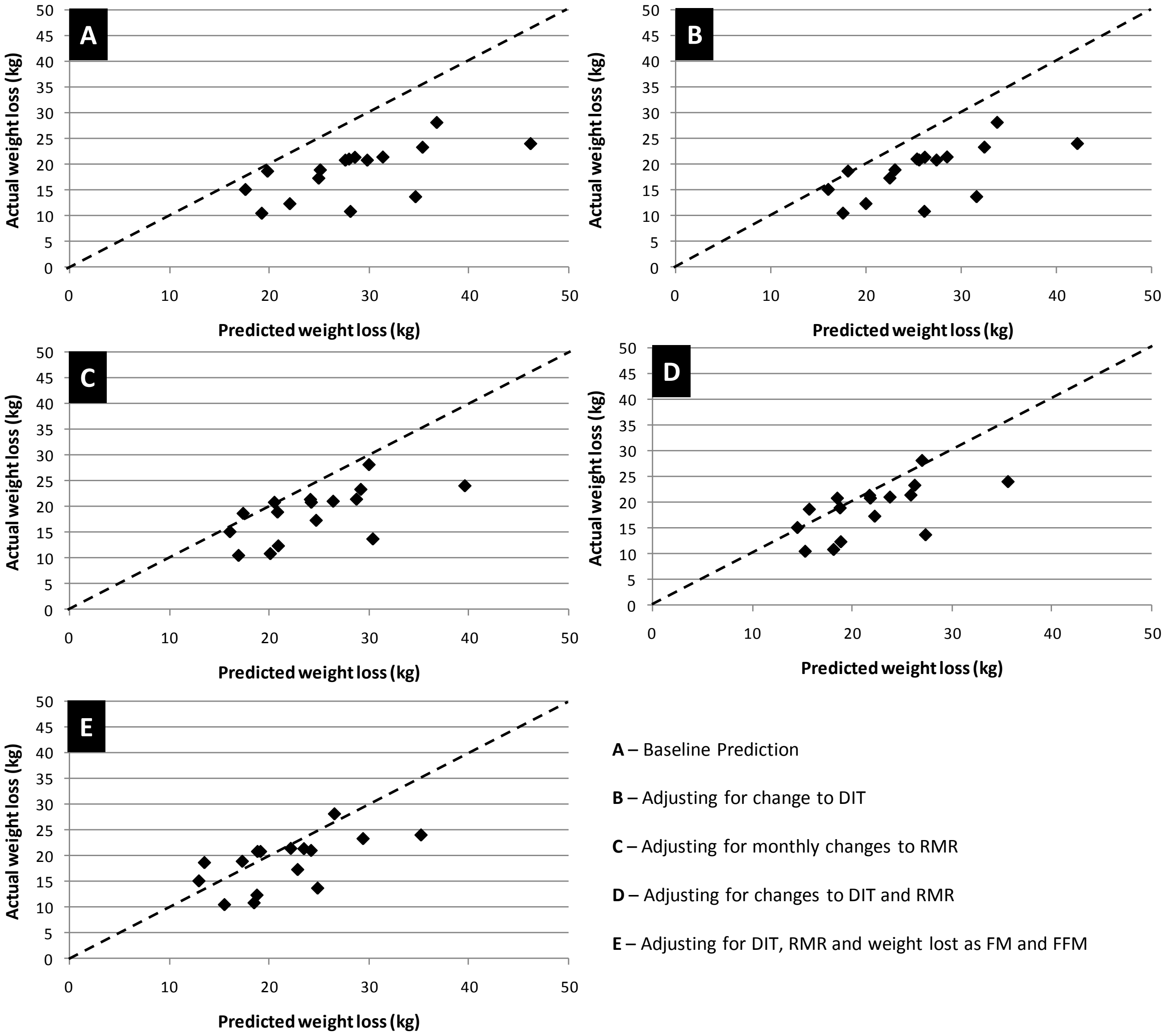
	Energy Deficit (kcal/d)	**Energy Deficit (%)**	**Predicted Weight Loss (kg)**	**Actual Vs Predicted Weight Loss (%)**
Approach 1 – Baseline Prediction	2611 ± 677	80.7 ± 3.5	28.5 ± 7.4 †	66.8 ± 15.3
Approach 2 – Adjusting for change to DIT	2387 ± 623	73.7 ± 3.4	26.0 ± 6.8 †	73.1 ± 16.8
Approach 3 – Adjusting for monthly changes to RMR	2236 ± 566	68.3 ± 5.3	24.4 ± 6.2 †	77.8 ± 18.0
Approach 4 – Adjusting for DIT and RMR	2012 ± 509	62.5 ± 4.8	22.0 ± 5.6	86.5 ± 20.0
Approach 5 – Adjusting for DIT, RMR and proportion of weight lost as FM and FFM	2012 ± 509	62.5 ± 4.8	21.4 ± 5.9	89.6 ± 23.8

DIT = dietary induced thermogenesis; RMR = resting metabolic rate; FM = fat mass; FFM = fat-free mass.

† Statistically significant difference compared with actual weight loss (18.6 ± 5.0 kg).


FFM
FM
RMR
FFM and FM (kg)
RMR (kcal/day)
75
70
65
60
55
50
45
40
35
30
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
†
†
†
*
**
Baseline Energy Balance
Week 4 Energy Restriction
Week 8 Energy Restriction
Post-intervention Energy Balance


◆ Month1
▨ Month2
○ Month3
Actual Weight Loss (kg)
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
16
18
Predicted Weight Loss (kg)



A – Baseline Prediction

B – Adjusting for change to DIT

C – Adjusting for monthly changes to RMR

D – Adjusting for changes to DIT and RMR

E – Adjusting for DIT, RMR and weight lost as FM and FFM