Why do obese patients not lose more weight when treated with low-calorie diets? A mechanistic perspective1,2

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ABSTRACT
Maximal weight loss observed in low-calorie diet (LCD) studies tends to be small, and the mechanisms leading to this low treatment efficacy have not been clarified. Less-than-expected weight loss with LCDs can arise from an increase in fractional energy absorption (FEA), adaptations in energy expenditure, or incomplete patient diet adherence. We systematically reviewed studies of FEA and total energy expenditure (TEE) in obese patients undergoing weight loss with LCDs and in patients with reduced obesity (RO), respectively. This information was used to support an energy balance model that was then applied to examine patient adherence to prescribed LCD treatment programs. In the limited available literature, FEA was unchanged from baseline in short-term (<12 wk) treatment studies with LCDs; no long-term (≥26 wk) studies were found. Review of doubly labeled water and respiratory chamber studies identified 10 reports of TEE in RO patients (n = 150) with long-term weight loss. These patients, who were weight stable, had a TEE almost identical to measured or predicted values in never-obese subjects (weighted mean difference: 1.3%; range: −1.7–8.5%). Modeling of energy balance, as supported by reviewed FEA and TEE studies, suggests that obese subjects participating in LCD programs have a weight loss less than half of that predicted. The small maximal weight loss observed with LCD treatments thus is likely not due to gastrointestinal adaptations but may be attributed, by deduction, to difficulties with patient adherence or, to a lesser degree, to metabolic adaptations induced by negative energy balance that are not captured by the current models. Am J Clin Nutr 2007;85:346–54.

KEY WORDS Obesity, diet, energy expenditure, doubly labeled water, adherence

INTRODUCTION
Low-calorie diets (LCDs), adopted as part of lifestyle management, are a cornerstone of the treatment of obese persons (1, 2). The aim of LCDs is sustained negative energy balance and, thereby, weight loss. However, a consistent observation spanning almost 5 decades is the modest weight loss, rarely >5–10 kg at 52 wk, observed with long-term LCD treatments (3, 4). This low efficacy of an important clinical therapy is so well accepted that little critical analysis of the underlying mechanisms appears in the medical literature.

In an effort to redress that imbalance of critical analysis, we examined the components of energy balance as they relate to the discrepancy between the observed and predicted weight loss of LCD treatments. We focus on maximum LCD-induced weight loss because it is amenable to quantitative analysis and prediction in an area that has not been fully clarified and in which ambiguities are limiting further development.

LOW-CALORIE DIETS AND WEIGHT LOSS
Subjects placed on an energy-deficit diet rapidly lose weight over the first 1–2 wk of treatment (5). A second, slower, weight-loss phase then follows, in which maximal weight loss in outpatients is usually observed at 26–52 wk (Figure 1) (6, 7). Maximal weight loss refers to the weight nadir; after that nadir is reached, weight typically drifts upward back toward the baseline weight over a period of months to years, as shown in the examples in Figure 1.

A consistent observation is the relatively small average maximal weight loss observed with long-term (≥26 wk) treatments. This low treatment efficacy is found in virtually all of the LCD studies of nondiabetic overweight and obese subjects reported over the past 5 y in 2 representative journals, the New England Journal of Medicine and JAMA (Table 1). The average maximal weight loss reported in treatment groups with mean baseline weights of 77 to 132 kg ranged from 1.7 to 8.1 kg.

MAGNITUDE OF LOW-CALORIE DIET WEIGHT LOSS

Simple clinical energy intake–restriction model
Three approaches are used for setting the LCD energy intake (EI) goals. They are an absolute reduction from baseline (eg,
—500 kcal/d), a relative reduction from baseline (eg, −25%), and an intake below that required for weight maintenance (eg, 1200–1400 kcal/d for women and 1400–1600 kcal/d for men).

The magnitude of LCD-induced negative energy balance used to predict treatment-related weight loss assumes that a 1-kg reduction in body weight requires an energy deficit of 7700 kcal (16). Ingesting 500 kcal/d less than required for weight maintenance results in an energy deficit of 3500 kcal/wk, which should produce a weight loss of ≈0.5 kg/wk. However, the observed rate and amount of weight loss are typically far less than this prediction. For example, the rate of subjects’ weight loss was <25% of the predicted value in some of the studies presented in Table 1.

### Energy-balance weight-loss model

What are the possible explanations for the poor predictive ability noted above? One possibility is that the energy deficit...
must be adjusted for reductions in energy expenditure (EE) due to reduced body weight as the diet progresses (17–19). The lowering of resting EE (REE), and thus total EE (TEE), is chiefly due to diet-related loss of cell mass in metabolically active tissues (20). In addition, the energy cost of physical activity is directly proportional to body mass, and the total energy expended in walking, running, climbing stairs, and other weight-related activities therefore declines with weight loss (21).

The specific metabolic rate of cells (ie, EE/unit of mass) may also vary with energy supply, and thus metabolic adaptations may further reduce the rate and amount of weight loss beyond that accounted for solely by changes in body mass. Two mechanisms are possible contributors to a reduction in the specific metabolic rate. One is an increased efficiency (net chemical or physical work done per kcal expended) and the other is a reduction in the level of work (total chemical or physical work performed). Thus, the magnitude of “predicted” weight loss with a specified energy deficit cannot be calculated as in the simple clinical model; indeed, reliable weight-loss predictions are much more complex (17–19). Accordingly, we present an approach for estimating both the adherence to a prescribed reduction in baseline EI and the related weight loss in accordance with LCD treatment.

Given a fixed reduction in caloric intake at baseline, the magnitude of negative energy balance will decline nonlinearly over time, and the compliant subject will eventually reach equilibrium at a new, lower body weight (17–19). More detailed examinations of weight-loss kinetics are reported by Kozusko (17), Antonetti (18), and Alpert (19).

A critical assumption in the modeling of EE is that subjects with reduced obesity (RO) are in energy equilibrium and thus are no longer losing weight. Even small changes in energy balance can have large relative effects on EE.

Two factors must be considered in presenting our model of energy balance–weight loss. First, we assume that fractional energy absorption [(FEA) ie, % of gross EI available after adjustment for fecal energy losses] is the same in the new steady state as it was at baseline before weight loss. An adaptive increase in FEA, or energy digestibility (22), would be one factor contributing to the less-than-predicted weight loss with LCDs.

Second, we assume that EE in the weight-reduced state is comparable to that in never-obese subjects of equivalent sex, age, body weight, and activity level. If major adaptations in EE occur with long-term weight loss, the actual magnitude of induced negative energy balance will be less than “expected” on the basis of the prescribed energy deficit. Expected values are usually derived from healthy, weight-stable, never-obese control subjects.

Alternatively, the metabolic adaptation hypothesis predicts that RO subjects maintain the same body mass as do comparable never-obese subjects who have a substantially lower EI (23). According to this theory, the RO subjects would maintain a higher body mass than never-obese subjects who have the same EI (23–26). An adaptive lowering of TEE greater than that expected for the body mass change would be another explanation for the relatively small weight loss observed with LCDs.

Calculations predicting the weight loss expected for a given reduction in EI assume that subjects are fully compliant with the prescribed energy deficit. Lack of adherence—ie, not maintaining the prescribed EI—is another explanation for the small maximal weight loss observed with LCDs. The interplay of these 3 factors—enhanced energy absorption, adaptations in energy metabolism, and poor patient compliance—with the induction of negative energy balance is not well characterized. We therefore systematically explored each of these topics.

LOW-CALORIE DIETS AND ENERGY ABSORPTION

Early estimates of fecal fat losses during prolonged periods of starvation and semistarvation are not useful in examining FEA with LCDs (27, 28). We also did not find any modern studies of FEA after long-term weight loss in RO subjects. However, several contemporary studies examined FEA during the active phase of LCD-induced weight loss. For example, stool samples from sedentary and exercising obese subjects show comparable energy absorption at baseline (94.7% and 94.6% absorption) and during consumption of a 900 kcal/d LCD (95.8% and 93.7% absorption) for 5 wk (29). A study of normal-weight men ingesting 806 kcal/d less than their maintenance energy requirement for 21 d reached a similar conclusion (95.6% energy absorption at baseline compared with 95.5% during underfeeding) (30). Thus, enhanced dietary energy absorption, at least during the early period of weight loss, does appear to contribute measurably to the smaller-than-expected weight loss with LCDs. Furthermore, it is worth noting that, even if energy absorption increased maximally (from ≈95% to 100%), the net increase in systemic EI would be only ≈100 kcal/d.

LOW-CALORIE DIETS AND ENERGY EXPENDITURE

TEE in adults includes REE and the nonresting EE, the latter of which is mainly composed of the energy expended in daily activities and the small thermic effect of food (≈10% of the food’s caloric value) (31). The doubly labeled water (DLW) method allows quantification of the TEE of humans living in their natural settings over a period of 1 to 2 wk (32, 33). When energy balance and body weight are in or near equilibrium, TEE is a measure of EI (31, 33).

The National Academy of Sciences/Institute of Medicine (NAS/IOM) published TEE prediction equations based on an international library of DLW studies (see Appendix A) (31, 34). Four variables were identified in sex-specific TEE prediction models: age, body weight, height, and level of physical activity. The goal of the NAS/IOM was to provide TEE prediction equations for estimating group weight-maintenance energy requirements.

The NAS/IOM TEE prediction formulas can model the relation between energy requirement and body weight, assuming subjects have normal FEA and are eumetabolic. An energy equilibrium state is required, because even a modest energy imbalance can influence the relation between body weight and energy expenditure (35). These empirical equations allow estimation of TEE associated with the new, lower body weight achieved with a LCD along with other calculations useful in exploring the basis of low maximal LCD-induced weight loss.

Systematic review

Do adaptations in energy expenditure occur in the RO state? To investigate this, we systematically examined the literature on the relation between measured and predicted TEE in those with RO after long-term (ie, ≥26 wk) weight loss. We searched Medline under the terms reduced-obese, post-obese, and formerly obese along with doubly labeled (or labeled) water. We accepted
studies for review if the subjects were otherwise healthy and had a period of weight stability before evaluation. Studies were excluded if any subjects were in an active weight-loss phase. Ideally, the study included a matched control group of never-obese subjects for comparison with the RO subjects. If such controls were lacking, we calculated a value by using the NAS/IOM TEE prediction formulas. We also included studies meeting similar criteria and reporting TEE measurements that were carried out with a respiratory chamber indirect calorimeter or metabolic chamber, and we required that these studies included matched, never-obese control subjects.

Of the 15 studies found for initial review (36–50), 4 were excluded because they did not fully meet our defined entry criteria. Two early respiratory chamber–indirect calorimeter studies were excluded, Geisser et al (33) included subjects undergoing to lose weight, and subject groups in the study of Lean and James (37) were not weight-matched. The DLW study of van Gemert et al (38) included 12-mo follow-up data on surgically treated obese patients, although subjects were still in minimal negative energy balance at the time of evaluation. A second, similar study from the same group was later reported by Westerterp et al (39), and we assumed, although the published manuscript did not state it, that these subjects were also in minimal negative energy balance. Accordingly, we excluded this report from the pooled studies reported below.

Of the remaining 11 studies, the respiratory chamber study of Astrup et al (40) examined the same 9 RO patients and matched control subjects across 3 levels of fat intake (20%, 30%, and 50% of EI). The TEE estimates of the 3 experimental protocols were averaged for presentation in pooled analyses, although the authors reported differences in TEE across the 3 periods (40). No mean differences between the RO subjects and the control subjects were observed in TEE at the medium (1963 and 1930 kcal/d, respectively) and high (1934 and 1919 kcal/d, respectively) fat intakes. TEE was higher by 4.5% in the RO subjects than in the control subjects (1989 and 1903 kcal/d, respectively) during low-fat feeding. Weinsier et al (41) reported a longitudinal DLW study that was later expanded on by Walsh et al (42). The required data were more complete in the earlier publication (41), and we therefore chose that study for analysis.

The 10 publications that were appropriate for review reported a total of 150 subjects in pooled studies (Tables 2 and 3); 104 were nonsurgical and 46 were surgically treated RO subjects. A scatter-plot of predicted or control TEE versus measured TEE is shown in Figure 2 for the 11 RO subjects reported by Black et al (45) and the weighted means reported in the 9 other studies. The weighted mean difference between measured and predicted TEE for all RO subjects combined was 20.1 kcal/d (range: –58–155 kcal/d).

The weighted mean percentage difference between measured and predicted TEE for all subjects combined was 1.3% (range: –1.7–8.5%) (Figure 3). The percentage differences between

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<tr>
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<th>No. of subjects, sex</th>
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1 CS, cross-sectional; DLW, doubly labeled water; L, longitudinal; LCD, low-calorie diet; RCIC, respirator chamber–indirect calorimeter; VLCD, very-low-calorie diet.
2 Comparison of subjects with reduced obesity and control subjects.
3 Control values derived from National Academy of Science/Institute of Medicine TEE prediction formulas.
4 Study did not provide separate data for males and females, and therefore weighted predicted TEE was calculated.
5 Patients were matched to control subjects by age and BMI; weight and height did not differ significantly.
6 Study included TEE results for 9 subjects randomly given 3 levels of dietary fat. The mean of the 3 periods was included for analysis; group × diet interaction was not significant.
7 Subjects consumed a high-carbohydrate diet before evaluation.
measured and predicted TEE were similar across surgical (n = 46) and nonsurgical (n = 104) groups and across DLW (n = 99 subjects) and respiratory chamber (n = 51) groups. Of the 5 respiratory chamber studies with control groups (Table 3), 1 study (49) reported significant differences (P = 0.01) between TEEs in the RO group and the control group. In that study, the RO subjects who were ingesting a low-fat (30%), high carbohydrate (55%) diet had a higher TEE (8.5%) than did the sex-, weight-, height-, body composition-, and age-matched control subjects.

Of the reviewed studies, 3 (n = 80 subjects) provided longitudinal DLW TEE data (Table 2). We pooled these studies and derived the weighted mean changes in body weight and TEE (Figure 4). The weighted mean baseline body weight of 103.2 kg decreased to 72.5 kg, for a weight loss of 30.7 kg. The subjects had a weighted mean EI (ie, TEE) of 2931 kcal/d at baseline and a TEE of 2363 kcal/d at follow-up, for a reduction of 567 kcal/d. The predicted change in TEE, according to the NAS/IOM formulas, was similar at 518 kcal/d. Thus, the pooled group of subjects had reduced their EI by 500 kcal/d and had a corresponding weight loss of 30 kg.

In the 2 excluded surgical studies in which subjects were in minimal negative energy balance at the time of evaluation—ie, the studies of van Gemert et al (36; n = 8) and Westerterp et al (37; n = 5)—the differences between the TEEs in RO subjects and the predicted TEEs were 1% and 6.7%, respectively. On the basis of these limited observations, we conclude that gastrointestinal FEA and TEE in RO subjects and comparable never-obese subjects are very similar when in or near energy balance.

Clinical comparisons

We can use the NAS/IOM equations, first, to calculate the magnitude of weight loss expected for a prescribed reduction in EI and, from that value, to estimate patient LCD adherence. The baseline (obese) TEE (and thus baseline EI) and the TEE at the reduced body weight are calculated on the assumption no changes occurred in physical activity levels. The difference between baseline and follow-up TEE is the estimated lowering of the EI accompanying LCD treatment. This value is compared with the prescribed energy deficit as a measure of diet adherence.

This analysis was applied to the weight-loss group of older men reported by Katzel et al (51). The 44 sedentary men in this study had mean baseline age, height, and body weight of 61 y, 1.75 m, and 94.3 kg, respectively. Assuming a low-active physical activity level as defined by NAS/IOM (31), the men at baseline had a predicted TEE (and, thus, an EI) of 2757 kcal/d. The subjects were prescribed a reduced energy (300–500 kcal/d) American Heart Association phase I diet. After 1 y, the weight loss was 9.5 ± 0.7 kg (range: 21 to 0.7 kg). The TEE predicted by the new lower body weight of 84.8 kg at 1 y is 2606 kcal/d, 151 kcal/d less than that predicted at baseline. The men in
the study of Katzel et al had thus apparently lowered their EI by less than half of the 400 kcal/d prescribed reduction (51).

We can also calculate the body mass expected from a 400 kcal/d (ie, 2394 kcal/d) reduction in EI intake for 1 y as 69.1 kg, which is 25.2 kg less than the actual baseline weight. This magnitude of estimated weight loss is consistent with the pooled longitudinal DLW study data summarized earlier (Figure 3). Subjects in that analysis started with a weight of 103.2 kg and subsequently lost 30.7 kg with a reduction from baseline EI (ie, TEE) of 567 kcal/d, and this loss is in line with the predicted 25.2-kg loss for the \(400\) kcal/d deficit prescribed by Katzel et al (51).

We next examined, for perspective, some of the studies presented in Table 1. Samaha et al (11) provided subjects weighing an average of 131.8 kg with a 500 kcal/d deficit diet and observed a 1.9-kg maximum mean weight loss. For each 1 kg of weight lost, Samaha et al had prescribed an energy deficit of 263 kcal. Desprès et al (12) observed an average 4.3-kg maximum weight loss in their patients who weighed a mean of 97 kg at baseline and who followed a 600 kcal/d prescribed energy-deficit diet (140 kcal \(\cdot d^{-1} \cdot kg^{-1}\)). Wadden et al (13) treated patients in the lifestyle modification group, who weighed an average of 105.1 kg at baseline, with a 1200–1500 kcal/d LCD (\(\geq1000\) kcal/d energy deficit) and reported a maximum mean weight loss of 8.1 kg (ie, \(\approx123\) kcal \(\cdot d^{-1} \cdot kg^{-1}\)). In their patients weighing a mean of 105 kg at baseline, Pi Sunyer et al (15) observed a maximum mean weight loss of 4.5 kg after a 600 kcal/d prescribed energy deficit (ie, 133 kcal \(\cdot d^{-1} \cdot kg^{-1}\)).

The maximum weight loss in these studies can also be compared with the weight losses observed in the reviewed longitudinal DLW studies. The subjects of Weinsier et al (41), with a baseline mean weight of 78.8 kg, reduced their weight by an average of 12.9 kg by lowering EI (ie, TEE by DLW) a mean of 138 kcal/d (11 kcal \(\cdot d^{-1} \cdot kg^{-1}\)). Amatruda et al (43) reported a mean 22-kg weight loss in women who had a average baseline weight of 83.7 kg and who reduced their EI by a mean of 231 kcal/d (ie, 11 kcal \(\cdot d^{-1} \cdot kg^{-1}\)). The surgically treated patients of Das et al (44), who had an average baseline weight of 139.5 kg, reduced their EI and body weight by a mean of 860 kcal/d and 53.4 kg (ie, 16 kcal \(\cdot d^{-1} \cdot kg^{-1}\)), respectively. Before their weight stabilized (beginning at 54 wk), the surgically treated patients of Westerterp et al (39) lost an average of 53.9 kg from a baseline mean of 158.6 kg, and their mean reduction in EI, based on a DLW method, was 908 kcal/d (or 17 kcal \(\cdot d^{-1} \cdot kg^{-1}\)).

The prescribed daily reduction in EI relative to the actual weight loss observed in the LCD studies, 123–263 kcal/kg, is in striking contrast to the actual reduction in EI and weight loss observed in the longitudinal DLW studies, 11–17 kcal/kg. Moreover, the \(\beta\)-coefficients for body weight in the NAS/IOM TEE prediction formulas (see Appendix A) are similar to the actual daily reductions in EI observed in the longitudinal DLW studies, 14.2 and 10.9 kcal \(\cdot d^{-1} \cdot kg^{-1}\) in men and women, respectively. Using a minimally overlapping longitudinal data set, the NAS/IOM report presented a tentative value of 16.6 kcal \(\cdot d^{-1} \cdot kg^{-1}\) as the coefficient required for anticipating the reduction in EI required for maintaining lower body weights. An additional report, published after completion of the current analyses, supports these observations. Using a combination of DLW and body-composition estimates, Racette et al (52) examined EI in calorie-restricted overweight volunteers at baseline and after 9–12 mo of LCD management. The reduction in EI was 166 kcal/d, and the corresponding weight loss over the study interval was \(\approx8\) kg; thus, the daily lowering of EI in relation to actual weight loss was \(\approx20\) kcal/kg.

**DISCUSSION**

The universally recognized but little studied phenomenon of low efficacy of LCD weight loss led us to look for possible underlying mechanisms. We examined 2 mechanisms, improved FEA and energetic adaptation to under-feeding. A third potential mechanism, low adherence to the prescribed energy deficit, was the default selection that was based on deductive logic after analysis of the first 2 mechanisms. Our findings, here formulated on the surprisingly limited available literature, identify low patient adherence to the prescribed energy deficit as the main basis for the modest weight loss of LCDs.

To arrive at our tentative conclusion we made a key assumption on the basis of a systematic literature review: that, after induction of a negative energy balance and maintenance of a new steady state, both net energy absorption and TEE in RO subjects remained similar to those in never-obese control subjects. Provided with evidence in support of these assumptions, we then applied a theoretical energy balance model fitted with empirical prediction formulas to show the large discrepancy between observed and estimated maximal weight loss with a defined reduction in EI. Our calculations show that, in general, obese patients have a weight loss less than half of that expected for the degree of prescribed LCD energy deficit. Moreover, it is likely that the low adherence phenomenon begins early in treatment and advances with time to account not only for the small maximal
weight loss but also for the gradual weight regain reported in most long-term studies.

In support of the low-adherence theory, Dansinger et al (14) evaluated over a 52-wk study period the weight- and risk factor-reduction effects of popular diets. Self-reported dietary adherence scores related a failure to fully comply at baseline to a gradual and substantial fall in reported compliance at the 52-wk evaluation. Dansinger et al (14) also observed a curvilinear correlation between dietary adherence and weight loss at 52 wk: those reporting full compliance lost ≈20 kg, whereas the weight loss reported in patients with low self-reported dietary adherence was negligible. The magnitude of weight loss observed in subjects reporting full compliance is thus very similar to the predicted LCD-induced weight loss discussed earlier in our review.

A descriptive analysis of these interrelations is shown in Figure 5, in a plot of “observed” weight loss over time in a LCD study (6) and a corresponding, empirically derived “predicted” weight-loss curve of substantially greater magnitude. Corresponding adherence scores over time, which provide a basis for the discrepancy between observed and predicted weight loss, are superimposed on the figure. Our findings and our hypothesis are based on a limited data set of experimental studies that included small samples of RO subjects, often without appropriate controls, and that encompassed both dietarily and surgically induced weight loss. A clear need exists for long-term studies, using appropriate methods and subjects, to fully explore the energetic, neurohormonal, and psychological mechanisms leading to the small maximal LCD-induced weight loss and limited success with long-term weight maintenance. Our study only further exposes the lack of compliance with LCDs, which is well recognized but not often articulated in the clinical setting, as a fundamentally limiting factor in current behavioral therapies aimed at long-term body-weight management.

An important observation of this review is that TEE in the RO state is very close to that predicted or observed in never-obese subjects (ie ~1%). Our findings for TEE are very similar to those forREE reported by Astrup et al (53) in their individual subject meta-analysis of data from multiple investigators. After adjustment for body composition, age, and sex, REE was 2.9% lower (P = 0.09) in the 124 RO subjects than in the control subjects. The individual subjects in the study of Astrup et al were collected from a larger dataset of published studies in which appropriate control for body composition was not possible. The finding of Astrup et al of a nonsignificant difference between observed and predicted REE based on body composition with long-term weight loss has been confirmed in 2 subsequent studies (54, 55).

Although the TEEs in the RO subjects and the never-obese were similar in our collective review of published studies, numerous reports have indicated rapid changes in energy expenditure with short-term underfeeding or overfeeding of animals (56) and humans (35, 54, 57, 58), particularly when measurements are made without an energy balance-stabilization period first (35, 59). Thus, changes occur in EE during the energy-restriction phase that could reduce the prescribed energy deficit, but these decrements in EE appear to be tied to the energy deficit, the rate of weight loss, or both (35, 60), and thus they would slow weight loss but not result in a premature weight loss plateau because, by definition, that plateau occurs at the point of energy balance. In this regard, there are reports of deviations from “predicted” or control values for sleeping metabolic rate (38, 49), EE with physical activity (21), or with specific variations in macronutrient intake (40, 49) in the RO subjects. We did not examine these topics, because they did not affect our already defined analysis plan for examining the basis of the small maximal LCD-induced weight loss. However, a clear need exists to expand on the limited number of studies in this area to gather definitive data on topics of great clinical relevance. Moreover, the extent to which biological mechanisms (60), other than the biological mechanism related to TEE, contribute to low patient compliance and weight relapse with LCDs remains largely unknown.

Thus, energetic adaptations may be present after long-term weight loss and subsequent weight maintenance, although the data available at present suggest that these are relatively small effects that cannot fully account for the limited magnitude of weight loss observed when obese subjects are treated with LCDs. Well-controlled, carefully designed, long-term studies are clearly needed to explore whether and to what extent adaptations in energy expenditure are present in weight-stable RO subjects.

Several important limitations of our study should be noted. First, we made the working assumption that, after induction of negative energy balance, most subjects would reach a new steady state within 6 mo to 1 y. The actual time required to reach a steady state may be longer (17–19), although information on this topic is limited because very few in-patient feeding studies lasting >6 mo are available for review. Second, surgical studies were included in our weight-loss database, although the weight-loss biology created by these procedures may not exactly mimic that observed with LCDs (61). Third, to keep our analyses focused, we did not explore the important topic of exercise and physical activity as components of energy exchange (21, 62). Our approach did not allow us to factor out possible subtle effects of long-term weight loss on the nonresting portion of TEE (63, 64).

In sum, this perspective was stimulated by the consistent observation spanning >5 decades of the relatively small magnitude of weight loss after prescription of LCDs. Our findings, based on a limited database of published studies, suggest that FEA and TEE are similar in reduced-obese and never-obese subjects. When treated with an LCD, obese subjects, according to our analysis, should lose far more weight than is observed in published long-term studies. Substantial resources are often committed to administering LCD treatments with a specific focus on the level of prescribed energy deficit. A critical need therefore
exists for elucidating the basis of poor patient adherence to prescribed energy deficits. This research effort could lead to even greater clinical benefits for the many obese patients with weight-related comorbidities.

We thank Sai Das for providing from her studies data that were needed for the preparation of this manuscript, and we thank George Blackburn for his suggestions with regard to certain aspects of our perspective.

REFERENCES


APPENDIX A

One of several reported sets of prediction formulas in the National Academy of Sciences/Institute of Medicine Macro-nutrient Report

Estimated total energy expenditure (TEE, kcal/d) of normal-weight, overweight, and obese subjects aged ≥19 y

Women:

$$\text{TEE} = 864 - [9.72 \times \text{age (y)}] + \text{PA} \times 14.2 \times \text{weight (kg)} + 503 \times \text{height (m)}$$ (I)

where PA is the physical activity coefficient and PAL is physical activity level, a measure of physical activity calculated as TEE/REE:

Sedentary: PA = 1.00 if PAL is estimated to be ≥1.0 < 1.4 Low-active: PA = 1.12 if PAL is estimated to be ≥1.4 < 1.6 Active: PA = 1.27 if PAL is estimated to be ≥1.6 < 1.9

Very active: PA = 1.54 if PAL is estimated to be ≥1.9 < 2.5

Men:

$$\text{TEE} = 387 - [7.31 \times \text{age (y)}] + \text{PA} \times 10.9 \times \text{weight (kg)} + 660.7 \times \text{height (m)}$$ (2)

Sedentary: PA = 1.00 if PAL is estimated to be ≥1.0 < 1.4 Low-active: PA = 1.14 if PAL is estimated to be ≥1.4 < 1.6 Active: PA = 1.27 if PAL is estimated to be ≥1.6 < 1.9

Very active: PA = 1.45 if PAL is estimated to be ≥1.9 < 2.5

1 Modified from reference 31.