Commentary

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

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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.

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,
LOW-CALORIE DIET WEIGHT LOSS

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

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TABLE 1
Rates of weight loss observed in low-calorie diet (LCD) studies published over the past 5 y in 2 representative medical journals

<table>
<thead>
<tr>
<th>Study and treatment protocol</th>
<th>Weight (kg)</th>
<th>Time to maximum</th>
<th>Rate of weight loss</th>
<th>Predicted rate of weight loss</th>
<th>Energy prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Maximum change (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>kg</td>
<td>kg</td>
<td>wk</td>
<td>kg/wk</td>
</tr>
<tr>
<td>Tate et al (8)</td>
<td>Internet education</td>
<td>78.8</td>
<td>−1.7</td>
<td>2.2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Internet behavior therapy</td>
<td>77.4</td>
<td>−4.1</td>
<td>5.3</td>
<td>12</td>
</tr>
<tr>
<td>Wirth et al (9)</td>
<td>Placebo group in drug study</td>
<td>98.2</td>
<td>−4</td>
<td>4.1</td>
<td>12</td>
</tr>
<tr>
<td>Foster et al (10)</td>
<td>Low-carbohydrate diet</td>
<td>98.7</td>
<td>−7</td>
<td>7.1</td>
<td>24</td>
</tr>
<tr>
<td>Conventional diet</td>
<td>98.3</td>
<td>−3.2</td>
<td>3.3</td>
<td>24</td>
<td>0.13</td>
</tr>
<tr>
<td>Samaha et al (11)</td>
<td>Low-carbohydrate diet</td>
<td>130.0</td>
<td>−5.8</td>
<td>4.5</td>
<td>12–24</td>
</tr>
<tr>
<td>Després et al (12)</td>
<td>Low-fat diet</td>
<td>131.8</td>
<td>−1.9</td>
<td>1.4</td>
<td>24</td>
</tr>
<tr>
<td>Placebo group in drug study</td>
<td>97</td>
<td>−4.3</td>
<td>4.4</td>
<td>24–36</td>
<td>0.12–0.18</td>
</tr>
<tr>
<td>Wadden et al (13)</td>
<td>Lifestyle modification group in drug study</td>
<td>105.1</td>
<td>−8.1</td>
<td>7.7</td>
<td>18–40</td>
</tr>
<tr>
<td>Heshka et al (6)</td>
<td>Self-help program</td>
<td>94.2</td>
<td>−1.9</td>
<td>2.0</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Commercial weight-loss program</td>
<td>93.1</td>
<td>−5.9</td>
<td>6.3</td>
<td>26</td>
</tr>
<tr>
<td>Dansinger et al (14)</td>
<td>Atkins Diet</td>
<td>100</td>
<td>−3.6</td>
<td>3.6</td>
<td>8</td>
</tr>
<tr>
<td>Zone Diet</td>
<td>99</td>
<td>−3.8</td>
<td>3.8</td>
<td>8</td>
<td>0.48</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>97</td>
<td>−3.5</td>
<td>3.6</td>
<td>8–26</td>
<td>0.13–0.44</td>
</tr>
<tr>
<td>Ornish Diet</td>
<td>103</td>
<td>−3.6</td>
<td>3.5</td>
<td>8–26</td>
<td>0.14–0.45</td>
</tr>
<tr>
<td>Pi-Sunyer et al (15)</td>
<td>Placebo group in drug study</td>
<td>105</td>
<td>4.5</td>
<td>4.3</td>
<td>36</td>
</tr>
</tbody>
</table>

1 NA, not applicable. Studies including LCD weight-loss treatments of nondiabetic overweight and obese subjects were from the New England Journal of Medicine and JAMA within the past 5 y, excluding reports specifically examining weight-loss effects of exercise combined with LCDs and studies in which time-dependent weight-loss curves were not provided. Maximal weight loss was estimated from information provided in the respective publications.

2 Rate of weight loss estimated as maximum weight loss/time to maximum.

3 The estimated approximate rate of weight loss was derived by assuming an energy content of weight change = 7700 kcal/kg. The values provided are for those studies reporting a suggested level of caloric intake for which an energy deficit — and, thus, a rate of weight loss—could be derived; remaining study estimates are NA.
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. 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 the 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
low-calorie diet.

jects 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

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects, sex</th>
<th>TEE method</th>
<th>Difference</th>
<th>Design</th>
<th>P</th>
<th>Weight-loss method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amatruda et al (43)</td>
<td>18, F</td>
<td>DLW</td>
<td>−24</td>
<td>−1.0</td>
<td>L</td>
<td>VLCD</td>
</tr>
<tr>
<td>Weinsier et al (41)</td>
<td>32, F</td>
<td>DLW</td>
<td>18</td>
<td>0.9</td>
<td>L</td>
<td>LCD</td>
</tr>
<tr>
<td>Das et al (44)</td>
<td></td>
<td>DLW</td>
<td></td>
<td></td>
<td>L</td>
<td>Gastric bypass</td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
<td></td>
<td>−58</td>
<td>−1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>24</td>
<td></td>
<td>−1</td>
<td>−0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black et al (45)</td>
<td>10, F/1, M</td>
<td>DLW</td>
<td>66</td>
<td>2.9</td>
<td>CS</td>
<td>LCD</td>
</tr>
<tr>
<td>Guesbeck et al (46)</td>
<td>8</td>
<td>DLW</td>
<td>−38</td>
<td>−1.3</td>
<td>CS</td>
<td>NS</td>
</tr>
<tr>
<td>Larson et al (47)</td>
<td>7, F/4, M</td>
<td>RCIC</td>
<td>62</td>
<td>3.0</td>
<td>CS</td>
<td>NS</td>
</tr>
<tr>
<td>Buemann et al (48)</td>
<td>15, F</td>
<td>RCIC</td>
<td>−27</td>
<td>−1.2</td>
<td>CS</td>
<td>NS</td>
</tr>
<tr>
<td>Astrup et al (40)</td>
<td>9, F</td>
<td>RCIC</td>
<td>45</td>
<td>2.3</td>
<td>CS</td>
<td>NS</td>
</tr>
<tr>
<td>Astrup et al (49)</td>
<td>8, F</td>
<td>RCIC</td>
<td>155</td>
<td>8.5</td>
<td>CS</td>
<td>0.01</td>
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<tr>
<td>Tatarrani et al (50)</td>
<td>8, F</td>
<td>RCIC</td>
<td>24</td>
<td>1.4</td>
<td>CS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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.

Table 2

Studies of total energy expenditure (TEE) in subjects with reduced obesity

Table 3

Results of pooled group analyses

<table>
<thead>
<tr>
<th>Group</th>
<th>Weighted mean difference</th>
<th>kcal/d</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsurgical (n = 104)</td>
<td>42.2 (−27–155)</td>
<td>2.2 (−1.2–8.5)</td>
<td></td>
</tr>
<tr>
<td>Surgical (n = 46)</td>
<td>−18.5 (−58–24)</td>
<td>−0.4 (−1.7–1.4)</td>
<td></td>
</tr>
<tr>
<td>DLW (n = 99)</td>
<td>−6.3 (−58–66)</td>
<td>−0.04 (−1.7–2.9)</td>
<td></td>
</tr>
<tr>
<td>RCIC (n = 51)</td>
<td>51.7 (−27–155)</td>
<td>2.8 (−1.2–8.5)</td>
<td></td>
</tr>
<tr>
<td>Total (n = 150)</td>
<td>−20.1 (−58–155)</td>
<td>−1.3 (−1.7–8.5)</td>
<td></td>
</tr>
</tbody>
</table>

1 DLW, doubly labeled water studies; RCIC, respirator chamber–indirect calorimetry studies.
2 Range in parentheses (all such values).
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, \( 3 \) \( (n = 80 \text{ subjects}) \) 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 \( 518 \text{ kcal/d} \). Thus, the pooled group of subjects had reduced their EI by \( 514 \text{ kcal/d} \) and had a corresponding weight loss of \( 30 \text{ kg} \).

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 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 \( (300–500 \text{ kcal/d}) \) American Heart Association phase I diet. After 1 y, the \( \bar{x} \pm \text{SD} \) weight loss was 9.5 \( \pm 0.7 \text{ kg} \) (range: \( -21 \text{ to } -0.7 \text{ kg} \)). 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

![FIGURE 2. Control or predicted versus measured total energy expenditure (TEE) for the group mean values of 9 studies and the data on individual subjects with reduced obesity from Black et al (45). The line of identity is shown.](https://academic.oup.com/ajcn/article-abstract/85/2/346/4649515/FIGURE2)

![FIGURE 3. Mean difference in total energy expenditure (TEE) from corresponding control or predicted values in studies meeting entry criteria. S, surgical studies; DLW, doubly labeled water–measured TEE; RCIC, respiratory chamber–indirect calorimeter–measured TEE. The vertical dashed line is the weighted mean percentage difference in TEE for all studies combined. (Additional study information is presented in Table 1.)](https://academic.oup.com/ajcn/article-abstract/85/2/346/4649515/FIGURE3)
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 was calculated as the difference between BL and FUP total energy expenditure. Bottom: the observed longitudinal changes in body weight.

FIGURE 4. Energy expenditure and body-weight changes observed in 3 pooled, longitudinal, doubly labeled water studies (n = 32, 18, and 30; references 41, 43, and 44). Top: the weighted mean values for measured and predicted energy intake (ie, total energy expenditure) at baseline (BL) and at post-weight-loss follow-up (FUP). The change (Δ) in energy intake was calculated as the difference between BL and FUP total energy expenditure. Bottom: the observed longitudinal changes in body weight.

The prescribed daily reduction in EI in relation to 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 β-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 · d−1 · 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 · d−1 · 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 ≈8 kg; thus, the daily lowering of EI in relation to actual weight loss was ≈20 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 reduction in energy expenditure, and this effect was 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 nonreducing 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 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 body weight at 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 nonreducing portion of TEE (63, 64).

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 for TEE 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, TEE 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

FIGURE 5. Weight loss "observed" (●) with a commercial low-calorie diet (LCD) treatment (6). An estimate of diet adherence (shaded bars) is based on the study of Dansinger et al (14) that examined self-reported adherence scores to popular weight-loss diets. The “predicted” (□) weight-loss curve is a hypothetical function that assumes patients fully adhere to the prescribed LCD energy-deficit diet.
exists for elucidating the basis of poor patient adherence to pre-"scribed energy deficits. This research effort could lead to even greater clinical benefits for the many obese patients with weight-related comorbidities.

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SBH, JHB, MLR, JWB, DAS, and AP were responsible for the conception of the study and the perspective under which it was conducted; SBH and AP conducted the analyses; and all authors were involved in the writing and revision of the manuscript. SBH, JHB, MLR, JWB, and NG are employees of Merck & Co, but their contribution is unrelated to the subjects of this report. None of the authors had a personal or financial conflict of interest.

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

Men:

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

(1)

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

Women:

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

(2)

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 = 1.14 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

*Modified from reference 31.*