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Review

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Dietary interventions for obesity: clinical and mechanistic findings

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Introduction

Dietary modification is a cornerstone of weight control. At a fundamental level, weight loss requires achieving a state of negative energy balance. The best way to attain this balance is a subject of much debate and ultimately relies on finding a strategy that people can follow in the long term. People seeking weight loss have a variety of methods to choose from, including calorie restriction with different macronutrient composition; avoidance (or consumption) of specific foods; and dietary patterns. Dietary approaches may work on distinct mechanisms related to weight control, and features of diets can make adherence more or less difficult. Knowledge of these mechanisms could help to optimize and tailor dietary approaches for obesity treatment.

In this narrative Review, we highlight well-known dietary approaches for obesity treatment in adults and potential mechanisms contributing to weight loss, emphasizing mechanisms that influence adherence. These topics are reviewed using meta-analyses and selected research studies. We address the following questions: (a) Among adults with overweight/obesity, what are the short-term (<12 months) and longer-term (≥12 months) weight losses with different degrees of prescribed energy restriction? (b) Does the timing (e.g., intermittent fasting), macronutrient composition (e.g., low carbohydrate versus low fat), or dietary pattern (e.g., Mediterranean) affect the amount of weight loss on a short- or long-term basis? (c) What physiological and behavioral mechanisms are associated with specific types of dietary interventions that may contribute to dietary adherence and weight loss?

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Dietary adherence

Substantial variability in weight loss is observed with all dietary interventions, some of which is likely attributable to participants' varying degrees of adherence. In persons with obesity, self-reports of adherence to calorie prescriptions typically underestimate energy intake by 30% to 50% as compared with measurement by doubly labeled water (1, 2). Given the expense of doubly labeled water and lack of accurate dietary biomarkers (3), investigators typically rely on participants' self-reported food and calorie intake. Newer approaches include calculating changes in energy intake with mathematical modeling and measurements of body weight (4, 5). Reduction in self-reported calories consumed is often used to quantify adherence to an energy-reduced diet. Diet adherence scores calculated from self-reported food intake can assess how closely patients followed a particular dietary pattern. Even with the inaccuracies of these methods, closer self-reported dietary adherence is associated with greater weight loss and less weight regain (6–10).

Figure 1 presents a conceptual framework of physiological, psychological, behavioral, and sociocultural/environmental mechanisms that may influence dietary adherence and subsequent weight loss. Adherence is influenced by the components of the prescribed diet and processes that precipitate eating (initiation), end an eating episode (satiation), and inhibit appetite between meals (satiety). The model builds upon the Satiety Cascade Framework by Blundell and others (11–14), modifications by Mela (15), and relevant behavioral adherence schemata (16). The Satiety Cascade posits that food choice, satiation, and satiety are influenced by sensory (e.g., recognition), cognitive (e.g., prior beliefs and associations, anticipated reward and pleasure), postingestive (e.g., texture, gastric stretch, and appetite-related hormones), and postabsorptive signals (e.g., insulin). We refer to aspects of this framework in reviewing the mechanisms associat-

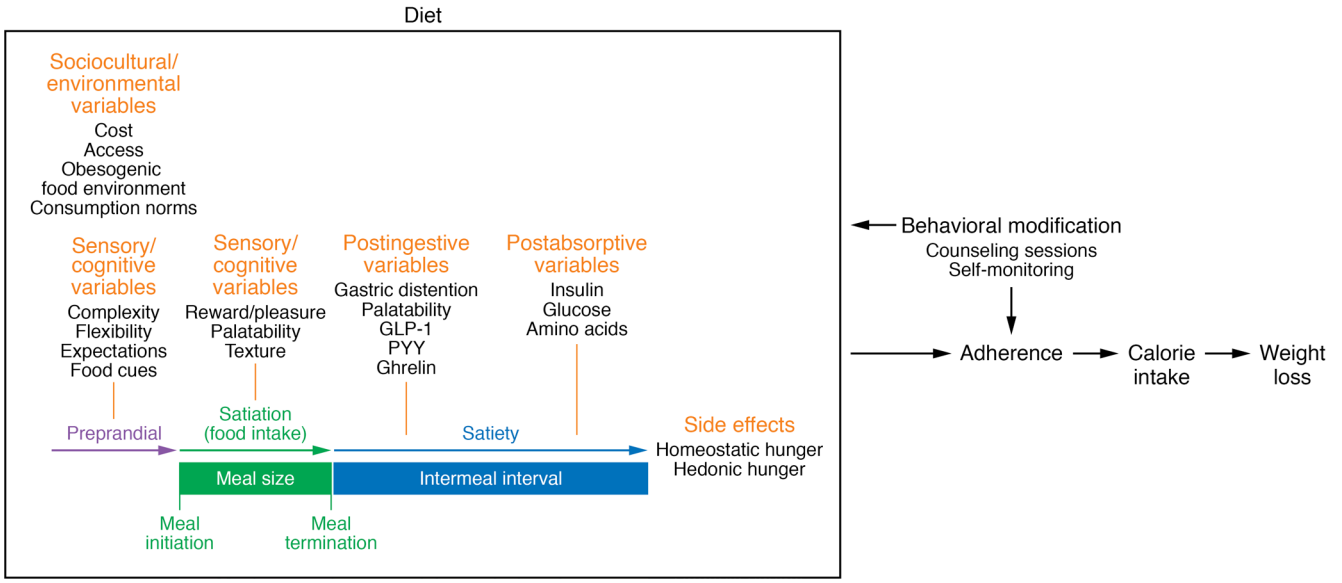


Figure 1. Conceptual model of mechanisms associated with different diets that can improve adherence and subsequent weight loss. The orange headings highlight variables associated with various diets that may influence individual adherence. Adapted from Blundell and others (11–14) and Mela (15) with permission.

ed with dietary approaches below. All diets should be prescribed with lifestyle modification to facilitate adherence (17), including recording of food and calorie intake using applications or paper diaries (18–22).

Energy-restricted diets

Energy balance relies on an interplay between energy intake and expenditure. Dietary energy can be derived from protein, carbohydrate, fat, and ethanol. Total energy expenditure is the sum of resting metabolic rate, thermic effect of food, and physical activity–related energy expenditure (including non-exercise activity thermogenesis) (23). To lose weight, "energy in" (i.e., dietary energy intake) must be less than "energy out" (i.e., total energy expenditure). Thus, most dietary interventions for weight loss prescribe some form of energy restriction.

Balanced-nutrient, low-energy diets

Low-energy diets (LEDs) are generally defined by energy intake targets of 800–1800 kcal/d, prescribed with higher calories for heavier individuals. A common prescription is 1200–1500 kcal/d for individuals who weigh less than 113.6 kg and 1500–1800 kcal/d for those who weigh at least 113.6 kg. Alternatively, an energy deficit of 500–750 kcal/d may be prescribed, based on energy expenditure estimations (24, 25). LEDs prescribe a balanced profile of nutrients, similar to recommendations for the general population (i.e., 45%–65% carbohydrate, 20%–35% fat [≤10% from saturated fat], and 10%–35% protein) (26, 27).

Very low–energy diets

VLEDs prescribe less than 800 kcal/d while aiming to provide essential nutrients. They are delivered as meal-replacement shakes or protein-sparing modified fasts consisting of lean meat, fish, and fowl supplemented with a multivitamin and 2–3 g/d of potassium. Both approaches provide approximately 70–100 g/d of protein, designed to spare the loss of lean body mass (28–30). The 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults suggested that VLEDs be prescribed in limited cases, such as in preparation for bariatric surgery (24). VLEDs should only be used as part of a comprehensive lifestyle intervention with appropriate medical supervision owing to rapid weight losses and potential for side effects (e.g., cholelithiasis, dehydration) (24, 31). Strict adherence to these regimens is only possible for limited durations because energy content is at or below resting metabolic rate. When patients reach their desired weight loss goals, calorie intake should be gradually increased to a level consistent with their new, lower body weight (e.g., increasing calories by 100 kcal/wk until weight stabilizes).

Weight loss

Greater caloric restriction, with its larger resulting negative energy deficit, is associated with a faster rate of weight reduction in the short term (32). A meta-analysis included six randomized controlled trials (RCTs) that compared low-fat LEDs with VLEDs, in which each approach was combined with lifestyle modification and had a follow-up of at least 1 year (28). LEDs prescribed for an average of 12.7 weeks induced a mean loss of 9.7% of initial weight, compared with 16.1% for VLEDs (Table 1). At >1 year, mean weight loss with LEDs had declined to 5.0%, which was similar to the 6.3% observed with VLEDs. Participant attrition was 22.6% with LEDs and 22.3% with VLEDs over a mean follow-up of 29 months. In another review of RCTs, participants randomized to LEDs lost 6.4 kg at 1 year, compared with 10.3 kg for those treated with VLEDs (for a median length of 10 weeks), both as combined with lifestyle modification (33). Six of these studies included data at 2 years, at which time participants originally assigned to LEDs had lost 2.8 kg, compared with 4.2 kg for those assigned to

Table 1. Summary of weight losses from select meta-analyses comparing different dietary approaches

Reference	Years included	Intervention	Comparison	Duration (months)	*n* of Studies	*n* Intervention	*n* Comparison	Intervention weight loss	Comparison weight loss	Mean difference (± SE or 95% CI)[A]	Heterogeneity (%)[B]	Attrition
Energy restriction												
28	1966–2005	VLEDs (<800 kcal/d)	LEDs (800–1800 kcal/d)	3	6	233	192	16.1% ± 1.6%	9.7% ± 2.4%	6.4% (± 2.7%)	NR	VLEDs: 0.8% ± 0.7%/week (22.3%; range = 14.6%–40.7% over a mean of 29 months)
				12–60	6	233	192	6.3% ± 3.2%	5.0% ± 4.0%	1.3% (± 5.1%)	NR	LEDs: 0.9% ± 0.4%/week ($P > 0.2$; 22.6%; range = 0%–51.9% over a mean of 29 months)
33	Inception–2014	VLEDs (<800 kcal/d)	Moderate energy restriction	VLEDs median duration = 2.5	10	403	341	−10.3 kg	−6.4 kg	−3.90 kg (−6.69, −1.11)	77	VLEDs: 19%
				Follow-up: 12								Moderate energy restriction: 20%
				Follow-up: 24	4	254	233	−4.2 kg	−2.8 kg	−1.39 kg (−2.63, −0.16)	0	Relative risk ratio = 0.96 (95% CI = 0.56, 1.66)
45	Inception–2016	Intermittent energy restriction	Continuous energy restriction	6–24	6	267	220	NR	NR	SMD: 0.08 (−0.14, 0.31)	NR	Mean = 31% (range = 12%–65%); no difference between groups
Macronutrients												
57	1966–1999	Ad libitum LFDs	Habitual diet or similar to that in population	2–12	19	1101	809	NR	NR	3.2 kg (1.9, 4.5)	$Q = 93.4$	NR
68	2000–2007	LCDs (≤60 g/d of carbohydrate)/ high-protein	LFDs (≤30% of energy from fat)/high-carbohydrate conventional diets	6	9	345	345	−8.04 kg	−4.02 kg	−4.02 kg (−4.54, −3.49)	77	36% for all participants; lower attrition rates for LCDs/HP compared with conventional/ LFDs/medium-protein groups
				12	7	309	308	−4.87 kg	−3.82 kg	−1.05 kg (−2.09, −0.01)	11	
70	Inception–2015	LCDs: 20–40 g/d of carbohydrate in the first phase or <20% of energy, mostly ad libitum diet	LFDs: <30% of energy from fat, most also calorically restricted	6–24	11	688	681	−7.58 kg	−5.41 kg	−2.17 kg (−3.36, −0.99)	82	LCDs: 12%–48%; LFDs: 10%–50%
67	1980–2005	LCDs: (≤60 g/d of carbohydrates) without energy intake restrictions	LFDs: (≤30% of energy from fat) with energy intake restriction	6	5	222	225	NR	NR	−3.3 kg (−5.3, −1.4)	65	LCDs: 30%; LFDs: 43%; odds ratio for completion of the trial = 1.8 (95% CI = 1.2, 2.6)
				12	3	137	138	NR	NR	−1.0 kg (−3.5, 1.5)	48	LCDs: 38%; LFDs: 46%; odds ratio for completion of the trial = 1.4 (95% CI = 0.9, 2.3)
69	1966–2014	LCDs: ≤120 g/d	LFDs: ≤30% of energy from fat	2–24	17	895	902	−7.8 kg	−5.9 kg	−2.0 kg (−3.1, −0.9)	NR	LCDs: 25.6%; LFDs: 25.4%
77	Inception–2012	VLCKDs: <50 g carbohydrates/ day or 10% of energy from carbohydrates	LFDs: Restricted energy with ≤30% of energy from fat	12–24	13	712	703	−4.45 kg	−3.54 kg	−0.91 kg (−1.65, −0.17)	0	Range: 13%–84%
80	1966–2013	LGIs	HGIs	6–17	14	913	857	NR	NR	−0.62 kg (−1.28, 0.03)	0	LGIs: 7%–41%; HGIs: 12%–70%
95	1947–2011	HP, LFDs: 25%–35% protein; energy matched	SP, LFDs: 12%–18% protein; energy matched	1–12	23	494	516	−6.92 kg	−6.12 kg	−0.79 kg (−1.50, −0.08)	71	HP/LFDs: 0%–44%; SP/LFDs: 0%–32%
				<3	10	142	147	−5.55 kg	−4.98 kg	−0.49 kg (−1.34, 0.37)	80	
				≥3	13	352	369	−8.04 kg	−7.07 kg	−0.97 kg (−2.07, 0.13)	75	
Mediterranean												
115	Inception–2011	Mediterranean	LFDs: ≤30% of calories from fat	24–48	6	1641	1009	−4.19	−1.95	−2.24 kg (−3.85, −0.63)	97	Mediterranean: 85%–95%; LFDs: 78%–93%
109	Inception–2010	Mediterranean	Other diets	1–60	16	1848	1588	NR	NR	−1.75 kg (−2.86, −0.64)	95	Mediterranean: 0%–28.2%; control: 0%–35.3%

HGI, high-glycemic index diet; HP, high-protein diet; LCD, low-carbohydrate diet; LED, low-energy diet; LFD, low-fat diet; LGI, low-glycemic index diet; NR, not reported; SMD, standard mean difference; SP, standard protein; VLCKD, very-low-carbohydrate ketogenic diet; VLED, very-low-energy diet. [A]Summary score is a mean difference unless otherwise indicated. Summary scores are presented as intervention versus comparison. [B]Heterogeneity is measured with I^2 unless otherwise indicated. This table only reflects a subset of analyses that the meta-analyses may have reported.

VLEDs. Participants were as likely to discontinue VLEDs as they were LEDs (risk ratio = 0.96; 95% confidence interval [CI] = 0.56, 1.66). Results of the systematic review from the 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults showed that LEDs, when combined with lifestyle modification, induced mean weight losses of 5–8 kg in 6 months, which were maintained at 1 year with continued lifestyle counseling (24). The review further found that VLEDs produced as much as twice the short-term weight loss produced by LEDs, but differences between the approaches declined over time.

Portion-controlled diets

One way to improve simplicity and adherence is to use portion-controlled servings of conventional foods or liquid meal replacements (and meal bars) that provide foods of predetermined quantity and calories. Prescribed diets of 1000–1500 kcal/d using portion-controlled foods increased initial weight losses by 2.5–3.0 kg at 3–6 months, as compared with the prescription of a self-selected diet of conventional foods with the same calorie goal (34–37). Portion-controlled meals, as compared with self-selected diets, continue to produce larger weight losses at 12–18 months, although both approaches are associated with gradual weight regain (34).

Mechanisms

In the studies reviewed, greater energy deficits induced with VLEDs were sufficient to produce greater mean short-term weight losses than LEDs. Portion-controlled diets appear to improve dietary adherence by reducing participants' tendency to underestimate calorie intake (2, 38). The use of meal replacements, in particular, reduces complexity related to planning and preparing foods, decreases cognitive demands and decision making, and reduces cues for overeating (39). Meal replacements may support adherence to calorie goals through sensory-specific satiety (40).

Importance of initial weight loss

Meal replacements have been used increasingly in RCTs to boost initial weight losses. Observational data from the Look AHEAD study, which provided meal replacements for the first 4 months of treatment, found that individuals who lost the most weight in the first 1–2 months had the largest weight losses at 1 year and were the most likely to achieve a loss of 10% or more of initial weight at this time (41). In a post hoc analysis of the study, 1-year losses of greater than 10% (achieved by 37% of Look AHEAD participants) were associated with significant reductions in all-cause mortality, as compared with a usual-care group, over a median follow-up of 10.2 years (42). The DiRECT trial compared best-practice routine care with an integrated weight-management intervention that included a total meal replacement diet of 825–853 kcal/d for 12–20 weeks. The latter approach was associated with greater odds of achieving a loss of at least 15 kg and diabetes remission at 1 and 2 years (43, 44). Taken together, these findings suggest that patients with type 2 diabetes and obesity should be prescribed meal replacements more frequently than LEDs of conventional foods to help them lose weight (43). VLEDs, with their large 1-year weight losses, could be valuable in producing greater long-term improvements in health than LEDs, despite the modest differences in long-term weight loss produced by these two approaches. A randomized trial would be needed to address this question, as would a cost analysis, as 6 months of participation in a medically supervised program with VLEDs supplied as meal replacements can easily exceed $3000.

Intermittent energy restriction

Intermittent energy restriction instructs dieters to alternate between fasting and unrestricted eating periods and includes intermittent fasting and time-restricted feeding. Intermittent fasting consists of "fast days" of ≥60% energy restriction on 2–3 days per week — e.g., on alternate days (ADF), or 2 non-consecutive days (5:2 diet) — and "fed days," with a specified dietary composition or ad libitum consumption at or above daily energy needs. Time-restricted feeding may take the form of eating for 8 hours and then fasting for the remaining 16 hours of the day. Adherence is often measured as the difference between self-reported energy intake and prescribed energy intake on fast and fed days.

Weight loss

Intermittent fasting and daily energy restriction result in similar short- and long-term weight loss, when isocaloric intakes are prescribed. A meta-analysis of 6 studies examining the effects of intermittent versus continuous isocaloric energy restriction over 6 months observed similar weight losses between interventions (standard mean difference [SMD] = 0.08; Table 1 and ref. 45). Participant attrition at ≥6 months was variable across studies but similar between the intermittent and continuous energy restriction groups. In one of the largest studies (n = 100) comparing ADF with daily energy restriction, those in ADF lost 6.0% of baseline weight at 1 year, which did not differ significantly from 5.3% observed in the daily (isocaloric) restriction group (46). A higher proportion of participants in the latter group reported adhering to their dietary goals. Participants in ADF reported eating more than their prescribed energy goal on fast days and less than their goal on feast days.

Mechanisms

Several factors could make intermittent fasting a potentially useful dietary approach from an adherence perspective, although there are not yet adequate data on this topic. Intermittent fasting may address the challenges of behavioral fatigue and dietary monotony that some individuals report with continuous energy restriction (47). Intermittent restriction only requires individuals to limit their intake for defined days, which may be easier for some to adhere to than continuous energy restriction. Further research is needed to determine whether intermittent energy restriction is particularly helpful with subsets of individuals who report that the monotony or daily demands of continuous energy restriction undermine their dietary adherence and, thus, ultimate weight loss. Moreover, long-term adherence to intermittent versus continuous energy restriction should be assessed to determine whether the former approach might be superior to the latter in facilitating weight loss maintenance, as compared with weight loss induction. Compared with continuous energy restriction, ADF and 5:2 intermittent fasting diets do not significantly increase hunger, fullness, desire to eat, or food preoccupation after 3–4 months (48, 49). However, at 1 year, greater hunger levels were reported with 5:2 intermittent fasting than with continuous energy restriction (50). A limited

number of controlled trials have addressed the effects of intermittent fasting on appetite; the majority examined ADF or 5:2 diets, and many studies had small samples. Investigators have hypothesized that intermittent energy restriction improves resting energy expenditure and metabolic flexibility, though these physiological benefits for weight management are unclear (51).

Macronutrient-focused diets

Finding the optimal macronutrient ratio to promote weight loss has received substantial attention. Diets with different macronutrient compositions may be prescribed using caloric restriction or ad libitum without a specific calorie goal (under the theory that lower calorie intake will be achieved by restriction or elimination of particular foods). The most common macronutrient manipulations are low fat, low carbohydrate, and high protein. There are no standard definitions of low versus high amounts of macronutrients, and many variations have been used. Inability to vary macronutrients independently of one another has largely clouded interpretation of these studies. Adherence is commonly based on the agreement between the primary macronutrient goal(s) of the assigned diet and participants' reported intake.

Low-fat diets

Low-fat diets (LFDs) are a standard weight loss strategy and generally prescribe less than 30% of calories from fat. They may be implemented by providing specific menus emphasizing low-fat foods, or having patients count fat grams rather than calories. Most LFDs used for obesity treatment include calorie restriction (52, 53).

Weight loss. LFDs, which are typically similar to the diets described in the comparison of LEDs and VLEDs, are among the best-studied approaches to weight loss. Several large, multicenter, randomized trials — Diabetes Prevention Program (DPP) and Look AHEAD — have demonstrated the efficacy of LFDs for losing weight and improving comorbid conditions as compared with usual care. DPP examined 3234 participants with overweight/obesity and impaired glucose tolerance randomly assigned to placebo, metformin (850 mg twice daily), or a lifestyle intervention designed to induce a 7% loss of initial weight (54). The lifestyle intervention instructed participants to reduce fat intake to less than 25% of daily calories and limit food intake to 1200–2000 kcal/d depending on initial weight (53). At 1 year, the lifestyle group lost 7.1 kg, compared with losses of 2.8 kg in the placebo group and virtually no weight change in the placebo group (55). At 1 year, the median, self-reported percentage fat intake was 27.1% in the lifestyle group (56). Average duration of treatment was 2.8 years, at which time lifestyle participants lost 5.6 kg, compared with losses of 2.1 kg and 0.1 kg in the metformin and placebo groups, respectively (54).

LFDs also have been prescribed without caloric restriction, allowing patients ad libitum consumption of select carbohydrates, while avoiding high-fat foods. Investigators have hypothesized that such diets, with the greater volume of food intake allowed, would increase satiety (while reducing hunger) and induce gradual weight loss. However, the weight loss efficacy of such diets is uncertain. One meta-analysis of trials 2 months or longer examined ad libitum LFDs compared with control diets in which participants were advised to maintain their regular diet (or to consume a diet with a fat content similar to that consumed by the community population) (Table 1 and ref. 57). Low-fat interventions had a mean, self-reported dietary fat reduction of 10.8% of energy. Compared with the control groups, the low-fat interventions produced a 272 kcal/d greater energy decrease and 3.2 kg greater weight loss. However, this meta-analysis included people across the weight spectrum. Few long-term, controlled trials have examined this question in patients with obesity.

Mechanisms. Several mechanisms could contribute to weight loss with LFDs (58). Some of these pertain to limiting fat itself, whereas others are a consequence of the increased proportion of carbohydrate and protein that occur with fat restriction. Fat lends flavor and palatability to foods and provides the "mouthfeel" that makes them hedonically rewarding. Fat has 9 kcal/g, compared with carbohydrates and proteins, which have 4 kcal/g. Fat is less satiating than carbohydrates or proteins, mostly because of its higher energy density and palatability (59–61). Fullness and satiation increase with the volume of food ingested. Thus, compared with high-protein or high-carbohydrate foods, isocaloric amounts of high-fat foods, by virtue of their smaller physical volume, will be less likely to trigger satiation signals such as gastric distention (62–64). These properties predispose people to overeat high-fat foods (15, 65). Decreasing fat typically allows patients to eat a greater volume of food, which facilitates satiation and decreases overall energy intake.

Low-carbohydrate diets

Low-carbohydrate diets (LCDs) emphasize restriction of carbohydrate and replacement with fat and/or protein. LCDs prescribe 60–130 g of carbohydrate per day (≤20%–45% of daily energy intake). Very-low-carbohydrate regimens recommend less than 60 g of carbohydrate per day.

Weight loss. LCDs generally produce greater short-term (<6 months) weight losses than LFDs, with roughly equivalent long-term (>12 months) weight losses between approaches. At least 10 meta-analyses have evaluated the effectiveness of these regimens for losing weight and improving metabolic parameters (66). Compared with LFDs, LCDs produced 3.3–4.0 kg greater weight loss at 6 months (67, 68). However, at 12–24 months, differences between these approaches declined to only 2–2.2 kg in favor of low-carbohydrate regimens (Table 1 and refs. 66, 69, 70). For example, at 6 months, participants assigned to a low-carbohydrate, high-protein, high-fat diet lost 7.0% of body weight, which was significantly more than the 3.2% produced by a low-calorie, high-carbohydrate, low-fat regimen. However, at 12 months, differences between groups were no longer significant (–4.4 vs. –2.5% of initial body weight, respectively) (71). In the DIETFITS trial, participants were randomized to a healthy LFD or LCD. Intake of total fat or digestible carbohydrates was prescribed as 20 g/d during the first 8 weeks, and participants gradually increased fat or carbohydrate intake until they reached the lowest level they believed they could maintain indefinitely. Weight loss did not differ between groups at 12 months (72). A meta-analysis of 19 trials further demonstrated that short- and long-term weight losses were similar with LCDs and LFDs when isocaloric regimens were prescribed (73).

Very-low-carbohydrate ketogenic diets. Very-low-carbohydrate ketogenic diets (VLCKDs) are one of the most popular forms of LCD and are designed to induce ketosis. They restrict carbohydrate to less than 20 g/d during phase 1, which usually lasts up to 12 weeks, and then gradually increase it to 80–100 g/d. The amount of carbohydrate restriction needed to achieve ketosis varies by person but is typically less than 50 g/d (74). Such diets usually provide 70%–80% fat, since eating too much protein can prevent ketosis (because amino acids can be converted to glucose via gluconeogenesis) (75).

A meta-analysis of six studies of VLCKDs, which lasted less than 4 weeks, revealed a mean weight loss of 10.0 kg (Table 1 and ref. 76). A different set of six studies lasted ≥4 weeks and reported an average weight loss of 15.6 kg. In a meta-analysis of studies lasting ≥12 months, VLCKDs resulted in modestly greater weight loss than energy-restricted diets, with less than 30% of calories from fat (weighted mean difference = –0.91 kg) (77). However, adherence to the carbohydrate prescription, as assessed by 3-day dietary recalls, was low (7, 77). For example, participants in the first phase of one VLCKD consumed 35 g/d more carbohydrate than prescribed and, at 1 year, ate 86 g/d more than prescribed (7).

Low–glycemic index diets. Low–glycemic index diets (LGIs) represent another low-carbohydrate approach. Carbohydrate quantity and type (e.g., whole grain versus refined grain) have differential effects on postprandial glucose (78). This is of uncertain benefit. Compared with isocaloric control diets, LGIs produced similar weight losses (SMD = –0.10; 95% CI = –0.22, 0.01) (79). High- and low-glycemic diets resulted in similar weight loss at ≥6 months (Table 1 and ref. 80). However, LGIs generally had more favorable effects on glucose (81).

Mechanisms. Many arguments that favor decreasing carbohydrate pertain to the effects of high-glycemic foods, including refined starches and sugar (82). According to the carbohydrate-insulin model, diets high in carbohydrate increase postprandial glucose and insulin secretion and direct metabolic fuels away from oxidation and toward storage in adipose tissue, decreasing energy expenditure and increasing hunger (82–84). Evidence supporting the model is mixed (85). Some studies show that LCDs are associated with suppression of appetite-stimulating hormones such as insulin and ghrelin (86). Postprandial secretion of the satiety hormones GLP-1 and PYY also tends to increase more with low-carbohydrate/high-fat meals than with isocaloric low-fat/high-carbohydrate meals (87, 88). However, one study found that compared with a ketogenic LCD, a plant-based LFD with a higher glycemic load and postprandial glucose and insulin response resulted in less energy intake and no significant differences in hunger (89). Low-carbohydrate foods may also reduce caloric intake by decreasing cravings and preference for high-carbohydrate and high-sugar foods (90).

Additional mechanisms related to ketosis arise with severe carbohydrate restriction. At 12 weeks, VLCKDs are associated with reduced hunger and desire to eat, though there are minimal effects on satiety (91, 92). Appetite-suppressing effects may be due to ketosis or other properties of VLCKDs, including increased protein or fat intake (91, 92). About 500 g of glycogen are stored in the liver and muscle, and each gram of glycogen is associated with approximately 3 g of water. VLCKDs deplete glycogen stores, and the accompanying diuresis explains some of the greater short-term weight losses with LCDs (93). Sustaining carbohydrate restriction sufficient to maintain ketosis is challenging. Few people have detectable urinary ketones after 3–6 months on VLCKDs, likely owing to imperfect adherence (71, 94).

High-protein diets

High-protein diets prescribe ≥25% of calories from protein or ≥1.6 g of protein per kg of body weight. Higher protein content is a feature of many lower-fat and lower-carbohydrate diets.

Weight loss. There is mixed evidence that high- versus low-protein diets result in differential weight losses. A meta-analysis of 24 trials comparing the short-term effects (mean trial duration of 12 weeks) of energy-restricted, isocaloric high-protein/low-fat versus standard-protein/low-fat diets found modest differences in weight between groups (–0.79 kg; 95% CI = –1.50, –0.08; Table 1 and ref. 95). A meta-analysis of 15 trials comparing the longer-term (≥12 months) effects of LFDs combined with either high or low protein intake revealed no differences in weight loss between diets (–0.39 kg; 95% CI = –1.43, 0.65) (96). The DIOGENES trial examined ad libitum, high- versus low-protein diets. After an initial 8-week LCD, compared with low-protein diets, participants randomized to high-protein diets regained 0.93 kg less and 2.8 kg less weight at 26 weeks and 1 year, respectively (97, 98). In another study testing the use of high protein for weight loss maintenance, weight loss did not differ among participants randomized to high-protein or high-carbohydrate diet at 64 weeks. However, participants who reported higher protein intake had greater weight loss than those with lower protein consumption (99).

Mechanisms. Proponents of higher protein intake note that protein is more satiating than carbohydrate or fat under most conditions (100, 101), which may result in weight loss through reduced caloric intake (102). These may be modest effects that fall short of producing additional clinically significant weight loss, as described above. Independent of its possible effects on appetite, higher protein intake spares the loss of fat-free mass during weight loss, particularly in older adults (103, 104). A high-protein diet compared with a moderate-protein diet may also create a negative energy balance that counteracts adaptive thermogenesis during weight loss maintenance (105).

Comparison of multiple macronutrient manipulations

Several trials have compared three or more macronutrient permutations or diet types. The POUNDS Lost study randomized participants to calorie-restricted diets low or high in fat (20% or 40%) with normal or high protein (15% or 25%). Carbohydrate content ranged from 35% to 65% of calories (106). Weight losses did not differ among participants and were 6–7 kg after 6 months and 5 kg at 2 years. Across diets, mean reported energy intake and target levels for macronutrients did not reach prescribed levels at 6 months or 2 years. Cravings, fullness, hunger, and diet satisfaction were similar across diets. Another study compared participants randomly assigned to the Atkins, Zone (macronutrient balance of 40% carbohydrate, 30% fat, and 30% protein), Weight Watchers (calorie restriction), or Ornish diets (<10% of calories from fat) and found no significant difference in weight loss at 1 year (6).

Only level of adherence to the prescribed diet was associated with weight loss. Taken together, these findings show that macronutrient composition has little effect on long-term weight loss, even with efforts to hold the level of caloric restriction constant.

Dietary patterns

Many scientists and consumers have shifted their attention to dietary patterns rather than focusing on specific foods or food types (107). Several types of dietary patterns, as exemplified by the Mediterranean diet, have evolved that place a greater concern on health than on weight loss per se. This approach tends to emphasize the quality and nature of macronutrients more than quantity. Dietary patterns examined to date generally produce modest weight loss, unless they are combined with energy restriction (108, 109).

Mediterranean diet

The term "Mediterranean diet" refers to a dietary pattern common in olive-growing areas of the Mediterranean region. This diet includes high consumption of vegetables, fruits, legumes, and grains; moderate consumption of red wine and dairy products; and relatively low intake of meat and meat products (110, 111). There is no consensus on the exact definition of a Mediterranean diet. Mediterranean diets not prescribed for weight loss recommend approximately 2226 kcal/d with 36.6% of daily intake from fat, including 18.8% as monounsaturated fat and 4.8% as polyunsaturated fat (112). Several tools have been developed to measure adherence to Mediterranean diets that are based on composite measures of self-reported food, food groups, nutrients, and/or ratios of nutrients (113, 114).

Weight loss. A meta-analysis of 16 RCTs of Mediterranean diets versus other diets (e.g., low-fat, high-carbohydrate; Table 1) suggested that the former diet reduced weight and metabolic abnormalities when total energy intake was restricted or when combined with increased physical activity (109). Mediterranean diets reduced weight more than control diets by a mean of 1.8 kg (95% CI = 0.6, 2.9) over a duration of 1–60 months. Larger reductions in weight were observed when the diets were also energy restricted (–3.9 kg; 95% CI = –6.5, –1.2) (109). A meta-analysis of six trials that compared Mediterranean with low-fat diets (≤30% of total energy as fat) found that at 2 years of follow-up, the Mediterranean diet produced greater reductions in weight (–2.2 kg) (115). The DIRECT trial showed stronger effects on weight loss of a calorically restricted, Mediterranean diet (–4.4 kg) and of a low-carbohydrate, non–calorically restricted diet (–4.7 kg) compared with a calorically restricted LFD (–2.9 kg) at 2 years (116). Across diets, self-reported adherence was 81% in the first month of the intervention and dropped to 57% at 24 months, with no significant differences among groups (117). In the ongoing PREDIMED-Plus intensive lifestyle intervention study, nearly 7000 participants were randomized to an energy-restricted Mediterranean diet (combined with physical activity and lifestyle counseling) or a usual-care control group. Mean 1-year weight loss from a subsample of participants was 3.2 kg (–3.7%) in the intervention group versus 0.7 kg (–0.8%) in control participants (95% CI = –3.1, –1.9) (118). (The trial's primary outcome is a composite score for cardiovascular disease events and has not yet been published.)

Mechanisms. Mechanisms associated with the effects of the Mediterranean diet, as a whole, have not been well investigated. The Mediterranean diet does not put a particular emphasis on macronutrients, an approach that may be helpful for individuals desiring flexibility. Individual components of the Mediterranean diet, such as nuts, have positive effects on decreasing hunger (119). However, it is important to monitor portion sizes, as many of the foods recommended in the Mediterranean diet, such as extra-virgin olive oil, are energy dense. Some patients may have difficulty accessing these foods owing to lack of availability and cost, which could limit adherence. The Mediterranean diet has a host of health benefits other than weight loss, including preventing cardiovascular disease events, which may make it advantageous for many individuals (110).

Factors to consider in selecting a diet

In the short term, calorie restriction, rather than dietary composition, is the central determinant of weight loss. The most effective diet for initial weight loss is one that someone can adhere to, although such adherence may be discoverable only by a trial of the regimen. Beyond the use of portion-controlled diets and provision of behavioral weight loss counseling, robust factors that facilitate adherence to a diet, on a short- or long-term basis, have yet to be identified.

Several investigators have begun to study diet prescriptions based on factors that include possible gene-diet interactions and baseline insulin levels (120–122). Yet, RCTs that used these factors to potentially promote dietary adherence (and weight loss) largely produced null findings. For example, the DIETFITS trial observed no interaction between weight loss and genotype pattern (low-fat sensitive or low-carbohydrate sensitive) or baseline insulin secretion (72).

Surprisingly, selection of diet based on patient preference, rather than random assignment, has little effect on adherence or weight loss (123, 124). In a double-randomized preference trial, participants were randomized to a choice between an LCD or LFD versus random assignment to a diet. At 48 weeks, estimated mean weight loss was 5.7 kg in the choice group, which did not differ significantly from the 6.7 kg loss in the no-choice comparison group. Dietary adherence as assessed by the percentage of deviation from the macronutrient intake target was similar between groups. Thus, while having a choice of diets does not appear to enhance weight loss, dieters nonetheless may be more satisfied when trying to lose weight by following a plan they like. Taken together, these studies underscore the critical need to explore factors that drive dietary adherence and weight loss, such as individual variability in physiological responses to different diets.

In addition to inquiring about which weight loss approaches a patient might wish to consider, health professionals also should assess the benefits of different dietary approaches in managing a patient's obesity-related comorbidities. For patients with type 2 diabetes, for example, LCDs appear to produce greater improvements in hemoglobin A_{1c} and reductions in diabetes medications than LFDs (with higher carbohydrates), despite comparable weight losses with the two approaches (125, 126). For patients with hypertension, a DASH-type diet could confer better blood pressure control than an LFD (127).

Conclusion

There is not a one-size-fits-all diet for obesity treatment. Adherence to a diet to produce an energy deficit to lose weight and then maintain the loss, regardless of which diet is chosen, is one of the most important factors for obesity treatment. Numerous dietary approaches, with varying calorie levels and macronutrient compositions, produce clinically meaningful weight loss in the short term, with weight regain common to all approaches over time. We observed wide variability in weight losses and adherence between participants who received the same dietary intervention in the same trial, as well as among trials conducted at different sites. There is not convincing evidence that one diet is universally easier to adhere to than another for extended periods, a feature necessary for long-term weight management. Progress in improving dietary adherence could result from greater efforts to examine mechanisms underlying interindividual variability in responses to dietary approaches. Identifying behavioral and metabolic phenotypes among dieters based on characteristics such as habitual hunger and satiation, as illustrated in Figure 1, could be used to improve the precision of dietary recommendations for obesity treatment to optimize adherence and subsequent weight loss. The more we understand the characteristics of individuals who are trying to lose weight, the more able we may be to identify dietary interventions that facilitate their efforts.

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