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Scientific evidence of diets for weight loss: Different macronutrient composition, intermittent fasting, and popular diets

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New dietary strategies have been created to treat overweight and obesity and have become popular and widely adopted. Nonetheless, they are mainly based on personal impressions and reports published in books and magazines, rather than on scientific evidence. Animal models and human clinical trials have been employed to study changes in body composition and metabolic outcomes to determine the most effective diet. However, the studies present many limitations and should be carefully analyzed. The aim of this review was to discuss the scientific evidence of three categories of diets for weight loss. There is no one most effective diet to promote weight loss. In the short term, high-protein, low-carbohydrate diets and intermittent fasting are suggested to promote greater weight loss and could be adopted as a jumpstart. However, owing to adverse effects, caution is required. In the long term, current evidence indicates that different diets promoted similar weight loss and adherence to diets will predict their success. Finally, it is fundamental to adopt a diet that creates a negative energy balance and focuses on good food quality to promote health.

Introduction

Obesity is a worldwide, multifactorial disease defined as abnormal or excessive fat accumulation that presents a risk to health. The disease is associated with several chronic morbidities, such as cardiovascular diseases (CVDs), diabetes, and cancer. Prevalence of overweight and obesity has tripled since 1975, reaching 39% and 13% of the world's population, respectively [1]. Because of its significant effects on health, medical costs, and mortality, obesity has become a public health concern.

The fundamental cause of obesity is an energy imbalance between calories consumed and calories expended; however, this involves a complex interplay of biological, genetic, and psychosocial factors [2]. Evidence has shown that a weight loss of ≥5% to 10% within 6 mo is necessary to reduce risk factors of comorbidities and to produce clinically relevant health improvements such as reductions in blood glucose, triacylglycerols, and blood pressure [3].

To achieve successful weight loss and sustain it over time, the Academy of Nutrition [4] recommends changes in lifestyle behavior; a diet that reduces excessive energy intake and enhances dietary quality; and an increase in energy expenditure. Furthermore, the successful treatment of overweight and obesity could require adjuvant therapeutics such as cognitive-behavioral therapy [4], pharmacotherapy [5], and even bariatric surgery [6]. These therapies are indicated for specific conditions and should be individually analyzed, which is a topic that goes beyond the scope of this review.

Regarding dietary interventions for weight loss, an individualized diet that achieves a state of negative energy balance should be prescribed [4]. Many dietary approaches can generate this desired reduction in caloric intake. Diets are usually based on the inclusion or exclusion of different foods or food groups (Fig. 1). Historically, several diets have become popular and then faded owing to a lack of reliable scientific support. In this context, this review aimed to provide scientific evidence to support the adoption of dietary strategies to promote weight loss. We classified these strategies into three main categories:

1. diets based on the manipulation of macronutrient content (i.e., low-fat [LF], high-protein [HP], and low-carbohydrate diets [LCDs]).
2. diets based on the restriction of specific foods or food groups (i.e., gluten-free, Paleo, vegetarian/vegan, and Mediterranean diets).
3. diets based on the manipulation of timing (i.e., fasting).

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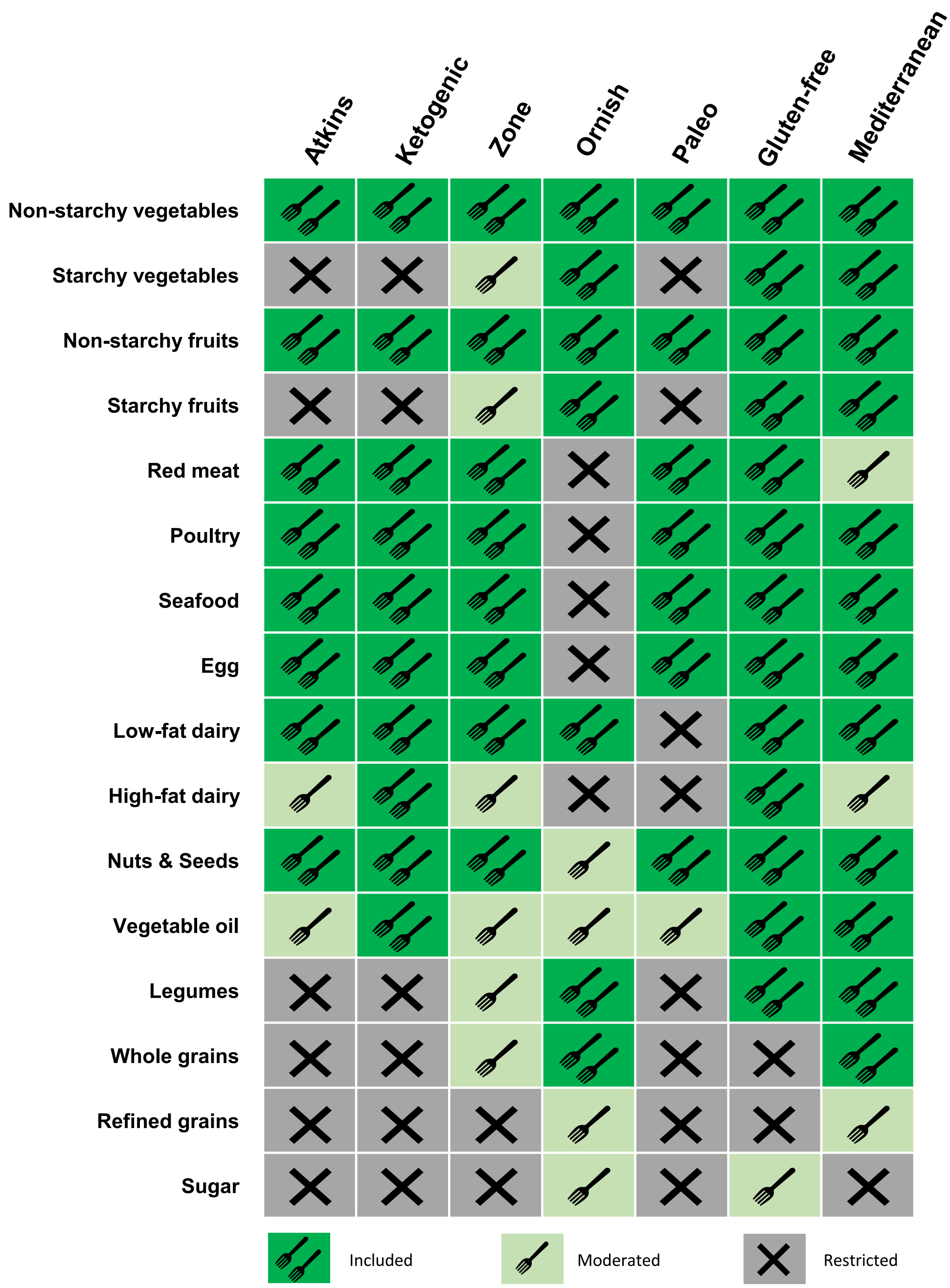

Fig. 1. Food groups included or excluded in popular diets: Atkins, Ketogenic, Zone, Ornish, Paleo, gluten-free, and Mediterranean.

Diets based on the manipulation of macronutrient content

The manipulation of macronutrient content in isocaloric diets has been studied to determine which composition best promotes weight loss while including other metabolic benefits. Increased protein and decreased carbohydrates are the most common modifications and have resulted in several popular diets created over time (Table 1; Fig. 2). Changes in the macronutrient composition affect hormones, metabolic pathways, gene expression, and the composition and function of the gut microbiome that might effect fat storage [7].

Metabolically, carbohydrates elevate insulin secretion, thereby directing fat toward storage in adipose tissue, described as the carbohydrate–insulin model of obesity [7]. In this context, LCDs ranging from 20 to 120 g of carbohydrates claim to treat obesity because they promote reduced insulin secretion and increased glucagon, which cause a metabolic shift to higher fat oxidation [8].

LCDs can be designed to be either normal-fat–HP or high-fat [HF]–normal-protein. However, despite the theory of the carbohydrate–insulin model, clinical trials comparing LCDs with low-fat diets (LFDs) in isoprotein diets reported similar weight loss [9–13] and even higher body fat loss when reducing fat but not carbohydrates [14]. Moreover, an important meta-analysis of 32 controlled studies concluded that energy expenditure and fat loss were more significant with LFDs when compared with isocaloric LCDs [15].

Table 1
Characteristics of popular diets based on manipulation of macronutrient content

Diet	Protein (%)	Lipid (%)	Carbohydrate (%)	Direct restriction of calorie intake?	Description
Atkins*	↑	↑	↓	No	Phase 1: <20 g CHO (2 wk) Phase 2: <50 g CHO
Ketogenic†	↔ (20)	↑↑ (>70)	↓↓ (5–10)	No	
Zone‡	↑ (30)	↑ (30)	↓ (35–45)	Yes	All meals in the Zone proportion
Ornish§	↔ or ↑	↓↓ (<10)	↔ or ↑	No	Vegetarian
Paleo‖	↑ (20–35)	↔ or ↑	↓ (30–45)	No	Mimic the ancestral hunter-gatherer diet

↑ increase; ↓ decrease; ↔ normal; CHO, carbohydrate;
*Recommends intake of 1500 to 1800 kcal/d (women) and 1800 to 2000 kcal/d (men) for weight loss purposes. There are no specific guidelines for protein and lipid intake.
†Recommends protein intake ~20% of energy. Calorie intake is usually not restricted.
‡Recommends intake of three meals and one snack a day with the Zone proportion; promote intake of unsaturated fat and healthier protein sources. Calories can be adjusted individually, but the general recommendation of weight loss is 1200 kcal (women) and 1500 kcal (men) daily.
§Recommends intake of beans, legumes, fruits, grains, vegetables and nonfat dairy products. Calorie intake is not restricted. Encourage management of stress and practice meditation.
‖Includes meat, nuts, eggs, healthy oils, and fresh fruits and vegetables. Cereal grains, legumes, dairy, and other processed/refined products are excluded. Gluten- and dairy-free.

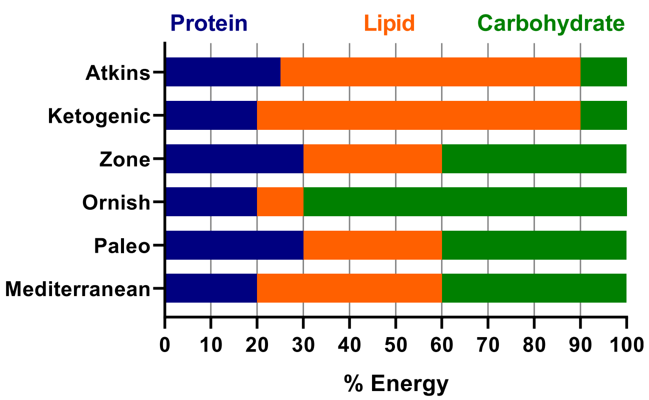

Fig. 2. Approximate macronutrient content of some popular diets: Atkins, Ketogenic, Zone, Ornish, Paleo, and Mediterranean.

Finally, individuals with insulin resistance (IR), glucose intolerance, or both may benefit from a LCD [16,17], although this has not been confirmed in a recent study with 609 individuals [12].

Another type of very LC–HF diet, known as the ketogenic diet (KD), prescribes a minimum of 70% of energy from fat and a severe restriction of carbohydrates to mimic a fasting state and induce ketosis [18]. The KD was introduced in 1920 to treat epilepsy in children and adults [18]. More recently, the KD has been used to promote weight loss and has the additional advantages of reducing hunger and appetite [10,19]. Overall, clinical trials have reported significant weight reduction for individuals on the KD [20–22], although many studies were uncontrolled [23,24]. Adverse effects such as constipation, halitosis, headaches, muscle cramps, and weakness were commonly observed [25]. Moreover, effects on lipemia and cardiovascular risk factors remain inconclusive [26] because studies have demonstrated either amelioration [27,28] or worsening [22,29] of the lipid profile and the development of hepatic steatosis [30].

Furthermore, observational data have demonstrated an increase in mortality associated with the long-term intake of both LCDs and high-carbohydrate diets (HCDs) with minimal risk at 50% to 55% (energy derived from carbohydrates). They also reported that animal-derived protein and fat were associated with higher mortality, whereas plant-derived protein and fat were associated with lower mortality [31].

Finally, high-protein diets (HPDs), in which ≥20% of energy is derived from protein, appear to offer advantages regarding weight loss and body composition in the short term [15,32]. Popular HP-HF diets, such as Atkins or Zone, promoted significant weight loss for short periods [33–36]. HP intake acts on relevant metabolic targets, increasing satiety and energy expenditure [37]. Conversely, in clinical trials >1 to 2 y, evidence indicated no significant differences in weight loss [12,33,35,36,38]. Moreover, HP-HF diets are often associated with a high intake of animal products and saturated fat, causing detrimental effects of increased low-density lipoprotein cholesterol [39,40].

In conclusion, in the short term, HP-LCDs are suggested to present benefits for weight-loss. However, owing to their major effects on metabolism and gut health, they should be considered as a jump-start weight loss tool rather than a diet for life. In the long term, current evidence indicates that a different ratio of macronutrients associated with a caloric restriction in healthy diets promotes similar weight loss [15,41].

Diets based on the restriction of specific foods or food groups

Different foods and food groups have emerged as villains and have been removed from specific diets to promote weight loss. The long list includes a vegetarian diet, which excludes all animal products; the Paleo diet, which restricts many food groups including grains, dairy, and legumes; and the popular gluten-free diet (GFD). The Mediterranean diet is not based on the complete restriction of a specific food group, but instead is characterized by a richness of plant-based food and moderation of refined grains, red meat, and dairy.

Plant-based diet for weight-loss

Vegetarian dietary patterns are very diverse due to the different reasons for its adoption and the wide variety of available food choices. A vegetarian plan can range from the simple exclusion of meat products to the raw vegan plan, which only includes raw vegetables, fruits, nuts, seeds, legumes, and sprouted grains [42]. Exclusion of animal products can reduce the intake of certain nutrients, which might lead to nutritional deficiencies of protein, iron, zinc, calcium, and vitamins D and B_{12} [42,43]. Discussion about these deficiencies and strategies for prevention goes beyond the scope of this review.

Table 2
Effects of different plant-based diets on weight loss and health benefits in humans

Intervention diet	Duration	Participants	Individuals completed the study, %	Changes in body weight	Metabolic changes	Reference
PBD or conventional diabetic diet (CD)	24 wk	74 patients with T2D (53% women; mean age 52 y)	84	PBD: −6.2 kg CD: −3.2 kg	↑ insulin sensitivity ↓ visceral and subcutaneous fat Improvement in oxidative stress markers	[47]
VD or control diet (CD)	18 wk	211 individuals with overweight and T2D (79% women, mean age 45 y)	VD: 66 CD:79	VD: −4.3 kg CD: −0.1 kg	↓ LDL, TC, HbA1c	[53]
Meat or vegetarian high-protein diets	2 wk	20 men with obesity (mean age 51 y)	100	Similar	Similar appetite control, concentration of ghrelin and peptide YY. Limitation: short term	[54]
Low-fat VD	7 d	1615 individuals (65% women; mean age 58 y)	Retrospective	−1.4 kg	↓ TC, blood pressure	[45]
PBD or control diet (CD)	24 wk	65 overweight/obesity (60% women; mean age 56 y)	70	PBD: −4.4 kg CD: −0.4 kg	↓ TC	[55]
PBD or control diet (CD)	10 wk	325 individuals (87% women, mean age 40 y)	Retrospective	PBD: −5.6 kg CD: −1.2 kg	↓ body fat	[56]
PBD or control diet (CD)	16 wk	75 overweight (89% women; mean age 53 y)	96	PBD: −6.5 kg CD: −0.2 kg/m^2	↑ β-cell function and insulin sensitivity	[57]

↑ increase; ↓ decrease; CD, conventional/control diet; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; PBD, plant-based diet; T2D, type 2 diabetes; TC, total cholesterol; TG, triacylglycerol; VD, vegan diet

Adoption of plant-based diets is growing because evidence has shown some health benefits when compared with omnivorous diets. They can protect against chronic diseases, such as CVDs [44,45], hypertension [46] and type 2 diabetes [47], and some cancers [48]. Further research will clarify whether these benefits are related to the reduction of animal products or the increased intake of fruits, vegetables, and fibers.

In observational studies, individuals on a plant-based diet usually present a lower body mass index (BMI) than non-vegetarians [49,50]. In interventional studies, prescription of vegetarian diets was well accepted [51,52] and was associated with weight loss (Table 2 [45,47,53–57]). Two meta-analyses reported a significant reduction of body weight after the adoption of vegetarian diets [58,59]. Subgroup analysis observed a higher reduction in weight loss with vegan diets compared with lacto-ovo-vegetarian diets [59]. It is likely that this reduction is due to the typically low energy density, LF and HF intake associated with plant-based diets [60].

In summary, evidence has supported the therapeutic use of plant-based diets as an effective treatment of overweight and obesity. However, further long-term trials are required to confirm the relevance of results, as some studies did not report differences in weight loss [53,61,62]. The adoption and implementation of a well-designed vegetarian diet require effective counseling and adequate nutritional supplementation.

Paleo diet for weight-loss

The Paleolithic diet, also called Paleo, is based on everyday foods that mimic the food groups of our preagricultural, hunter–gatherer ancestors. The diet claims to help optimize health, minimize risks for chronic disease, and result in weight loss. These statements are supported by the theory that the hunter–gatherer diet and lifestyle sustained humanity for ∼2.4 million y, causing humans to be genetically adapted to it. According to proponents of the Paleo diet, profound changes in diet and other lifestyle conditions after the introduction of agriculture and animal husbandry 10 000 y ago have been too recent on an evolutionary time scale for an adjustment of the human genome [63,64].

Only foods that were available to hunter–gatherers are included in the diet. These include meat, nuts, eggs, healthy oils, and fresh fruits and vegetables. Cereal grains, legumes, dairy, and other processed/refined products are excluded [64]. The Paleo diet features characteristics such as a lower ratio of ω-6 to ω-3 fatty acids and lower sodium, along with a high content of unsaturated fatty acids, antioxidants, fiber, vitamins, and phytochemicals that operate synergistically to promote health benefits [64]. The diet is high in protein (20–35% of energy) and moderate in fat and carbohydrates (22–40% of energy, specifically restricting a high glycemic index) [65]. Finally, the Paleo diet yields a healthier net alkaline load compared with the net acid load estimated for the typical Western diet [64].

Much has been studied about the beneficial metabolic outcomes of the Paleolithic diet. Evidence has demonstrated several improvements such as ameliorations in metabolic syndrome (MetS) [66], increase in insulin sensitivity [67], reduction of cardiovascular risk factors [68,69], increased satiety [70–72], and beneficial modulation of intestinal microbiota [73].

Specifically, regarding Paleo diet for weight loss, scientific evidence points toward consistent reduction of body weight and body fat mass either in short- [69,71,74–76] or long-term studies [77–79] (Table 3 [69,74,76,77,79,80,81]). Low adherence [71], poor palatability, and high costs are common issues reported by those who follow the Paleo diet [82].

In summary, although evidence suggests general health benefits and weight loss, further research is needed to support the popular claims of the Paleo diet. As an important limitation, the Paleo diet presents a potential deficiency risk that includes vitamin D, calcium [74], and iodine [83].

Gluten-free diet for weight-loss

Gluten is a protein complex found in cereals such as wheat, rye, barley, and oats [84]. Studies have shown that the main fraction of gluten, namely gliadin, cannot be completely digested by the gastrointestinal (GI) tract, triggering an intestinal inflammatory response in susceptible individuals [85].

Celiac disease, wheat allergy, and non-celiac gluten sensitivity represent the main gluten reactions mediated by the immune system [85]. The treatment for these disorders is based on the complete dietary exclusion of all gluten-containing food, which is well

Table 3
Evidence of the Paleolithic diet on weight loss and metabolic changes in humans

Intervention diet	Duration	Participants	Individuals completed the study, %	Changes in body weight	Metabolic changes	Reference
PD	3 wk	20 healthy (50% women; 20–40 y)	70	−2.3 kg	↓ waist circumference and blood pressure	[74]
PD	5 wk	10 postmenopausal women with overweight/obesity	100	−4.5 kg	↓waist circumference, blood pressure, glucose, TC, TG, HOMA indices, and liver TG (49%)	[80]
PD or NNR	2 y	70 postmenopausal women with obesity (mean age 60 y)	PD: 77 NNR: 63	Fat mass: PD: −11.1 kg NNR: −5.5 kg	↓ fat mass, abdominal obesity and TG	[77]
PD or ADA recommendations	14 d	24 patients with T2D (mean age 57 y)		PD: −2.4 ± 0.7 kg ADA: −2.1 ± 1.9 kg	Greater benefits on glucose and lipids profile on PD	[81]
AHA recommendations and PD	2 consecutive 3 m	20 volunteers with hypercholesterolemia (50% women; 40–62 y)		PD: −10.4 kg AHA: −3.3 kg	↑ TC, LDL, and TG ↑ HDL	[69]
PD or conventional low-fat diet	2 y	70 postmenopausal women with obesity (mean age 61 y)		PD: −8 kg LFD: −5 kg	Higher ↓ in liver fat 6 mo: ↓ BMI and body fat (%)	[79]
PD	12 wk	32 patients with T2D (34% women; mean age 60 y)	90	−7.1 kg	Improvements in insulin sensitivity, glycemic control, and leptin.	[76]

↑ increase; ↓ decrease; ADA, American Diabetes Association; AHA, American Heart Association; BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostatic model of assessment; LDL, low-density lipoprotein; NNR, Nordic nutrition recommendations; PD, Paleolithic diet; T2D, type 2 diabetes; TC, total cholesterol; TG, triacylglycerol

established by the scientific literature [85]. However, the market for gluten-free products has been growing for the past 15 y, mainly due to individuals who adhere to a GFD to reduce body weight or improve diet quality [86]. Despite the popular association of gluten and weight loss, controlled studies are scarce in the scientific literature [86].

Evidence supports a possible obesogenic effect of gluten. First, a cereal-based diet impaired insulin sensitivity and blood pressure control and increased the levels of C-reactive protein in pigs [67]. In rodents, two pioneer studies reported obesogenic effects of gluten using the nutritional model of obesity: An HFD added with gluten induced higher weight gain, adiposity, blood glucose, inflammation, and IR, partly by reducing the thermogenic capacity of adipose tissues [87,88].

To our knowledge, no controlled clinical study in humans has investigated the association between gluten and weight loss. The National Health and Nutrition Examination Survey (NHANES) showed that healthy gluten-free followers had lower BMIs and significant self-reported weight loss of 1.3 kg over 1 y but no significant difference in prevalence of MetS or CVD [89]. In non-celiac athletes, a short-term GFD had no overall effect on performance, GI symptoms, well-being, or inflammatory markers [90]. Furthermore, there is a lack of knowledge demonstrating causality in regard to the role of gluten itself, since the GFD is associated with increasing calories and decreasing intake of food fibers and fermentable oligosaccharides, disaccharides, monosaccharides and polyols naturally present in gluten products [91].

In summary, to date, little has been studied about gluten and body weight evolution. It is well known that gluten intake can increase inflammatory status [92], cause intestinal dysbiosis [93], and increase intestinal permeability [94]. However, it is not known whether gluten presents obesogenic properties and, if it does, the metabolic mechanism involved is unknown [95].

Mediterranean diet for weight-loss

The Mediterranean diet is a balanced diet characterized by high consumption of vegetables, fruits, legumes, whole-grain cereals, seafood, olive oil, and nuts. Red meat, dairy and alcohol are recommended in moderation [96]. The Mediterranean diet is rich in plant-based foods, having high levels of antioxidants and dietary fiber, and low glycemic load compared with other diets [36]. It also has an adequate ratio of monounsaturated to saturated fatty acids.

Studies reported weight loss associated with the Mediterranean diet in the short [97–99] and long term [36,99] (Table 4). However, meta-analysis studies observed that the overall amount of weight loss was similar compared with other diets in overweight and obese individuals [100,101].

Nevertheless, the main relevance of the Mediterranean diet has been related to its strong evidence-based health and metabolic benefits. Due to the high nutrition quality of its food composition, the Mediterranean diet has been considered a healthy eating pattern for many conditions. Studies have demonstrated that the Mediterranean diet improves outcomes for glycemic control in patients with type 2 diabetes [102,103]. Hence it is one of the diets recommended by the American Diabetes Association. The Mediterranean diet has been associated with a reduction of inflammatory markers [104], and important reduction of cardiovascular risk factors and mortality [104,105]. Moreover, this diet was efficient in decreasing inflammation [97] and cardiovascular risk even in the absence of meaningful weight loss [106]. More recently, the association with amelioration of non-alcoholic liver disease [107] and cancers [108] has been promising but requires further investigation.

Diets based on the manipulation of timing (fasting)

To achieve the negative energy balance required for weight loss [4], most weight control programs use a 20% to 40% continuous (daily) calorie restriction. However, more recently the manipulation of timing, namely intermittent calorie restriction or intermittent fasting (IF), has received considerable interest as an alternative strategy. IF consists of abstaining from food and caloric beverages for a certain period of time alternated with normal eating. Several variations of IF differ in length and frequency of the fast cycles. Moreover, modified IF allows a small amount of intake to avoid persistent hunger [109]. IF is often combined with regular

Table 4
Effects of the Mediterranean diet on weight loss and health benefits in humans

Intervention diet	Duration	Participants	Individuals completed the study, %	Changes in body weight	Metabolic changes	Reference
MD (calorie-restricted) or LFD (calorie-restricted) or LCD (non-restricted)	2 y	322 moderately obese (14% women, mean age 52 y)	85	MD: −4.6 kg LFD: −3.3 kg LCD: −5.5 kg	MD: ↓ fasting glucose and insulin (among participants with diabetes) MD and LCD: ↑HDL, ↓TG, ↓LDL	[36]
MD (no control group)	2 y	124 patients with T2D (77% women, mean age 56 y)		6 mo: −1.2 kg 1 y: −1.5 kg 2 y: −3.7 kg	Improvement in self-reported lifestyle behaviors	[99]
MD supplemented with olive oil or MD supplemented with nuts or control diet	4.8 y	288 patients with high CV risk (57% women, 55–80 y)			↓ incidence of major CV events in MD supplemented with olive oil or nuts	[105]
LCD-MD or TM, and the ADA diet	1 y	259 patients with overweight and diabetes (48% women, mean age 55 y)	75	LCD-MD: −10.1 kg TM: −7.4 kg ADA: −7.7 kg	LC-MD and TM: greater glycemic control, ↑HDL, ↓ HbA1 and TG compared with ADA	[98]
Control diet followed by isocaloric MD	5 wk + 5 wk	19 men with MetS (24–65 y)		MD: −10.2% vs control	↓ waist circumference, C-reactive protein, and inflammation score	[97]

↑ increase; ↓ decrease; ADA, American Diabetes Association; CV, cardiovascular; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LCD, low-carbohydrate diet; LDL, low-density lipoprotein; LFD, low-fat diet; MD, Mediterranean diet; MetS, metabolic syndrome; T2D, type 2 diabetes; TG, triacylglycerol; TM, traditional Mediterranean diet

exercise and even other diets. The most common types of IF include periodic fasting or 5:2 diet, alternate-day fasting, time-restricted feeding, and religious fasting (Table 5 [109–128]).

The basic premise of fasting is to promote changes in metabolic pathways, cellular processes, and hormonal secretions [129]. Major physiologic responses of fasting on health indicators include greater insulin sensitivity [110] and reduced levels of blood pressure [111], body fat [112], glucose [113], atherogenic lipids [130], and inflammation [131]. In animals, fasting ameliorated functional outcomes of diseases including cancer [132], type 2 diabetes [133], and CVD [114].

Emerging findings in rodents also observed the potential of fasting to delay aging, although the magnitude of the effects remains controversial. Depending on the species, the age at regimen initiation and the fasting cycle, the results ranged from a negative effect to as much as 30% life span extension [115,134,135].

In humans, 12 to 24 h of fasting typically results in a ≥20% significant decrease in serum glucose and depletion of the hepatic

Table 5
Effects of different intermittent-fasting diets on body weight and metabolic parameters

IF diet	Description of diet	Evidence in rodents [reference]	Evidence in humans [reference]
Periodic fasting or 5:2 diet	2 d of fasting (0–25% of caloric needs) and 5 d of *ad libitum* eating during the week		- Weight loss, improvement in insulin sensitivity and health biomarkers [117] - ↓ postprandial lipemia, insulin secretion and blood pressure [109]
Alternate-day fasting	Fast day (0–25% of caloric needs) alternated with *ad libitum* eating	- No changes in body weight, increase in life span [115] - No changes in weight, ↓ serum glucose and insulin levels [113] - ↓ body weight, heart rate, blood pressure similar to calorie restriction [114] - ↓ total intraabdominal fat mass, but no changes in high-fat–induced muscle insulin resistance [118] - Prevented the onset of T2D, similar to calorie restriction [121]	- No changes in body weight. ↑ insulin sensitivity [110] - No effects in glucose, lipid, or protein metabolism in healthy lean men [122] - Similar changes in weight, body composition and insulin sensitivity compared with calorie restriction [116] - 5.8% weight loss and ↓ cardiovascular risk (LDL, TG,and blood pressure) [111] - ↓ weight, body fat, and blood pressure; no control group [112]
Time-restricted feeding	*Ad libitum* eating within specific windows (<8 h/d)	- Protection against obesity, hyperinsulinemia, hepatic steatosis, and inflammation [123] - Stabilized and reversed the progression of metabolic diseases in mice with preexisting obesity and T2D [124]	- Extended morning fasting did not result in compensatory intake at lunch meal in obese individuals [125] - Improvement in health-related biomarkers, ↓ fat mass, and maintain muscle mass in resistance-trained males [126] - No changes in weight, ↑ insulin sensitivity, β-cell function. ↓ oxidative stress [127]
Religious or spiritual fasting (Ramadan)	12–16 h/d of fasting for the Ramadan month		- Weight loss (2.5 kg for men; 0.9 kg for women) regained within 2 wk [120] - Weight loss, ↓ total glucose, cholesterol, TG, and LDL levels [128] - No changes in weight, ↑ glucose, TC, and LDL in normal-weight and obese men [119]

↑ increase; ↓ decrease; ADF, alternate day fasting; IF, intermittent fasting; LDL, low-density lipoprotein; T2D, type 2 diabetes; TC, total cholesterol;TG, triacylglycerol; TRF, time-restricted feeding glycogen. Under these circumstances, the body switches to a ketogenic metabolic mode using non-hepatic glucose, fat-derived ketone bodies, and free fatty acids as energy sources [129]. The restriction of carbohydrates also triggers these metabolic changes.

Regarding the effects of IF on weight loss, the average reported weight loss in cohorts with overweight and obesity has ranged between ~4% and 10% over dieting periods of 4 to 24 wk [111,112,116,117,130,131,136]. Nevertheless, some contradictory effects of IF were observed. In rats, alternate-day fasting (a type of IF) was unable to eliminate HF, diet-induced, muscle IR [118] and did not promote changes in body weight [113,115]. In several clinical studies, the lack of an appropriate control group might suggest that the beneficial improvements of IF could be comparable to other types of calorie restriction.

Fasting is also adopted in several religious and spiritual traditions, and thus is intensely studied in this population. Ramadan is a month during which healthy adult Muslims fast for an average of 12 to 16 h/d [137]. Results describing the effects of Ramadan on body weight have been inconclusive. Several studies reported a weight loss [138–141], whereas many others showed no significant changes [119,142,143]. Very often, a weight regain is observed a few weeks after the fasting period [120,140,141].

In summary, there is growing evidence demonstrating the metabolic health benefits of IF. In rodents, these appear quite profound, whereas in humans they are sparse and need further investigation, especially in long-term studies. It has been suggested that IF does not produce superior weight loss in comparison with continuous calorie restriction plans [130], and there are limited data regarding other clinical outcomes such as diabetes, CVD, and cancer. IF diets seem safe and tolerable for adults, but it is unclear if periods of fasting and hunger lead to overeating [144]. Adverse effects of fasting, which are similar to the KD, are often moderate and include halitosis, fatigue, weakness, and headaches [145]. It is also important to emphasize that fasting diets might be harmful to specific populations such as children, the elderly, and underweight individuals.

Alternative dietary approaches

There are several alternative dietary approaches with promising favorable outcomes in patients with overweight and obesity. For instance, the replacement of two to three meals a day with “meal replacements” that contain all recommended nutrients has been described as an approach that promotes significant weight loss [146–148]. Studies also reported reductions in cardiovascular risk factors [147] and improvement in metabolic parameters [149] associated with meal replacements. However, use of meal replacement products is not sustainable in the long term due to severe energy restriction [149].

Furthermore, the benefits and disadvantages of a long list of other weight loss diets, including the Whole30 diet, the Dukan diet, the South Beach diet, the HCG diet, and the Detox Diet, and commercial weight loss programs such as Weight Watchers [150] require deeper scientific investigation. A complete review of all weight loss dietary approaches would not be feasible, giving the plethora of studies and trials. Hence, a few diets of primary importance were selected and discussed in this review.

Adherence

Adherence to a diet is defined as the degree to which participants meet diet requirements [151]. Many factors influence adherence to a dietary program including food preferences, cultural or regional traditions, food availability, food intolerances, and motivation. Furthermore, diet cannot be addressed only as a biochemical process, since it is strongly influenced by human behavior and environmental factors.

Advancing the search for an optimal dietary weight loss approach suggests that a higher level of adherence, regardless of the type of diet, is a determinant factor in predicting success. Dansinger et al. [152] reported that amount of weight loss was associated with self-reported dietary adherence, but not with diet type. Alhassan et al. [153] showed that adherence was significantly correlated with weight loss within each diet group after 1 y. Corral et al. [154] observed lower weight regain with higher adherence during the previous weight loss diet. Heymsfield et al. [155] also attributed the small weight loss observed in some individuals to difficulties in adherence. Conversely, Borradaile et al. [156] reported no differences in weight loss between groups when the participants were assigned to their preferred diet.

Finally, strategies to improve adherence to diets promise to be powerful tools to improve success with weight loss dietary therapies [157].

Final remarks and conclusion

The creation of new diets will continue to follow popular trends. However, the belief that these diets promote weight loss has emerged more from personal impressions and reports published in books, rather than from rigorously controlled research.

Over the past several decades, efforts have been concentrated on clinical trials to determine the best diet for the treatment of obesity. Unfortunately, the evidence remains inconclusive and contested, and the trials present important limitations (Table 6).

In the short term, diets promote different degrees of success, but in the long term, the small differences do not instill confidence for prescribing one diet over another. The number of unanswered questions remains large. Why do some individuals experience successful weight loss, whereas others are more resistant to losing

Table 6
Limitations commonly encountered in clinical trials aiming to compare diets for weight loss

Type of limitation	How the limitation creates bias?
Duration of the trial	- Relatively short observational period may underestimate long-term effectiveness
Sample size	- High individual variation requires a large number of participants - Low adherence and dropouts during the trials reduce the sample size
Inappropriate control group	- Often trials are uncontrolled, and outcomes are compared with baseline - Inappropriate diets used as control may influence the results (i.e., trials adopt different diets as controls, making it impossible to compare them)
Definition/Parameters of the diet	- Some parameters of a diet are defined by the researcher creating variability among trials (i.e., carbohydrates in LCD range from 5% to 45%; proteins in HPD range from 20% to 50% in trials)
Estimation of food intake and energy expenditure	- Under- or overestimation of nutrient and calorie intake - Under- or overestimate of energy expended with physical exercise and daily activities (i.e., work, housekeeping, short walks)
Control of individual food choice	- Individual food choice is variable, making it difficult to control all food sources in a diet (i.e., a person following an LCD may prioritize high or low glycemic index carbohydrates source; a person following an HFD may prioritize saturated or unsaturated fat)
Adherence	- Precise measurement of adherence to the assigned diet is a challenge creating possible errors to the result

HFD, high-fat diet; HPD, high-protein diet; LCD, low-carbohydrate diet

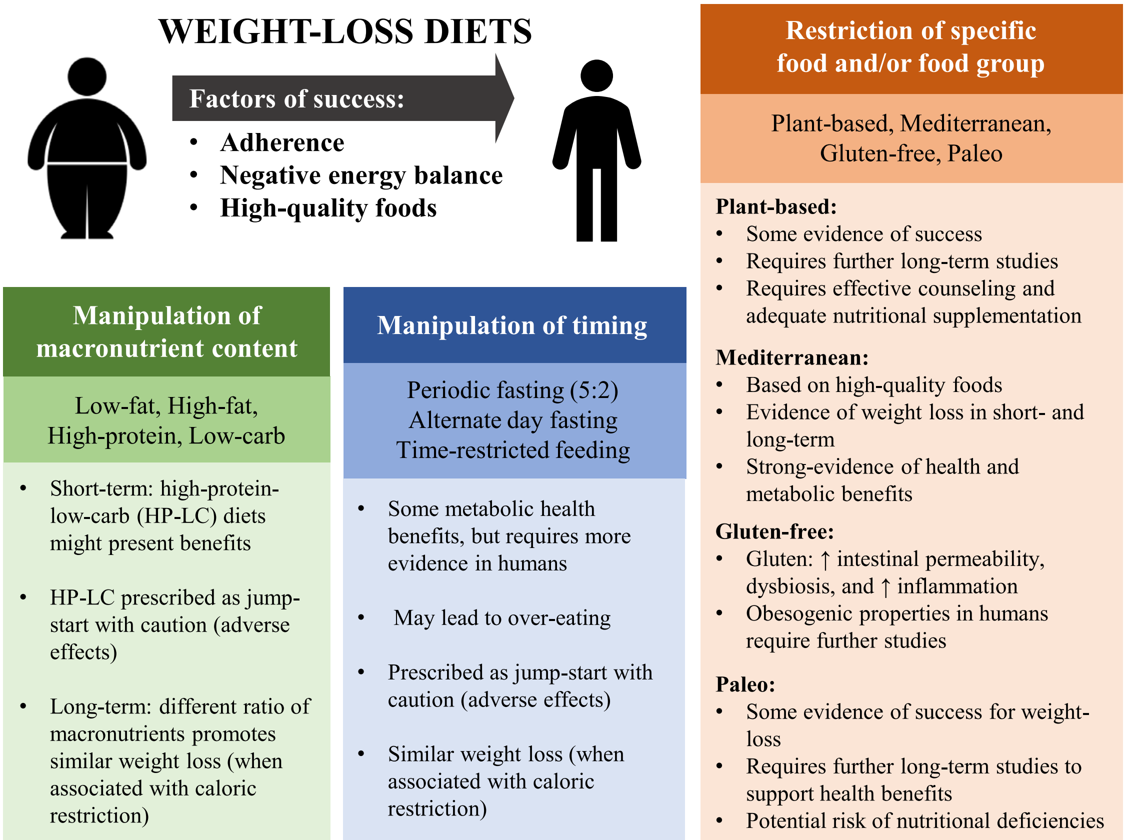

Fig. 3. Characteristics of diets for weight-loss. Diets were classified into three categories: diets based on the manipulation of macronutrient content (green), manipulation of timing (blue), and restriction of specific foods and/or food groups (orange). Scientific evidence concludes that there is no optimally effective diet to promote weight loss. The fundamental point to success is to adopt a diet that is based on high-quality foods, creates a negative energy balance, and promotes a good level of adherence. HP, high-protein; LC low-carbohydrate.

weight? How do different diets change hormonal secretion, gut microbiome composition, and gene expression? How do these changes regulate appetite and energy expenditure? In the future, further investigation into these factors (such as hormone profiles, gut microbiome composition, and genetics/epigenetics) might allow us to indicate the most successful diet for each individual.

Our our limited knowledge allows us to conclude that there is no optimally effective diet for all individuals to lose weight. In the short term, diets based on HP-LCcomposition or fasting might be considered as a jump-start. However, caution is required due to adverse effects. In the long term, diets, such as the Mediterranean diet, that prescribe high-quality foods should be encouraged. Finally, the fundamental point is to adopt a diet that creates a negative energy balance and is based on adequate food quality to promote health. Adherence will predict long-term success (Fig. 3).

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