Current Obesity Reports
https://doi.org/10.1007/s13679-021-00424-2

OBESITY TREATMENT (D BESSESEN, SECTION EDITOR)

Time-Restricted Eating, Intermittent Fasting, and Fasting-Mimicking Diets in Weight Loss

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Accepted: 7 January 2021

Abstract

Purpose of Review This article reviews the current literature on dietary interventions, including time-restricted eating (TRE), intermittent fasting (IF), and fasting-mimicking diets (FMD) and their effects on weight loss.

Recent Findings Dietary interventions, primarily known for their potential health benefits, are attracting considerable interest also for their effects on weight loss.

Summary The literature suggests that many popular diets can induce weight loss but only a limited number of studies actually demonstrate long-term weight loss efficacy. Here we present an update on the latest studies on some of the most popular dietary interventions able to trigger the physiology of fasting and highlight their impact on weight loss in overweight or obese individuals.

Keywords Obesity · Time-restricted eating · Intermittent fasting · Fasting-mimicking diet · Weight loss

Introduction

The number and prevalence of overweight and obese individuals is increasing globally [1]. According to data collected in 195 countries between 1995 and 2015, since 1980 the prevalence of obesity has doubled in almost a third of the countries and has continuously increased in most other countries. In 2015, the Global Burden of Disease study reported that a total of 107.7 million children and 603.7 million adults were obese. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been much greater compared to that in adult obesity [2].

High body mass index (BMI) in overweight and obese subjects is a major risk factor for many chronic pathologies, including cardiovascular diseases [3], kidney [4], and liver chronic diseases [5], diabetes [6, 7], cancers [8], and musculoskeletal disorders [9]. A BMI > 25 has been associated with 4 million deaths worldwide, more than 60% of which occurred among obese people (BMI > 30). Nearly 70% of the deaths related to high BMI were associated with cardiovascular disease. Among the factors contributing to the obesity increase are the greater availability of energy-dense foods and reduced physical activity. Due to the complexity of the food environment and difficulties in implementing the policies directed at combating the obesity pandemic in the different countries, most interventions have proven largely ineffective in reducing obesity rates [10]. These findings highlight the need for interventions that may function simultaneously as a preventive as well as a treatment strategy, aimed at reducing the prevalence of overweight or obese individuals and the associated disease burden.

Pharmacological interventions, such as orlistat or naltrexone/bupropion, can be effective in inducing weight loss [11], but can be associated with short-term adverse side effects, especially gastrointestinal distress, and are also likely to contribute to long-term side effects. Novel therapeutic strategies, focused primarily on dietary interventions, have gained scientific and public attention: time-restricted eating (TRE), intermittent fasting (IF), and periodic fasting/fasting-mimicking diet (FMD) have emerged as dietary modifications able to affect many of the pathologies associated with an elevated BMI [12]. Indeed, animals undergoing different types of

This article is part of the Topical Collection on *Obesity Treatment*

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Published online: 29 January 2021

fasting can live longer than those that eat every day while simultaneously promoting health benefits [13], including resistance to diabetes [14–16], cancers [17–19], and neurodegenerative disease [20–22]. Moreover, studies in rodents and humans receiving the FMD combined with standard cancer therapies have shown that these dietary interventions exert additive and possibly synergistic effects when combined with drugs [23]. The efficacy of these interventions could be based on very different mechanisms but is also likely to rely on common effects [24].

In this review we provide an overview over the latest studies using these dietary interventions, focusing our attention on their impact on weight loss (Table 1).

Time-Restricted Eating

Lifestyle choices, including exercise and healthy nutrition, have the greatest impact on body weight. The amount of food but also the timing when food is consumed plays an important role in body weight regulation. In a study by Arble et al., night-active mice fed a high-fat diet during the day gained significantly more weight than mice fed at night, in spite of both groups consuming equivalent amounts of calories and exhibiting similar levels of activity [25]. This finding has relevance to human weight management as well: in a cohort of 420 overweight/obese patients that participated in a 20-week weight-loss intervention, those study participants who ate their main meal late (lunch time after 15:00 h) lost significantly less weight than early eaters. The lack of significant differences in caloric intake, macronutrient distribution, or energy expenditure between late and early eaters pointed out the importance of the time of day when food is consumed [26]. Similar conclusions have been reported in a rodent study which adopted a TRE with a 8–10 h feeding window during the active phase [27], and human studies which either aligned the feeding window to the early to mid-part of the day [28–31] or allowed participants to self-select a window [32] as well as observations on the association between shift workers and increase in BMI and weight gain [33–35]. However, a recent clinical study concluded that the amount of calories consumed and not the time or range of feeding affects weight loss [36].

Thus, the efficiency of metabolic regulation and weight-loss can be affected by synchronizing feeding/fasting cycles with light/dark circadian rhythms [12] as energy homeostasis is maintained by the interaction of peripheral signals with the CNS and any disruption of the circadian rhythms impacts metabolic processes, such as body weight control [37]. In rodent models, restricting food access to the nocturnal phase, when they are more active, can promote natural feeding rhythms and restore synchrony with circadian oscillations and prevent obesity [27, 38, 39]. The circadian clock interacts with nutrient-sensing pathways as shown in several studies where time-restricted eating during the active phase restores cycling of metabolic regulators such as cAMP response element binding protein (CREB), mammalian target of Rapamycin protein (mTOR), and 5' AMP activated protein kinase (AMPK) as well as oscillations of circadian clock genes and their targets. In diet-induced models of obesity, these parameters are all dysregulated but can be normalized by time-restricted feeding during the active phase [25, 40]. Interestingly, mice on a high-fat diet become obese under ad libitum feeding conditions, while time-restricted feeding during the active phase prevents obesity despite similar calorie consumption [15]. Among the factors that influence the circadian rhythm, glucose appears to be a particularly potent entraining factor [41, 42].

Based on these considerations, in recent years TRE has emerged as a dietary intervention to maintain a consistent daily cycle of feeding and fasting to support circadian rhythms. TRE, particularly eating within 8 to 12 h, in rodent models and supported by largely observational studies in humans, has been shown to induce health benefits such as a reduction in fat mass, increased lean mass and reduction of inflammation, improved heart function with age, increased mitochondrial volume, ketone bodies production, and improved repair processes [39].

TRE may also improve body weight regulation by extending the duration of the fast, i.e., the duration between meals. Many studies have shown that overweight and obese adults without metabolic diseases, who habitually eat for more than 14 h, can achieve weight loss when adopting an 8–10-h interval of TRE over 12 weeks [32]. Notably, TRE plans differ in the restriction time window that allows meal consumption which could explain differences in the degree of effectiveness. Gabel et al. [28] examined the impact of time-restricted eating on body weight and metabolic disease in a cohort of 23 obese people. The intervention plan of 8-h time restricted eating (ad libitum feeding between 10:00 and 18:00 h, water fasting between 18:00 and 10:00 h) for 12 weeks decreased body weight by ~ 3% and reduced systolic blood pressure relative to a no-intervention historical control group. This degree of weight loss was comparable to the 3.5% reduction in body weight achieved in a 10-h time restricted feeding study for 16 weeks [32]. Furthermore, these results are similar to those obtained with the 4- to 8-h TRE trials by Moro et al. [43, 44] which resulted in ~ 1–3% body weight reductions after 8 weeks.

A pilot study on a small group ($N = 10$) of overweight sedentary old women and men who received an intervention of 16 h of fasting per day for 4 weeks resulted in a 2.6-kg reduction of mean body weight; however, it remains unclear if this weight loss relates to fat mass or lean body mass loss since the body composition was not measured [45]. No changes on cognitive and physical function, but an increase in walking speed were reported. Adverse events were reported by two study participants who experienced mild adverse events,

Table 1 Recent human studies reporting dietary interventions triggering the physiology of fasting

Intervention	Duration	Type of intervention	Study population	Number	Results	Reference
TRE	16 weeks	10–12-h time restriction	Overweight and obese	8	↓ BW: 3.5%	Gill S and Panda S, 2015 [32]
	8 weeks	8-h time restriction	Resistance trained	34	↓ FM: 2.8%	Moro T et al., 2016 [43]; Tinsley GM et al. 2017 [44]
	5 weeks	6-h time restriction	Prediabetics overweight and obese men	8	= BW	Sutton EF et al., 2018 [31]
	12 weeks	8-h time restriction	Overweight and obese	23	↓ BW: 5.2% good sleepers; 2% poor sleepers	Gabel K et al., 2018 [28]
	4 days	6-h time restriction	Overweight and obese	18	↓ BW	Ravussin E et al., 2019 [29]; Jamshed H, 2019 [30]
	4 weeks	8–10-h time restriction	Overweight and obese	10	↓ BW: 2.6 kg (2.2%)	Anton SD et al., 2019 [45]
	12 weeks	10-h time restriction	Overweight and obese	24	↓ BW: 3%; ↓ FM: 3%; ↓ WC: 4%	Wilkinson MJ et al., 2020 [46]
	12 weeks	8-h time restriction	Overweight and obese	20	↓ BW: 3.7%; ↓FM 4%; ↓ fat free mass: 3%; ↓ visceral fat: 11.1%	Chow LS et al., 2020 [48]
	8 weeks	4-h and 6-h time restriction	Obese	20 and 19	↓ BW: 3%; ↓ Insulin resistance; ↓ oxidative stress; ↓ energy intake	Cienfuegos S et al., 2020 [47]
FMD	3 months	Cycle of 5 days/month	Healthy subjects	38	↓ BW: 3.0%	Brandhorst S et al., 2015 [23]
	3 months	Cycle of 5 days/month	Healthy subjects	100	↓ BW: 3.4%	Wei M et al., 2017 [93]
IF 5:2 diet	12 weeks	1670–2500 kJ/day on fasting days	Type 2 diabetes mellitus and obese	63	↓ BW: 6.2%	Carter et al., 2016 [69]
	52 weeks	500–600 kcal/day on fasting days	Type 2 diabetes mellitus and obese	137	↓ BW: 6.8%	Carter et al., 2018 [70]
	104 weeks	Follow-up of Carter et al., 2018	Type 2 diabetes mellitus and obese	137	↓ BW: 3.86%	Carter et al., 2019 [62]
	12 weeks	2092–2510 kJ/day on fasting days	Type 2 diabetes mellitus and obese	41	↓ BW: 3.27%	Corley et al., 2018 [91]
	6 months	2710 kJ/day on fasting days	Obese	107	↓ BW: 7.8%	Harvie et al., 2011 [72]
	12 months	2100 kJ/day and 2520 kJ/day for women and men on fasting days, respectively.	Obese	146	↓ BW: 5.63%	Headland et al., 2019 [66]
	12 weeks	75% calorie restriction on fasting days	Overweight and obese	150	↓ BW: 7.1%	Schübel et al., 2018 [104]
	6 months	400–600 kcal/day on fasting days	Obese	112	↓ BW: 8.4%	Sundfør et al., 2018 [105]
	6 months	600 kcal/day on fasting days	Obese	24	↓ BW: 5.5%	Conley et al., 2018 [106]
IF ADF	12 weeks	75% calorie restriction on fasting days	Obese	64	↓ BW: 3.19%	Bhutani et al., 2013 [79]
	8 weeks + 24 weeks follow-up	zero-calorie ADF	Obese	25	↓ BW: 5.91%	Catenacci et al., 2016 [65]
	8 weeks	75% calorie restriction on fasting days	Overweight	31	↓ BW: 5.22%	Cho et al., 2019 [71]
	12 weeks		Obese	35	↓ BW: 12%	Coutinho et al., 2018 [86]

Table 1 (continued)

Intervention	Duration	Type of intervention	Study population	Number	Results	Reference
		550 and 660 kcal/day on fasting days; 3 days a week				
	8 weeks	1700–1800 kcal/day in every other days; 3 days a week	Overweight and obese	15	↓ BW: 7.11%	Eshghinia and Mohammadzadeh., 2013 [76]
	8 weeks	75% calorie restriction on fasting days; consumed either as Lunch (ADF-L), dinner (ADF-D) or small meals (ADF-SM)	Obese	74	ADF-L↓ BW: 3.8%, ADF-D↓ 4.2%, ADF-SM↓ 4.6%	Hoddy et al., 2014 [83]
	8 weeks	75% calorie restriction on fasting days	Obese	59	↓ BW: 4.06%	Hoddy et al., 2015 [89], Hoddy et al., 2016 [82]
	8 weeks	70% or 100% calorie restriction on fasting days; 3 days a week. 70% IF and 100% IF groups were provided 100% calories and 145% of baseline calories on feast days, respectively.	Obese	88	↓BW: 6.04%	Hutchison et al., 2019 [107]
	8 weeks	25% of their energy needs on the fasting days, and 125% of their energy needs on the feast days (24 h period); ADF-HF (45% fat) or ADF-LF diet (25% fat)	Obese	35	ADF-HF-↓ 4.8%, ADF-LF-↓ 4.2%	Klempel et al., 2013 [80]
	6 months + 6 months follow-up	25% of energy needs on fast days; 125% of energy needs on feast days	Obese	100	↓BW 6%	Trepanowski et al., 2017 [63]
	24 weeks	25% of energy needs on fast days; 125% of energy needs on feast days	Overweight and obese	100	↓ BW: 7.3%	Trepanowski et al., 2018 [73]
IF ADF	12 months	25% of energy needs on fast days; ad libitum on feast days	Overweight and obese	100	↓ BW: 6%	Kalam et al., 2019 [108]
	10 weeks	25% of energy needs on fast days; ad libitum on feast days	Obese	16	↓ BW: 5.8%	Varady et al., 2009 [78]
	12 weeks	25% of energy needs on fast days; ad libitum on feast days	Overweight and obese	60	↓ BW: 5.2%	Varady et al., 2011 [88]
	12 weeks	25% of energy needs on fast days; ad libitum on feast days	Healthy and overweight	32	↓ BW: 6.5%	Varady et al., 2013 [77]
	16 weeks	3 days 75% calorie restriction, 3 days CR and 1 day ad libitum	Obese	162	↓ BW: 10%	Bowen et al., 2018 [68]

BW, body weight; *FM*, fat mass; *WC*, waist circumference

including headaches and dizziness. Overall, TRE is reported as an acceptable and feasible eating plan for overweight subjects although these conclusions are limited by the small number of participants, the lack of a control group, and the absence of a dietary intake assessment.

Several human studies have been published in support of the efficacy of TRE in overweight people: Wilkinson et al. [46] evaluated the outcomes of TRE on 19 patients with metabolic syndrome who limited their calorie intake to a 10-h window. After 12 weeks of intervention, each patient improved in at least one of the metabolic syndrome criteria, including a reduction in waist circumference and in abdominal fat, and ~ 3% of weight loss compared to their baseline. Cienfuegos and colleagues [47] conducted a clinical trial to compare the effects of two popular forms of TRF (4 and 6 h) on body weight and cardiometabolic risk factors. Eight weeks of both TRE interventions resulted in comparable reductions in body weight (~ 3%), insulin resistance, and oxidative stress. Moreover, a small group of overweight participants (17 women and 3 men) following a 12-week TRE intervention program significantly reduced body weight (3.7%), fat mass (4%), lean mass (3.0%), and visceral fat (11.1%) [48].

Lastly, a recent meta-analysis of 19 randomized controlled trials showed that TRE significantly reduces body weight and fat and improves risk factors for cardiometabolic parameters in short-term interventions. More studies are required to confirm long-term effects on cardiovascular disease, type 2 diabetes, and mortality [49].

The gut microbiome provides an additional link between nutrition, TRE, and control of the body weight: nutrition plays an important role in gut microbiome modulation as different diets can modify the gut microbial composition. The microbiome population and their metabolites can have both beneficial and detrimental effects on host metabolism [50]. A misalignment in cellular metabolism in combination with nutrient quality and unfavorable gut microbiota composition may predispose to obesity and metabolic syndrome [24]. TRE may in turn coordinate the circadian rhythm between the host metabolism and gut microbiota. Zeb et al. [51] demonstrated that 16 h of TRE over 25 days can modulate the circadian gene expression profile and increases gut microbial diversity in humans by stimulation of Sirtuin 1 (Sirt1) [52–54]. These studies further establish a positive correlation between Sirt1 and *Prevotellaceae*, *Bacteroidia*, and *Dialister*. *Bacteroidia* are inversely correlated with LDL-cholesterol and triglyceride levels and exhibit an anti-obesity effect. Accordingly, a previous study suggested that the increased abundance of *Bacteroidetes* species is associated with weight loss in mice [55]. The abundance of these bacterial species in the intestine is positively or negatively associated with circadian rhythm, indicating an important role for the microbiome as an integrator of the effects of TRE.

Despite the promising outcome of TRE, its success could be compromised by adherence difficulties. In the study by Gill and Panda, all the participants reduced their eating duration, but the number of days that participants adhered to their eating windows is not known. Interestingly, all study participants expressed an interest in continuing the TRE regimen after the conclusion of the study. In contrast, in the Antoni et al. [56] study, participants rated the regimen difficult to follow, and 57% felt unable to maintain the TRE protocol beyond the 10-week intervention.

It is also important to point out that TRE could result in skipping breakfast by an extending the morning fast. Skipping breakfast, associated with low fiber intake in diet, may diminish gallbladder motility and/or changes in the bile composition, both of which increase the risk of gallstone formation and hospitalization, as emerged in the first National Health and Nutrition Examination Survey (NHANES I) [57]. Moreover, a prospective cohort study of a representative sample of American adults showed that skipping breakfast was associated with an increased risk of mortality from cardiovascular diseases [58]. For these reasons, skipping breakfast is strongly discouraged and in the perspective of a restricted time of eating plan needs to be considered and should be avoided.

In summary, while limited data from short-term trials suggest that TRE appears to promote weight loss similarly to daily caloric restriction, it may be a difficult intervention to adhere to long-term and may interfere with lifestyle choices and/or work hours such as for shift workers. Furthermore, in order to determine the effect of TRE on body weight and other metabolic disease variables, future longer-term trials with larger numbers of subjects will be needed to determine the degree of weight loss that can be achieved and sustained.

Intermittent Fasting

Intermittent fasting (IF) has been in the focus of lay people and scientists alike in recent years with many animal studies pointing towards weight loss benefits and overall health improvements in mice maintained on IF regimens [12, 59, 60]. Recently, clinical trials have demonstrated that at least some of the effects of intermittent fasting observed in animal models may translate to human health benefits. With the availability of various fasting regimens, it has become important to identify which approach is most effective and which group of individuals is likely to be most responsive [61–73]. Here, we will discuss recent clinical trials of different IF approaches and their effectiveness for weight loss. Three major types of IF plans have been tested in clinical trials: 0% alternate day fasting (0% ADF, no caloric food is allowed on alternate days), 25% alternate day fasting (25% ADF, ~ 25% of usual caloric requirement is allowed on fasting days), 5:2 fasting (low calorie or zero calorie food is allowed for 2 days a week,

ad libitum food can be consumed on the remaining 5 days of the week) [74].

Alternate Day Fasting In a mouse model of diet-induced obesity, mice lose a significant amount of weight when either fed a high-fat diet (HF) or a low-fat diet (LF) is given in combination with ADF. Mice on low-fat ADF had the lowest fat mass and highest lean mass after a 4-week intervention compared to groups fed on HF ad libitum, HF-AFD, or LF ad libitum [60]. Mice on the ADF diet had a 12% extension in lifespan and had consistently lower body weight throughout life compared to ad libitum fed mice (an average of ~ 17.1% less) [75]. The majority of published human trials employed a 25% ADF, where one low-calorie meal is allowed on fasting days. Ten out of 10 clinical trials with 25% ADF intervention consisting of 15–100 subjects and duration ranging from 6 to 12 weeks (except Trepanowski et al. [63] which was for 52 weeks) reported weight loss [74] with 5 studies reporting a clinically significant weight loss of >5 kg [63, 65, 76–78], and a weight loss of >3 kg in the remaining studies [79–83]. The effects on lean mass preservation were not conclusive with three studies reporting a significant reduction [65, 82, 83], and four reporting non-significant reductions [63, 77–79], while one study reported a non-significant trend for increased lean body mass [80]. Lean body mass was not measured in the remaining two studies [76, 81]. In a case report to evaluate ADF as an alternative therapy to insulin for type 2 diabetes, 3 out of 3 patients discontinued insulin after days 5, 13, and 18 respectively. The three patients followed ADF for 7–11 months and were able to lose 9.8 kg of weight on average; in addition, two out of three patients discontinued all diabetic medication at the end of this intervention [84].

In order to evaluate the effect of ADF on weight loss and further weight maintenance and to compare the benefits to daily caloric restriction (DCR), Trepanowski et al. [63] conducted a randomized clinical trial on 100 metabolically healthy obese adults with a mean BMI of 34 kg/m^2. The participants followed 6 months of weight loss diet wherein the ADF group consumed 25% of their estimated baseline energy intake on fast days and 125% on feast days, the DCR group consumed 75% of baseline energy intake on all days. This was followed by a 6-month weight maintenance period where the ADF group was instructed to eat 50% on fast days and 150% on feast days and the DCR group were instructed to eat 100% of their daily energy needs. Similar weight loss was observed in both ADF and CR groups at the end of the weight-loss period (6-month: − 6.8% vs. − 6.8%) and maintenance period (12-month: − 6.0% vs. − 5.3%). Fat mass, lean mass, blood pressure, heart rate, cholesterol, triglycerides, fasting glucose, fasting insulin, insulin resistance, and C-reactive protein showed improvement in both the groups, but measurements did not show any significant differences between the groups at either 6-month or 12-month. Notably, participants in the ADF group ate more (~ 800–1000 kcal instead of the recommended 400–500 kcal) on fast days and less (~ 1400 kcal instead of the recommended ~ 2100 kcal) on feast days than prescribed, while participants in the DCR group met their recommended energy goals. The dropout rate was higher in the ADF group (38%), than in the DCR group (29%) or the control group (26%) [63]; an initially surprising finding since ADF requires participants to restrict calorie intake only on defined days which was thought to be potentially more achievable and have higher levels of adherence than DCR [85]. A number of other studies have observed similar effects: while ADF is an efficient intervention for weight loss, it is not significantly better than DCR in terms of weight loss, as well as the majority of the other health parameters measured [63, 65, 68, 71, 77, 86].

5:2 Fasting *5:2* Dieting is a more popular form of intermittent fasting in which calorie intake is restricted to ~ 25% of the baseline energy intake twice a week [64]. In a 6-month randomized clinical trial of 107 overweight or obese premenopausal women (BMI 30.6 ± 5.1 kg/m^2) to quantify the effects of 5:2 dieting as compared to DCR [72], the 5:2 diet and DCR were equally effective in producing weight loss (5:2 group vs. DCR group reported average weight loss of 6.4 kg and 5.6 kg, respectively). Another study aimed at comparing 5:2 diet with DCR found no statistically significant difference in the time to achieve a 5% loss in body weight between the groups (median time of 59 days for 5:2 diet group vs. 79 days for DCR group) [67].

In a long-term study to evaluate glycemic control and weight loss in patients with type 2 diabetes over a 12-month period, 137 participants were randomized into either a 5:2 strategy ($n = 70$, 500–600 kcal/day for 2 non-consecutive days every week and normal diet for rest 5 days) or DCR ($n = 67$, 1200–1500 kcal/day for all 7 days a week) [70]. Weight loss in both groups was significant with the 5:2 diet group losing 5.0 kg vs. 6.8 kg in the DCR group, but there was no significant difference between the groups. Interestingly, subjects in both study arms lost most of the body weight in the first 3 months of the study and then maintained it for the rest of the study period. Mean weight loss between 3 and 12 months in the DCR group was 0.4 kg and 0.2 kg in 5:2 group. This is in line with the results from a pilot study where similar weight loss was observed during a 3-month study period [69]. A follow-up study of the same study published at the end of a 24-month observation period demonstrated that both groups maintained some of the lost weight (3.9 kg lower than the study's baseline). In fact, participants in both the 5:2 group and the DCR group regained the lost weight (DCR and 5:2 group regained 22% and 42.6% of the lost weight, respectively) between 12 and 24 months [62]. Notably, during this follow-up period, subjects in the 5:2 group lost more fat-free mass (loss of 0.8 kg and 2.2 kg in DCR and 5:2 group, respectively) than the DCR group at 24 months [62]. This contradicts a previous review reporting better conservation of fat-

free mass with a 5:2 diet as compared to DCR [87]. This difference could be partly explained by the length of the dietary interventions in the studies: trials by Varady and others [72, 78, 79, 88] were generally of shorter duration (up to 6 months) whereas the trial by Carter et al. [62] followed the participants for 24 months.

Although no major adverse effects of intermittent fasting have been reported, common complaints associated with this dietary intervention include the following: feeling cold, headaches, lack of energy, and occasional dizziness [72, 89]. Intermittent fasting is safe for most individuals, but it would be difficult to recommend for patients with type 2 diabetes using insulin/sulfonylureas medication due to the risk of hypoglycemia [90]. The risk of a hypoglycemic event is two-times higher on fasting days as compared to non-fasting days [91]. Therefore, ADF or 5:2 fasting requires close monitoring by trained medical professionals and the careful adjustment of glucose lowering medications to avoid severe adverse events in people with type 2 diabetes [69].

Fasting Mimicking Diet

Periodic fasting describes periods of water-only fasting, or very low-calorie diets, for 2 or more days separated from the next cycle by at least 1 week [12]. Water-only or similar therapeutic fasting induces many metabolic health benefits, but it must be done in specialized clinics since it is associated with rapid weight loss, and the risk of malnourishment, hypoglycemia, and hypotension if done outside of a clinic [92]. For these reasons it is normally carried out for periods lasting from 1 week to several weeks once a year in specialized clinic. To overcome the side-effects and safety concerns associated with water-only fasting done outside specialized clinics, a plant-based fasting-mimicking diet (FMD) was developed [23]. The FMD is low in protein and sugar, but relatively high in fat content. Differently from the therapeutic fasting done for longer periods once a year or less, the FMD was developed to be used in periodic cycles from every 2 weeks to every several months and to last from 4 to 7 days for humans and 2 to 5 days for mice. The 5-day human FMD provides approximately 55% of the recommended daily calorie intake on day 1 and 35% on the subsequent days 2–5. Studies in mice, as well as a randomized clinical trial on generally healthy human subjects, highlight the beneficial effects of FMD cycles on aging and disease markers and risk factors. In mice, the FMD extends median lifespan, reduces inflammation and cancer incidence, enhances cognitive performance, and improves overall health [22, 23, 93–95].

The efficacy of the FMD in reducing body weight in humans was first tested in a pilot study conducted on 38 generally healthy human subjects randomized either to the FMD for 5 days every month for 3 months (3 cycles) or to a control group in which study subjects continued to consume their normal diet. In the FMD group, the body weight was reduced by 3.1% but the relative lean body mass (adjusted for body weight) was increased after three FMD cycles [23]. These pilot study results were confirmed in a larger randomized clinical trial to evaluate the effects of the FMD on risk factors for metabolic syndrome, cardiovascular diseases, cancer, and aging. The randomized cross-over study included 100 generally healthy participants which completed three cycles of 5 days of FMD per month for 3 months compared to a control arm during which subjects consumed an unrestricted diet. In the 71 subjects who completed the FMD cycles, a reduction in body weight, waist circumstance, and BMI was observed. In a post hoc analysis, the FMD was more effective on elevated markers in at-risk participants than in those who had risk factors values within the normal range at baseline: subjects with a BMI of greater than 30 (obese) experienced a greater reduction in BMI by the end of the three FMD cycles than those with a BMI of less than 25 (normal weight) and BMI of 25 to 30 (overweight) [93]. Adverse events reported in this study, including mild and moderate fatigue and weakness, demonstrate that the FMD can be considered safe and feasible.

Obesity is characterized by the presence of chronic inflammation and dysregulation of host-microbiota relationship which affects adiposity and weight-gain through several pathways [96–99]. Epidemiological analysis reporting cross-sectional studies in patients with inflammatory bowel disease (IBD) showed that about 15–40% of adults with IBD are obese, and 20–40% are overweight, and that obesity might contribute to the pathogenesis of IBD through mucosal barrier dysfunction with bacterial translocation and resulting activation of adipocytes [100]. In a dextran sodium sulfate (DSS)–induced mouse model of IBD, periodic FMD cycles reduce systemic and intestinal inflammation, and stimulate the enrichment in microbial populations and reversion of intestinal pathology caused by DSS [95]. In this mouse model, the FMD induces an increase in protective *Lactobacillaceae*, *Bifidobacteriaceea*, and *Allobaculum* microbial genus belonging to the *Erysipelotrichaceae* family, associated with protection from obesity and insulin resistance [101, 102]. In comparison, water-only fasting reduces inflammatory markers but without reversing IBD pathology. These studies indicate that the nutritional composition of the FMD itself, and not just the calorie restriction associated with it, is a key regulator of microbial and anti-inflammatory changes [95]. However, despite the promising results, further preclinical and clinical studies are necessary to clarify the effect of FMD on the gut and related diseases, as well as diabetes and other degenerative diseases. In fact, in mouse models of type 2 and type 1 diabetes, FMD cycles have shown to modulate b cell regeneration, and promote insulin secretion and glucose homeostasis confirming the potential of FMD in the treatment of metabolic dysfunctions related to obesity [16].

Conclusions

Dietary interventions involving some form of fasting have emerged as potential therapeutic regimes for the prevention of a wide range of pathologies, including metabolic diseases, cardiovascular diseases, cancer, neurodegenerative diseases, and obesity. However, long-term studies, including randomized controlled trials with a follow-up of more than 1 year, are needed in order to confirm their lasting effects on health and how to address compliance. While animal studies and some clinical trials can control food intake patterns, having a set time window to consume food may remain very challenging for humans. A meta-analysis conducted on 121 randomized studies including 21,942 overweight and obese patients compared the efficacy of popular chronic dietary interventions on weight loss and improvements in cardiovascular risk factors [103]. These diets showed that after 6 and 12 months the differences in weight loss achieved were modest and were in 100% unsuccessful in terms of weight reduction maintenance at the 12 months follow-up. In long term, only the Mediterranean diet has shown to maintain the improvements in cardiovascular risk factors. Taken together, despite the potential capability of each diet to be effective in reducing body weight, the choice of a weight loss plan should be based on the ability of each patient to adhere to it. However, the extreme difficulty of adhering to a chronic dietary program, including IF and TRE, inevitably directs our attention to the development of interventions with a high efficacy based on short-term intervention periods to have long-term success.

Compliance with Ethical Standards

Conflict of Interest V.D.L. has equity interest in L-Nutra, a company that develops medical food. V.D.L. and S.B. have filed patents related to the FMD at the University of Southern California (USC). The University of Southern California has licensed intellectual property to L-Nutra. As part of this license agreement, the University has the potential to receive royalty payments from L-Nutra.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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