



Intermittent Fasting: Is the Wait Worth the Weight?

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Abstract

Purpose of Review We review the underlying mechanisms and potential benefits of intermittent fasting (IF) from animal models and recent clinical trials.

Recent Findings Numerous variations of IF exist, and study protocols vary greatly in their interpretations of this weight loss trend. Most human IF studies result in minimal weight loss and marginal improvements in metabolic biomarkers, though outcomes vary. Some animal models have found that IF reduces oxidative stress, improves cognition, and delays aging. Additionally, IF has anti-inflammatory effects, promotes autophagy, and benefits the gut microbiome. The benefit-to-harm ratio varies by model, IF protocol, age at initiation, and duration.

Summary We provide an integrated perspective on potential benefits of IF as well as key areas for future investigation. In clinical trials, caloric restriction and IF result in similar degrees of weight loss and improvement in insulin sensitivity. Although these data suggest that IF may be a promising weight loss method, IF trials have been of moderate sample size and limited duration. More rigorous research is needed.

Keywords Intermittent fasting · Fasting · Obesity · Calorie restriction · Metabolism · Insulin resistance · Weight loss

Abbreviations

IF	Intermittent fasting
CR	Calorie restriction
ICR	Intermittent calorie restriction
ER	Energy restriction
TRF	Time-restricted feeding
PF	Prolonged fasting
ADER	Alternate-day energy restriction

CER	Continuous energy restriction
RCT	Randomized controlled trial
GIR	Glucose infusion rate
Si	Insulin sensitivity
ROS	Reactive oxygen species
ad lib	Ad libitum

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Introduction

With more than two in three adults suffering with overweight or obesity, Americans are searching for effective weight loss methods [1]. Fasting, called “the next big weight loss fad” [2], has long been integral to many religious and ethnic cultures [3]. Intermittent fasting (IF) has many forms (Table 1); the basic premise involves taking periodic breaks from eating. Common forms of IF include fasting for up to 24 h once or twice a week with ad libitum (ad lib) food intake for the remaining days, which is known as periodic prolonged fasting (PF) or intermittent calorie restriction (ICR) [4•]; time-restricted feeding (TRF), such as eating for only 8 h then fasting for the other 16 h of the day; and alternate-day fasting (ADF) [5, 6]. Most ADF programs involve alternating feast (ad lib intake) and fast days ($\leq 25\%$ of energy needs) with some protocols allowing no caloric intake on fast days [4•].

Table 1 Comparison of different types of intermittent fasting

Type of IF	Description	Metabolic states involved
Alternate day fasting	Alternating feast (ad lib intake) and fast days ($\leq 25\%$ of energy needs)	Fed, post-absorptive, fasting (short duration, likely <36 h between meals)
Time-restricted fasting	Eating only during certain time periods (i.e., 8 h), then fasting for remaining hours of the day	Fed, post-absorptive (maximum duration between meals is usually <16 h)
Periodic fasting	Fasting for up to 24 h once or twice a week with ad lib intake on the remaining days	Fed, post-absorptive, fasting (up to 48 h between meals depending on whether fast days are consecutive)

Thus, the degree of fasting varies in ADF based on the specific protocol.

IF continues to gain attention with new evidence from basic science research and clinical trials. This paper reviews these developments. First, we provide an overview of the key aspects of metabolism involved in fasting. Next, we review clinical trial data of IF outcomes including changes in weight loss and body composition, insulin sensitivity (Si), cardiovascular biomarkers, aging and cognition, psychosocial factors, and the gut microbiome. We review potential cellular mechanisms for these effects including modulation of oxidative stress, inflammation, and autophagy. Finally, we assess the clinical implications of these results and identify directions for future research.

Methods

We searched PubMed/MEDLINE and clinicaltrials.gov for relevant clinical trials and animal studies in English with the search terms: intermittent fasting, periodic, time-restricted, adipose, alternate-day fasting, ADF, and obesity, from 1970 to 2018. We reviewed references from key papers to identify additional articles. Reviews are cited to provide readers with more details and references than is possible here.

In order to provide depth in this review, studies were mostly limited to those on ADF and modified ADF. While TRF is another branch of IF, TRF-only studies were excluded from this review due to their variability, particularly in regard to the definition of TRF and whether breakfast- or dinner-skipping are considered types of TRF. Additionally, this review excludes papers on fasting-mimicking diets (FMD), as we consider most FMD protocols to fall under the category of very low-calorie diets (VLCD). Lastly, we excluded studies that focused on comorbidities of obesity, such as type 2 diabetes

(T2D), as these comorbidities add complexity beyond the scope of this paper. We focused on pertinent publications from the last 5 years that meet these criteria, but did not exclude older, high-impact papers.

Overview of Human Metabolism: the Fed-Fast Cycle

Glucose is the primary energy source for most tissues during the day. Fatty acids (FA) represent an alternative fuel source for the most metabolically active organs including the muscle, liver, and brain and rise overnight during fasting. In 1963, Randle proposed a theory of energy metabolism during feeding and fasting known as the “glucose-fatty acid cycle” whereby glucose and FA compete for oxidation [7]. Since 1963, this cycle and its underlying mechanisms have been elucidated [8]. The fed-fast cycle has four stages: the fed state, the post-absorptive or early fasting state, the fasting state, and the starvation or long-term fast state (Fig. 1) [9].

The Fed-Fast Cycle, Circadian Rhythmicity of FFA, and Intermittent Fasting

The circadian clock regulates gene expression and broadly affects various organs and the network of neurohormonal weight control signals [16]. Overnight fasting, or fasting during sleeping hours, is associated with a nocturnal rise in plasma free fatty acids (FFA), ghrelin, growth hormone, and increased hepatic gluconeogenesis [17]. Adipose tissue (AT) orchestrates the cycling of triglycerides (TG) by controlling the uptake, esterification, and release of FFA to meet the metabolic demands of the liver and muscle tissue. Hence, integration of circadian rhythms and eating may be beneficial.

The Effects of Intermittent Fasting

The following sections summarize the current literature on various effects of IF.

Alterations in Weight and Body Composition

Nearly all IF studies have resulted in some degree of weight loss, ranging from 2.5–9.9% [18, 19], and associated fat mass loss. Numerous studies have been conducted on IF (Table 2), but IF protocol, duration, and baseline characteristics of the sample population have varied greatly.

The literature distinguishes between ADF and ICR regimens. Heilbronn et al. evaluated 22 days of ADF (0% intake on fast days, ad lib feast days) in 16 healthy subjects with

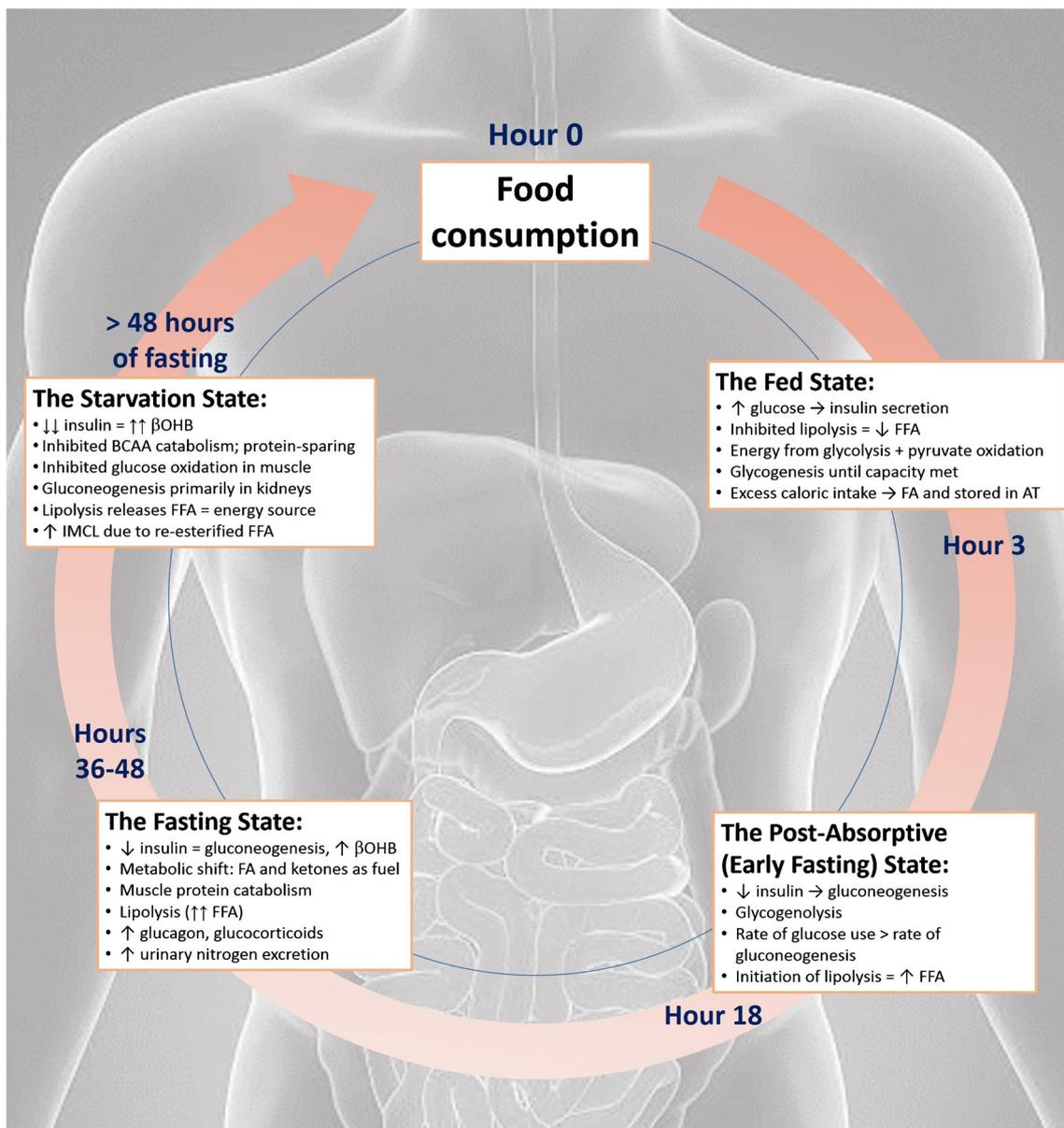


Fig. 1 The fed-fast cycle [9–14, 15]. The four stages of the fed-fast cycle. Only the fed and post-absorptive states are relevant to normal eating routines. Based on the IF regimen, an individual often goes

through the fed, post-absorptive, and fasting states. Additionally, while the figure is cyclic, it is possible to return to the food consumption point at any time

normal BMI [18]. ADF resulted in minor weight loss (2.5%), fat loss (4%), and increased fat oxidation [18]. In contrast, Eshghinia and Mohammadzadeh evaluated 6 weeks of ADF (very low-calorie diet (VLCD) on fast days, ad lib feast days) in women with overweight or obesity [33]. ADF led to 7.1% weight loss and visceral fat mass loss (5.7%). Another study assessed the effects of 8 weeks of ADF with either a high- or low-fat diet in 32 women with obesity [34]. Weight, fat mass, and waist circumference decreased similarly in both groups.

When comparing ADF to no-intervention control, ADF resulted in 6.5% weight loss relative to the control group [5]. However, dietary satisfaction is also important to consider

when evaluating weight loss methods. In the same study, hunger did not change in either group, but satisfaction and fullness increased in the ADF group only [5]. This is of particular clinical significance, as diets are often not sustainable due to dissatisfaction with dietary restrictions.

An RCT comparing ADF, CR, and no-intervention control found that mean weight loss was not significantly different at 6 or 12 months between ADF and CR, but dropout rate was significantly higher in the ADF group [23••]. Mean LDL cholesterol levels were significantly elevated (+ 11.5 mg/dL [95%CI, 1.9–21.1 mg/dL]) in the ADF group at month 12 compared to the CR group. A

Table 2 This table highlights adult human RCTs studies that meet the following criteria: published between 2003 and 2018; IF evaluated as primary variable; IF regimen greater than 1 week. TRF and PF studies were excluded due to the scope of this paper. The studies are ordered by highest *N* and longest duration

First author, Year ^{a,b}	Study population	Study design		Key results
		Groups and characteristics (<i>N</i> , mAge ^d , BMI ^e)	IF regimen	
Harvie 2013 [20]	<i>N</i> = 115 Women only Age 20–69 BMI 24.0–45.0 and/or body fat >30% DR 11% in ICR group; 26% in ICR + PF and 33% in DER	ICR (<i>n</i> = 37, 45.6 ± 8.3, 29.6 ± 4.1) ICR + PF (<i>n</i> = 38, 48.6 ± 7.3, 31.0 ± 5.7) CER (<i>n</i> = 40, 47.9 ± 7.7, 32.2 ± 5.6)	25% energy needs ⁴ restricted in all, energetic groups ICR without ad lib protein, fat: CR and carb restriction on 2 consecutive d/wk ICR + protein, fat (ICR + PF): same as ICR but with unlimited protein and fat on restricted days CER: daily 25% CR	<ul style="list-style-type: none"> • ↓ weight, body fat in ICR > CER groups • ↑ Si with both ICR • Less FFM loss in ICR groups • Short term: ICR superior to CER re: Si and ↓ body fat
Harvie 2011 [21]	<i>N</i> = 107 Women only Age 30–45 BMI 24.0–40.0 DR 21% in ICR group; 13% in CER group	ICR (<i>n</i> = 53, 40.1 ± 4.1, 30.7 ± 5.0) CER (<i>n</i> = 54, 40.0 ± 3.9, 30.5 ± 5.2)	25% energy restriction ⁴ as ICR (2 d/wk) or CER (7 d/wk)	<ul style="list-style-type: none"> • ICR and CER equally effective for weight loss • Comparable ↓ leptin, free androgen index, RP; total and LDL cholesterol, TG, BP + ↑ sex hormone binding globulin • Modest ↓ in Si, fasting insulin—greater in ICR • ↓ weight in combo, ADF, exercise groups • ↓ LDL, fat mass, waist circumference; ↑ HDL in combo only
Bhutani 2013 [22]	<i>N</i> = 83 80 F/3 M Age 25–65 BMI 30.0–39.9 DR: 9 dropped out of ADF, 8 out of exercise. No dropouts in exercise or control groups.	ADF + exercise (combo, <i>n</i> = 18, 45 ± 5, 35 ± 1) ADF (<i>n</i> = 25, 42 ± 2 yo) Exercise (<i>n</i> = 24, 42 ± 2, 35 ± 1) Control (<i>n</i> = 16, 49 ± 2, 35 ± 1)	ADF: 25% energy needs ² fast day, ad lib feast day Exercise: moderate intensity exercise 3 d/wk	<ul style="list-style-type: none"> • ↓ weight (−6.8% in ADF and CR at 6 months, 6.0% in ADF and 5.3% in CR at 12 months) • ↑ HDL in ADF at month 6, not at month 12 • ↑ LDL in ADF at month 12 • NS differences between groups in BP, heart rate, TG, fasting glucose, fasting insulin, Si, CRP, or homocysteine
Trepanowski 2017a [23••]	<i>N</i> = 79 66 F/13 M Age 18–65 BMI 25.0–39.9 DR: 38% in ADF, 29% in CR, 26% in control	ADF (<i>n</i> = 25, 46 ± 2, 34 ± 1) CR (<i>n</i> = 29, 44 ± 2, 35 ± 1) Control (<i>n</i> = 25, 44 ± 2, 34 ± 1)	ADF: 25% energy needs ¹ on fast days, 125% feast day with dietary counseling for the first 12 wk CR: 75% needs ¹ daily + dietary counseling for the first 12 wk only Control: 100% needs daily; no intervention	<ul style="list-style-type: none"> • ↓ weight (−6.8% in ADF and CR at 6 months, 6.0% in ADF and 5.3% in CR at 12 months) • ↑ HDL in ADF at month 6, not at month 12 • ↑ LDL in ADF at month 12 • NS differences between groups in BP, heart rate, TG, fasting glucose, fasting insulin, Si, CRP, or homocysteine • ↑ FFM:total mass ratio in ADF and CR (NS difference) • ↓ leptin in ADF and CR (NS difference) • No change in circulating adiponectin, resistin, IL-6, or TNF=α in any group
Trepanowski 2017b [24]	See Trepanowski, 2017a [23••]	See Trepanowski, 2017a [23••]	See Trepanowski, 2017a [23••]	<ul style="list-style-type: none"> • Only the first 28 weeks of Trepanowski, 2017a [23••]
Trepanowski 2017a [23••]	See Trepanowski, 2017a [23••]	See Trepanowski, 2017a [23••]	See Trepanowski, 2017a [23••]	<ul style="list-style-type: none"> • Only the first 28 weeks of Trepanowski, 2017a [23••]

Table 2 (continued)

First author, Year ^{a,b}	Study population	Groups and characteristics (N, mAge ^d , bBMI ^e)	Study design	Duration	Key results
Teng 2013 [25]	N = 56 Men only Age 50–70 BMI 23.0–29.9 DR: NR	ICR (n = 28, 59.6 ± 5.4, 26.8 ± 1.7) Control (n = 28, 59.1 ± 6.2, 26.7 ± 2.3)	IF regimen ICR: 300–500 kcal/d deficit with 2 d/wk. Muslim Sunnah fasting. Fasting day included light meal before sunrise, no food and drink during the day (~ 13 h) and complete meal after sunset Control	3 mon	<ul style="list-style-type: none"> ↓ weight, %fat, energy intake, fat intake, BP, LDL, total cholesterol in ICR ↓ damage of DNA cells in ICR ↑ fat intake in control • Maintained or ↑ weight, BMI, %fat in control group • ↓ weight, fat mass to greater degree in ICR • ↓ REE greater in ICR after adjusting for changes in body composition
Byrne 2017 [19•]	N = 51 Men only Age 25–54 BMI 30.0–45.0 DR: NR	ICR (n = 26, 39.9 ± 9.2, 34.6 ± 4.2) CER (n = 25, 39.3 ± 6.6, 34.4 ± 3.3)	During ER weeks, 67% energy needs ³ for weight maintenance	32 wk Interspersed: 8 × 2-wk blocks of CR and 7 × 2-week blocks of energy balance	<ul style="list-style-type: none"> • ↓ weight in ADF, CR, exercise groups • ↓ LDL in ADF and CR only; ↑ HDL in exercise only
Varady 2011 [26]	N = 49 40 F/9 M Age 35–65 BMI 25.0–39.9 DR: NR	ADF (n = 13, 47 ± 2, 32 ± 2) CR (n = 12, 47 ± 3, 32 ± 2) Exercise (n = 12, 46 ± 3, 33 ± 1) Control (n = 12, 46 ± 3, 32 ± 2)	ADF: 75% energy needs ² on fast days, ad lib feast days CR: 75% energy needs ² daily Exercise: moderate intensity 3 d/wk Control: usual	12 wk	<ul style="list-style-type: none"> • ↓ weight, waist and hip circumference (NS difference between groups) • ↑ Healthy Eating Index at 12 mon in CER only
Keogh 2014 [27]	N = 36 Women only Age ≥ 18 BMI ≥ 27.0 Healthy or T2D managed by diet alone DR: 40% in first 8 wk, 20% between 8 and 52 wk	ICR (n = 19, 59.5 ± 8.7, 33.1 ± 3.8) CER (n = 17, 60.8 ± 12.5, 33.0 ± 7.5)	ICR: 1-week 'normal' diet followed by 1-wk CR (5500 kJ) CER: every day CR (5500 kJ)	8-wk weight loss intervention, 12-wk weight loss maintenance	<ul style="list-style-type: none"> • ↓ anger, tension, confusion, weight, BMI, body fat in IF group • NS changes in mean depression scores
Hussin 2013 [28]	N = 31 Males only Age 50–70 BMI 23.0–29.9 DR: 0 subjects in ADF, 1 in control	FCR (n = 16, 59.7 ± 6.6, 26.7 ± 1.8) Control (n = 15, 59.7 ± 6.2, 26.8 ± 2.6)	IF: 300–500 kcal/d reduction from baseline ⁶ + 2 d/wk of Muslim Sunnah fasting; with counseling Control: ad lib, no counseling	3 mon	<ul style="list-style-type: none"> • ↓ weight, fat mass, TG, leptin in ADF • ↑ adiponectin, LDL particle size in ADF • Unchanged LDL, HDL, homocysteine, resistin • ↓ weight, BMI, body fat %, depression in ICR
Varady 2013 [29]	N = 30 22F/8M Age 35–65 BMI 20.0–29.9 DR: 6.2% (2 of 32)	ADF (n = 15, 47 ± 3, 26 ± 1) Control (n = 15, 48 ± 2, 26 ± 1)	ADF: 25% energy needs ² on fast day (meals provided), ad lib feast day Control: ad lib daily	12 wk	<ul style="list-style-type: none"> • ↓ weight, fat mass, TG, leptin in ADF • ↑ adiponectin, LDL particle size in ADF • Unchanged LDL, HDL, homocysteine, resistin • ↓ weight, BMI, body fat %, depression in ICR
Teng 2011 [30]	N = 25 Men only	FCR (n = 12, 59.3 ± 3.4, 27.0 ± 1.7a)	Control: ad lib daily	3 mon	<ul style="list-style-type: none"> • ↓ weight, BMI, body fat %, depression in ICR

Table 2 (continued)

First author, Year ^{a,b}	Study population	Groups and characteristics (N, mAge ^d , bBMI ^e)	Study design	Duration	Key results
	N completers (female/male), inclusion criteria ^c , dropout rate (DR)		IF regimen		
Catenacci 2016 [31]•	Age 50–70 BMI 23.0–29.9 DR: 14% (4 of 28)	Control (n = 13, 58.3 ± 6.3, 26.5 ± 1.8)	ICR: –300 to –500 kcal/day +2 days of fasting/wk for 3-mon period Control: no intervention ADF: 0% energy needs ⁵ on fast day, ad lib feast day Control: 400 kcal/d deficit	8-wk intervention 24-wk follow-up	• ↑ energy component of QOL in ICR • ↓ weight in both groups, NS difference • ADF group regained more FFM and CR group regained more FM (NS)
Harder-Lauridsen 2017 [32]	N = 25 19 F/6 M Age 18–55 BMI: ≥ 30.0 DR: 7 withdrew prior to randomization; all 25 completed intervention Males only Age ≥ 18 BMI 18.5–2.05 DR: 10% in ADF, 0 in control	ADF (n = 10, 23 ± 3.6, NR) Control (n = 10, 24 ± 1.8, NR)	While on bed rest ADF: 25% energy needs ² on fast days (1 meal/d), 175% needs on feast days (4 meals/d) Control: 100% needs ² (3 meals/d)	8 days	• NS differences in weight, body composition, biomarkers, or glycemic control • ↓ systolic blood pressure in ADF • ↓ FFM in both groups

Abbreviations: N (sample size of completers), F (females), M (males), mAge (mean age), bBMI (baseline BMI), IF (intermittent fasting), ADF (alternate-day fasting), mon (months), wk (weeks), d (day), yo (years old), combo (combination), LDL (low-density lipoprotein cholesterol), HDL (high-density lipoprotein cholesterol), NS (not statistically significant), FFM (fat free mass), BP (blood pressure), NR (not reported)

^aInclusion age in years and inclusion BMI in kilograms per square meter. Mean age (mAge) presented as mean ± SEM when available. Mean baseline BMI (bBMI) presented as mean ± SEM when available

^bEnergy needs calculated by ¹ doubly labeled water technique, ² Mifflin-St. Jeor equation, ³ measured REE (indirect calorimetry) × self-reported physical activity level, ⁴ calculated resting metabolic rate × activity factor, ⁵ [(372 + 23.9 × FFM) × 1.5], ⁶ Diet history questionnaire (DHO)

preplanned secondary analysis compared changes in body composition and fat distribution measured by DEXA and MRI at week 24 [24]. There was no significant difference between ADF and CR in the relative amounts of fat mass, FFM, or visceral and subcutaneous fat loss.

In a study comparing ICR and CER in men with obesity, greater weight loss was seen in the ICR group (12.6 vs. 7.2%) [19•]. Fat mass loss was also greater in the ICR group (12.3 vs. 6.6 kg), but changes in fat free mass (FFM) were similar [19•]. Teng et al. evaluated ICR compared to no-intervention control in men (BMI 18.5–29.9 kg/m²) [30]. The ICR group had decreased weight and fat mass, but weight and fat mass increased in the CER group. FFM was similar pre- and post-intervention in both groups. In contrast to these two studies, Bhutani et al. found that only subjects in the ADF plus exercise group experienced decreased fat mass, not those in the ADF or exercise groups alone [22]. To further add complexity to the mixed results, other studies comparing IF and CER have seen similar weight effects in both groups [21, 27•, 31•, 35•]. For example, Catenacci et al. observed 8.8% weight loss in the ADF group and 6.2% in the CER group after 8 weeks, though the between group difference was only marginally significant [31•].

While weight and fat mass decreased in most studies, it is important to consider protocol adherence and dropout rates in IF interventions. Some studies have found that the ADF group ate more than prescribed on fasting days and less than prescribed on feast days [23••]. Based on these findings, two questions arise. First, does IF, or simply the intervention itself, lead to weight loss? Secondly, does the ADF intervention become CER in the real-world setting due to difficulty following the protocol? Furthermore, dropout rates have been as high as 40%. Thus, despite the statistical significance of weight loss results, the clinical significance and practicality of sustaining an IF regimen are questionable.

Effects on Glucose Metabolism and Insulin Sensitivity

Si may be assessed by several methods, including HOMA-IR and hyperinsulinemic euglycemic clamp [36]. Halberg et al. evaluated Si by hyperinsulinemic euglycemic clamp in eight healthy men (BMI 25.7 ± 0.4 kg/m²) pre- and post-ADF with 20 h of fasting [37]. Insulin-mediated glucose uptake was assessed by glucose infusion rate (GIR). The final clamp was performed after a 36 h fast. Although subjects maintained stable weight, Si improved, as indicated by significant increases in GIR, adiponectin, and inhibition of insulin-mediated lipolysis. Soeters et al. sought to replicate these results in a crossover study of eight healthy men who followed a standard diet or ADF with 20 h of fasting for 2 weeks [38]. Weight remained unchanged. Unlike the Halberg study,

glucose uptake and Si were unchanged during the clamp performed 14-h post-fasting [38]. Thus, it is unknown when Si improves the most post-fasting and if this is a sustainable change, particularly in healthy men. However, a more clinically relevant question is whether IF can benefit subjects with impaired baseline Si.

In a study comparing ADF and CER, there were no between group differences in lipids or Si [31•]. This differs from results of a larger randomized controlled trial (RCT), which found that Si and fasting insulin improved more in the ICR group, compared to the CER group, despite similar effects on weight and other biomarkers [21]. A preplanned secondary analysis of a 2017 RCT [23••] found that serum leptin decreased similarly in both CR and ADF groups, and HOMA-IR decreased more in the ADF group (–42%) than in the CR group (–18%) [24].

Another RCT reinforced these findings [20]. Subjects were randomized to one of three CR protocols: CER; carbohydrate- and energy-restricted ICR with ad lib protein and fat (IECR+PF); or carbohydrate- and energy-restricted ICR without ad lib protein and fat (IECR) [20]. Both IECR groups experienced greater improvements in Si than the CER group at 3 months. Both groups also experienced a larger reduction in body fat than the CER group, although total weight loss at 3 and 4 months was not significantly different.

Because IF in animal studies were associated with decreased serum glucose and insulin, these beneficial effects were anticipated in humans. However, human trials have shown only stable or decreased fasting insulin with no change in fasting glucose [20, 21, 33, 39–41], which is a difficult endpoint to translate to the clinical setting. Thus, while some animal studies [42] suggest an association between IF and Si, the results may not be extrapolated to humans.

Cardiovascular Effects

Limited literature exists on the cardiovascular effects of IF in humans. A 2010 study in rats found that IF compared to daily CR improves glycemic control and protects the myocardium against ischemia-induced cellular damage and inflammation [43]. ADF in male C57BL/6 mice for 4 weeks was associated with a decreased proportion of visceral fat, increased adiponectin, decreased resistin, and improved lipid profiles [44]. IF also resulted in increased adiponectin prior to and after induced myocardial infarctions [43].

A 2016 crossover study of 10 healthy participants (BMI 25–45 kg/m²) found significant alterations in postprandial glucose and lipid metabolism [45•]. The study, which evaluated total (100%) and partial (75%) CR compared to no CR, suggests that CER could alter cardiometabolic risk, independent of weight change [45•].

Fasting is part of the Latter-Day Saints (LDS) religious practice. A meta-analysis of two observational studies on a predominantly LDS population found that those who routinely fasted were 35% less likely to develop coronary artery disease (95% CI, 0.46–0.94) and 44% less likely to develop T2D (95% CI, 0.36–0.88) compared to those who followed normal eating patterns [46]. Routine fasting was also associated with a lower BMI. This population had a lower prevalence of smoking, however, which may confound the association between fasting and clinical outcomes. Nonetheless, the findings suggest that IF could also alter cardiometabolic risk factors. Additionally, a randomized comparison of IF and CER found comparable reductions in leptin, free androgen index, C-reactive protein, total and LDL cholesterol, TG, and blood pressure as well as similar increases in sex hormone binding globulin and insulin-like growth factor (IGF) binding proteins 1 and 2 [21]. These findings reinforce the potential cardioprotective effects of IF, though more studies need to be conducted in humans.

Impact on Aging and Cognition

Animal models provide preliminary evidence that CR and IF may delay aging. Evidence includes improved biomarkers, reduced oxidative stress, and preserved memory [47–49]. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses [50]. Both CR and ADF diets reduce age-related deficits in cognitive and motor function in animal models. The combination of CR and IF has been found to promote longevity and increase resistance to age-related diseases in rodents and monkeys [48]. ADF in mice has been shown to reduce serum glucose and insulin and to increase neuronal resistance to injury, even with isocaloric intake and stable weight [51]. Inbred male mice following an ADF regimen have also shown prolonged lifespan under certain conditions, but strong interactions exist between the genotype, age at initiation, and effect of ADF on body weight and aging [52]. While animal models have provided some promising results, the paucity of human studies prohibit extrapolation of these effects to human models.

In a subset of subjects ($n = 11$), Heilbronn et al. found increased muscle gene expression of SIRT1 post-ADF [39]. SIRT1 is an enzyme that may be implicated in human longevity [53]. Additionally, women had slightly impaired glucose response though this did not change in men. Women had unchanged insulin response, though there was a significant reduction in men. Hence, there may be gender differences in the metabolic response to ADF.

The SIRT1 finding is consistent with another study in which human serum collected pre- and post-intervention was used to culture hepatoma cells. Cells that were cultured in

post-intervention sera had increased SIRT1 levels and decreased TG. Additionally, post-intervention cells had decreased proliferation, increased stress resistance, and upregulation of longevity-inducing genes, all of which suggest that IF plays a role in aging and longevity [54]. However, a different 3-week ADF protocol (25% ER on fast days) was not associated with changes in whole-blood SIRT1 RNA [40].

Most studies assessing IF and aging are conducted on animals. Furthermore, evidence regarding biomarkers of aging and cognition is mixed, and the conclusions of these studies cannot yet be generalized to the larger population.

Psychosocial Impact

Because long episodes of fasting may lead to large portions of unhealthy foods at the end of the fast, it is questionable whether weight loss benefits of IF can be maintained. Binge eating disorder (BED), which affects 2.8 million Americans, is especially prevalent among individuals with obesity and those seeking weight loss [55]. BED is larger than normal food consumption in a small time period, often accompanied by a loss of control over eating [56]. Some studies suggest that IF may have implications on depression and BED.

Hoddy et al. found that 8 weeks of ADF in 59 subjects with obesity decreased depression and binge eating ($p < 0.01$) [57••]. While the decrease in depression and binge eating was statistically significant, it does not appear clinically significant, as the absolute changes were minimal. Additionally, purgative behavior and fear of fatness remain unchanged, although ADF increased restrictive eating and improved perceived body image [57••]. It is important to consider whether the decrease in depression and binge eating indicators is clinically significant enough to risk increased restrictive eating. Further, it is essential to define “restrictive eating” consistently among studies, as Bhutani et al. found that in subjects randomized to ADF or ADF plus exercise, restrained eating increased while uncontrolled eating decreased [22].

Despite the acute psychosocial benefits that Hoddy et al. and Bhutani et al. found, research studies should evaluate the long-term associations between IF, BED, and depression in order to minimize risk of negative psychosocial effects. In the interim, CER seems more appropriate for individuals at risk of any eating disorder, including BED.

Interaction with the Gut Microbiome

The microbiome modulates adiposity and protects against the development of obesity-associated metabolic dysfunction. This recent discovery has sparked interest in modulators of microbial balance. Preliminary animal models suggest that IF may be one of these modulators [58]. ADF in mice,

compared to isocaloric ad lib intake, induced white adipose tissue (WAT) beiging, weight loss, and changes in the gut microbiota, including an increase in the Firmicutes:Bacteroides ratio [59]. This was associated with improvements in liver steatosis and metabolic syndrome. However, in microbiota-depleted mice, ADF did not improve obesity or liver steatosis, thus suggesting that the gut microbiota is necessary for ADF to show these benefits. Furthermore, isocaloric ADF in mice modulates the gut microbiota, benefiting adiposity; this has been recently reviewed [60].

Cellular Metabolism Underlying Effects of IF

In addition to its role as an energy carrier, beta-hydroxybutyrate (β OHB) binds to extracellular receptors and inhibits class I histone deacetylases, which may promote resistance to oxidative stress [61, 62]. Thus, epigenetic modifications are likely driven by fasting-induced β OHB elevations. Increases in β OHB alter gene expression in nutrient-sensitive pathways that are implicated in longevity. β OHB also has been shown to promote anti-inflammatory effects by blocking activation of the NLRP3 inflammasome [63] and activating a neuroprotective subset of macrophages in the mouse brain [64]. In addition to the association between IF and neuronal resistance, animal studies have found that IF can affect oxidative stress.

Oxidative Stress

CR reduces oxidative stress by limiting mitochondrial generation of ROS and increasing endogenous antioxidant activity; this results in reduced oxidative damage to cellular proteins, lipids, and nucleic acids [65, 66]. However, IF has mixed effects on oxidative stress in animal models [67]. In theory, IF may induce hormesis, resulting in beneficial adaptive changes that include activation of AMP-activated protein kinase, mitochondrial network and peroxisome remodeling, and increased production of antioxidant enzymes [47, 68, 69].

In 8-month-old mice at high risk of lymphoma, ADF was associated with a significant reduction in lymphoma (0 vs. 33% of controls), decreased spleen mitochondrial ROS generation, and increased antioxidant superoxide dismutase activity [70]. However, Cerqueria reported increased oxidative stress in 8-week-old Sprague-Dawley rats who underwent 32 weeks of ADF [71]. The ADF group had worsened glucose tolerance, lowered adiponectin, and increased insulin receptor nitration and release of ROS in intra-abdominal AT and muscle [71]. Hence unlike long-term CR, long-term ADF may be associated with worsened Si and oxidative stress. Another study further informed these mixed results. One month of ADF in 8-week-old Sprague-Dawley rats had complex,

tissue-specific effects on ROS balance in rats [72]. For example, biomarkers of oxidative damage were increased in the liver and the brain but were reduced in the heart [72]. Hence, the effects of IF depend on the animal model, age at initiation, and tissue sampled.

Autophagy is a catabolic process of nutrient recycling that is essential for defense against oxidative stress. Nutrient sensing pathways induce autophagy [73]. IF has been shown to restore autophagic function, thereby preserving organelle quality. This restorative function is impaired by insulin resistance [74] and obesity-induced diabetes in mice fed a high fat diet [75]. However, data on the mechanisms of IF in humans are limited. Twenty-three pre-menopausal women (BMI 25–29.9 kg/m²) followed an ICR diet (2 days per week of 65% CR) for one menstrual cycle [76]. After the intervention, 196 metabolites increased (including β OHB and acylcarnitine) and 331 metabolites significantly decreased (including succinic acid, alanine, glutamic acid, and tyrosine). This group also compared the effects of their ICR protocol on the metabolome in another group of pre-menopausal women and found many similar trends [77].

Inflammatory Effects

Oxidative stress is closely linked to inflammation. Ten subjects with obesity and asthma followed an ADF protocol for 2 months [41]. Body weight decreased a mean 8% and peak expiratory flow and asthma quality of life scores increased [41]. This intervention was associated with significant reductions in inflammatory markers, including TNF- α and ceramides, and markers of oxidative stress, including protein carbonyls and 8-isoprostane.

In mice, IF increases vascular endothelial growth factor (VEGF) in WAT, with associated alternative macrophage activation and WAT beiging [78]. Gene expression of VEGF, alternative macrophage activation, and beige adipocyte-related proteins are also positively correlated in human AT. This suggests that IF may regulate this same pathway.

Fasting is associated with elevations in FFA and ketone bodies, including β OHB, which may have opposing effects on inflammation. Elevated FFA during fasting may activate proinflammatory pathways [79] and reduce Si [80], while elevations in β OHB may activate anti-inflammatory pathways and alter fuel metabolism as reviewed above. Our group is currently conducting a pilot clinical trial on the effects of dietary supplementation of medium chain triglycerides (MCT), which are metabolized into β OHB (NCT02783703). MCT supplementation may activate anti-inflammatory pathways through β OHB without the detriments of elevated FFAs.

FFA released from lipolysis in mast cells may play an important role in eicosanoid release and control of immune activation [81]. Saturated FFA induce an inflammatory response

in macrophages while unsaturated FFA do not [82]. Hence, FFA released from lipolysis play an important role in obesity-induced AT inflammation [83], immune regulation [84], and stimulating hepatic VLDL production [85].

Sustained fasting is associated with acute hepatic steatosis and increased insulin resistance [86]. Normal weight subjects who fasted for 72 and 120 h had increased intramuscular lipids (IMCL) [87, 88]. A 60-h fast in healthy males was associated with elevated IMCL, increased insulin resistance, and a nine-fold elevation in FFA [87]. Prolonged elevations in FFA, combined with metabolic syndrome and insulin resistance, contribute to increasing hepatic IMCL and lipotoxicity, which leads to nonalcoholic steatohepatitis [88]. However, ADF in mice has been shown to induce metabolic changes that protect against steatosis [89]. Increases in ketogenesis during fasting protects against steatohepatitis in mice [90]; thus, IF may have these same protective effects in humans.

The effects of IF on inflammation have been minimally studied in humans. While cellular level mechanisms have been evaluated in animal models, the application in human models is scarce. Cellular analysis and animal models suggest opposing influence of FFA and ketone bodies on inflammation. Despite understanding these cellular mechanisms, it is unclear whether IF has beneficial effects on oxidative stress and inflammation in human.

Clinical Implications

While several rodent studies have demonstrated the statistical significance of IF on weight loss and metabolic biomarkers, it is important to consider the clinical significance of these findings. For example, while LDL cholesterol levels at month 12 were significantly in the ADF group, it is unlikely that an 11 mg/dL difference would have implications on provider recommendations. Additionally, human studies suggest that IF regimens are difficult to sustain due to dietary restrictions [18, 51] and implications on hunger and satisfaction [18, 71, 91].

Research is not robust enough to suggest that healthcare professionals should be recommending IF to patients as standard practice. It is unknown which individuals would most benefit from IF and which form of IF is most effective. It is anticipated that IF would most benefit motivated individuals who are able to avoid overeating following fasting periods. Further, individuals who are highly involved in social events may find it difficult to comply with IF regimens, and skipping social events because they occur during planned fasting periods is unlikely to be beneficial or sustainable. Additionally, the decision to follow an IF regimen depends on the individual's goals and desired outcomes. For those interested in weight loss methods, CER may be easier and as effective as IF [92]. Those interested in increasing their FFM may benefit more by combining IF with endurance exercise [22]. There

may also be potential contraindications to IF, including certain health conditions, medications, psychosocial barriers, and eating practices. Should IF become part of standard practice, a multidisciplinary approach should be used. Collaboration of registered dietitians, physicians, and other essential healthcare providers will ensure the safety of the patient and decrease the possibility of adverse effects such as weight regain, depression, and BED.

Future Research

Considering the American preference for highly palatable, calorically dense foods, it is crucial for researchers and health practitioners to find unique strategies appropriate to this culture. Longer, statistically powered trials in humans are needed to elucidate the current literature. First, the definitions of IF regimens must be clearly defined. For instance, caloric intake on fast days should be consistent across ADF protocols. These studies should account for the types of foods eaten on ad lib days and how these choices influence weight loss and metabolic markers.

Future research should also determine whether outcomes differ by IF regimen. This would enable practitioners to better recommend dietary changes. For instance, individuals seeking weight loss may require a different IF regimen than those pursuing cardioprotective benefits. There are several trials currently underway that aim to determine the effects of IF on numerous outcomes such as cancer, Alzheimer's, diabetes, and longevity [93]. Given the positive outcomes thus far, IF may prove to be a promising approach to improving health once it is determined which individuals will best benefit and be able to sustain it.

Conclusions

Animal models and human trials suggest that IF may have beneficial effects on weight, body composition, cardiovascular biomarkers, and aging. At the cellular level, IF may also increase resistance against oxidative stress, decrease inflammation, and promote longevity. However, studies vary greatly on their definition of IF, the prescribed protocol, and the duration of IF. Additionally, the studies have been conducted in diverse populations with mixed results.

Due to the increasing prevalence of overweight and obesity, Americans are searching for effective weight loss methods. The paucity of research on IF makes it difficult to prescribe IF as a reliable method for successful long-term weight loss and maintenance. However, IF appears to be a viable weight loss method, though CER may be as effective. It is important to consider desired outcomes when choosing whether an IF is an appropriate diet. Given that CR is a proven method of weight

loss, more research is needed to assess whether IF is a sustainable treatment for obesity as well as if the benefits of IF are maintained long-term.

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Compliance with Ethical Standards

Conflict of Interest Mary-Catherine Stockman declares that she has no conflict of interest.

Dylan Thomas declares that he has no conflict of interest.

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- Of importance
- Of major importance

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