Science Review:
Intermittent Fasting (IF) and Emerging Clinical Applications

Introduction

Our human ancestors evolved and developed adaptive mechanisms that allowed survival during periods of food availability and scarcity with seasonal fluctuations of both types and quantities of nutrients.[1] In this context, modern humans now face a different challenge with increased food abundance and food accessibility. Not only has the number of commercial food establishments increased dramatically in the last few decades, a large percentage of nonfood establishments (e.g., retail outlets, gas stations, office buildings, etc.) also have made food readily available.[2] Further, the increase in food and beverage portion sizes and the ubiquitous food advertising lead people to unintentionally overconsume calories.[3,4] The resulting epidemic of obesity, diabetes, metabolic dysfunction, and associated conditions is leading healthcare professionals and researchers into a quest for approaches to mitigate these adverse health outcomes.

Continuous energy restriction (CER), or traditional dieting, is a method to increase metabolic health by consistently restricting daily caloric intake (reducing 20-40% of caloric intake) without malnutrition or deprivation of essential nutrients.[5] However, practicing CER while increasing energy expenditure via physical activity can be challenging to adhere to. Even when weight loss is achieved, weight regain eventually occurs to many people due to adaptive physiological changes following weight loss.[6] Intermittent fasting (IF), also commonly known as intermittent energy restriction (IER), may be an alternative, potentially more agreeable, approach to reduce energy intake.[7]

Mechanisms of action

An intermittent energy deficit via dietary restriction can be considered a hormetic stimulus, defined as a moderate stressor that results in adaptive responses leading to increased activation of cellular protection and restorative mechanisms.[8] The proposed mechanisms via which IF may lead to improved health outcomes are believed to be linked to IF's effects on multiple, interrelated cell signaling pathways:[9]

- Activation of more efficient respiratory pathways such as AMP-dependent kinase (AMPK) and sirtuins leads to improved mitochondrial efficiency and reduced production of reactive oxygen species (ROS)
- Activation of the Forkhead box (FoxO) pathway facilitates autophagy (a process in which cells degrade intracellular debris, thereby eliminating dysfunctional proteins and organelles)
- Downregulation of insulin-like growth factor-1 (IGF-1) receptor-dependent pathways and target of rapamycin (TOR)-dependent activities results in inhibition in cell proliferation and glycolysis
- Inhibition of nuclear factor-κB (NF-κB) activity produces anti-inflammatory effects
- Activation of the nuclear factor-like 2 (Nrf2) pathway increases the expression of antioxidant enzymes

Different IF approaches

IF can be achieved via different protocols described in **Table 1**.

Table 1. Description and example of IF protocols.[11-17]

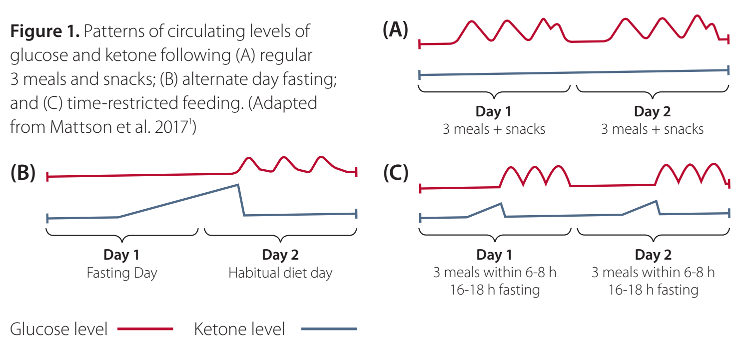
Protocol		Example
Intermittent fasting (IF)	Time-restricted feeding (TRF)	Meals ideally consumed within 6-8-hour eating window each day, allowing at least 16 hours fasting
	Alternate day fasting (ADF)	Fast (no caloric intake) every other day and consume a habitual diet on nonfasting days
	Modified ADF (mADF)	Very limited caloric intake (500-600 kcal) on fasting days and habitual intake on feeding days
	5:2 protocol	Restricted caloric intake (500-600 kcal) 2 consecutive or nonconsecutive days per week with generally unrestricted intake on the other 5 days of that week
	Prolonged fasting	No caloric intake (food or drinks) for ≥ 72 hours
	Short-term fasting	No caloric intake (food or drinks) for < 72 hours
	Fasting mimicking diet (FMD)	Commercial diet consisting of plant-based, low-protein, reduced caloric meal plan for 3 cycles of 5 days per month
Intermittent restriction or "diet breaks"		Repeating blocks of daily caloric restriction followed by energy balanced conditions (e.g., caloric intake is 65% of weight maintenance requirements for 2 weeks followed by return to energy balance conditions for a further 2 weeks and repeat of this 4-week cycle until weight loss goals are achieved)

Reduced nutrient intake from IF may result in compensatory metabolic effects such as:[10]

- Reduced blood levels of glucose and insulin together with hepatic glycogen depletion
- Improved insulin sensitivity, increased fat oxidation, and beneficial changes in body composition
- Improved cellular utilization of ketones and fatty acids and beneficial changes in lipid profile (e.g., decreased total cholesterol, triglycerides, and LDL cholesterol and increased HDL cholesterol levels)

However, different IF protocols have been shown to produce subtle differences in positive metabolic changes. For instance, ADF leads to a gradual and lengthier increase in ketone levels on fasting day until the first consumption on the second day, whereas TRF results in an increase in ketone levels during the last 6-8 hours of the 16-18-hour fasting time (**Figure 1**).[1]

Figure 1. Patterns of circulating levels of glucose and ketone following (A) regular 3 meals and snacks; (B) alternate day fasting; and (C) time-restricted feeding. (Adapted from Mattson et al. 2017[1])



Research Highlights

- ✓ Energy restriction consists of periods with limited or no caloric intakes that results in adaptive mechanisms to support homeostasis.[8,9]
- ✓ Energy restriction/fasting protocols are associated with beneficial metabolic effects such as reduced blood levels of glucose and insulin, improved insulin sensitivity, and beneficial changes in body weight and body composition.[10]
- ✓ Energy restriction can be achieved via continuous energy restriction (CER) and various methods of intermittent fasting (IF). IF may be an alternative, potentially more agreeable, approach to reduce energy intake.[7]

Potential clinical applications

Investigating long-term energy restriction in humans can be challenging. The first long-term human energy restriction clinical trial is the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial, which found that a 12% reduction in caloric intake for up to 2 years reduced risk for age-related diseases such as diabetes, heart disease, and stroke.[18,19]

Due to its multiple effects, IF protocols may have several potential clinical applications such as weight management, diabetes management, cardiometabolic improvement, and cognitive and brain health support (evidence from key human clinical trials and/or preclinical studies for each application is briefly summarized in **Table 2** along with references).

Choosing between IF and energy restriction protocols

At this point, head-to-head studies of different IF and energy restriction protocols are lacking. However, it is possible to differentiate between protocols based on emerging clinical applications (see Table above) as well as individual practical lifestyle aspects (see **Figure 2**).

Practicality and safety of IF

The macronutrient composition of IF can be personalized. One trial compared high-fat version with low-fat version of mADF in adult women with obesity and found that both were effective in improving body weight and cardiometabolic risks over 8 weeks.[20] Another trial found that both were equally effective in improving LDL particle size and distribution in men and women with obesity over 10 weeks.[21]

Fast day meal timing may also be flexible to increase tolerability and long-term adherence to ADF or mADF protocols. One trial reported that eating the fast day meal at lunch time, moving the fast day meal to dinnertime, or dividing the fast day meal into smaller meals were equally effective in improving body weight and body composition in adults with obesity over 8 weeks.[22]

Exercise combined with IF may lead to greater weight loss than exercise alone or IF alone.[23] One trial found that exercise could be easily incorporated into the ADF regimen either on fast days or feed days, and exercise on fast days did not result in increased hunger or extra food intake in subjects with obesity over 12 weeks.[24]

For people using type 2 diabetes (T2D) medication, IF may require medication changes and regular monitoring—especially in the initial stages of dietary change—to prevent hypoglycemia.[25] One trial reported that sulfonylureas and insulin dosage needed to be adjusted on fasting days according to participants' baseline HbA1c levels (e.g., discontinuing sulfonylureas and insulin on fasting days only and discontinuing long-acting insulin the night before a fasting day for those with HbA1c levels between 7 and 10%) and recommended that patients work with endocrinologists while adapting to IF regimens.[25]

For people with type 1 diabetes (T1D) and obesity, a 12-week pilot trial demonstrated IF (as 5:2 protocol) to be a safe and effective alternative to traditional CER for weight loss, and moderate adjustment in their basal insulin doses (10% reduction on nonfasting days and 50% reduction on fasting day) effectively prevented hypoglycemia.[26]

Fasting protocols have not been investigated in children, elderly, underweight individuals, and those receiving insulin or insulin-like drugs. Fasting periods longer than 24 hours should be overseen by a healthcare practitioner. Proper intake of noncaloric fluids is crucial to ensure adequate hydration. Lastly, fasting may result in changes in circadian rhythms of endocrine and gastrointestinal systems.[27,28]

Figure 2. Choosing an energy restriction protocol—practical and clinical considerations.[11-17]

ADF and mADF	5:2 protocol	TRF	Diet breaks	CER
• Struggling with consistent caloric restriction for weight loss • Needs support with restrained eating • Variable schedule suits a restricted intake on certain days of the week • Weight loss goal more aggressive timing that 5:2 (i.e., restrict to ~500 kcal on 3/4 versus 2 days per week	• Struggling with consistent caloric restriction for weight loss • Struggling with weight maintenance (e.g., consider 6:1 protocol) • Needs support with restrained eating • Variable schedule suits a restricted intake on certain days of the week • Wants higher ketone levels • Clinical note: longer menstrual cycle has been described	• Needs support with overall calorie intake each day • Could be integrated with other caloric restriction protocols • Insulin sensitivity (eTRF) • Consistent morning glucose issues • May work well for ketogenic dietary pattern due to feelings less hungry (narrower eating time-frame)	• Good approach for those who find long-term consistent protocol challenging • Generally prefers consistency with eating habits • Longer weight loss timeframe is appropriate • Has struggled with weight regain in the past—wants to avoid negative adaptive changes	• Prefers consistency with eating habits

Table 2. Brief summary of key preclinical and clinical evidence of various IF approaches.

	Brief summary of key preclinical and clinical evidence				
	ADF	mADF	5:2	TRF	FMD
Weight management	Significant reduction in body weight (-8.8%), total fat mass (-1.1%), and visceral fat mass (-2.4%) in men and women with obesity over 8 weeks. Efficacy comparable to standard CER.[29] **Preclinical**: decreased incidence and lower cumulative clinical disease score in the multiple sclerosis rodent models.[30,31]	Significant reduction in body weight (-6%) and visceral fat mass (-0.4 kg) in men and women with obesity over 12 months. Efficacy comparable to standard CER.[14]	Significant reduction in body weight (-5.5% to -8.4%) over 6 months in subjects with overweight, obesity, metabolic syndrome, and type 2 diabetes. Efficacy comparable with standard CER.[7,13,32] For weight loss maintenance from 6 months to 12 months in adults with BMI 30-45, efficacy comparable to CER.[7] Safe and feasible way to support weight management with improved wellbeing over 8 weeks in patients with multiple sclerosis in a pilot trial.[33]	**18-20-hour fast**: Significant reduction in body weight and spontaneous reduction in energy intake over 2 weeks in adults with T2D and obesity taking metformin in a pilot study.[16] **16-hour fast**: Significant reduction in body weight (~2.5%) and spontaneous reduction in energy intake in men and women with obesity over 12 weeks with ad lib eating (no defined caloric restriction during 8-hour eating window).[34]	3 cycles of a 5-day FMD (5 days per month) reduced body weight, trunk, and total body fat and reduced waist circumference over 3 months in generally healthy adult participants.[35] **Preclinical**: 3 FMD cycles attenuated disease symptoms and promoted increased remyelination of axons in a rodent model of multiple sclerosis.[36]
Insulin resistance/T2D management	In men and women with obesity, fasting glucose seen to reduce with ADF and not CER over 8 weeks.[29]	Significant reduction in fasting insulin in men and women with obesity and insulin resistance over 8 weeks.[37]	Significant reduction in HbA1c in men and women with T2D over 12 months. Efficacy comparable to CER. Reductions in dosage of diabetes medication were comparable to CER, but 5:2 had a greater reduction in insulin usage.[25] Marked reduction in insulin resistance over 3-6 months in women who were overweight; efficacy comparable to or greater than CER.[11,13] Modest reduction in postprandial insulin in men with overweight or obesity over 2 months. Efficacy comparable to CER.[38]	**18-20-hour fast**: Lower self-reported morning glucose and greater proportion of evening glucose in the desired range over 2 weeks in adults with T2D and obesity taking metformin in a pilot study (most of whom achieved 17-hour fast).[16] **18-hour fast**: In overweight men in a proof-of-concept study, eating within a 6-hour window, with food intake skewed toward earlier in the day, resulted in greater beta cell responsiveness and reduction in insulin resistance compared with matched food intake consumed over a 12-hour window over 5 weeks with no weight loss.[15]	**Preclinical**: A short-term diet that mimics period fasting beneficially modulated beta cell number and promoted insulin secretion and glucose homeostasis and reversed both T1D and T2D phenotypes in mice.[39]
Cardiometabolic risk improvement	Significant reduction in total cholesterol, LDL-C, and TG, but also HDL over 8 weeks in men and women with obesity. Efficacy comparable to CER.[29] Significant reduction in LDL-C concentration and increase in integrated LDL particle size over 12 weeks in adults with overweight or obesity. Efficacy comparable to CER.[40]	In men and women with obesity, significant reduction in TG with mADF but not CER over 12 months.[14] Significant reduction in total cholesterol, LDL-C, TG, and systolic blood pressure over 8 weeks in men and women with obesity.[41]	Significant improvement in diastolic blood pressure, HDL-C, TG over 12 months in adults with BMI 30-45. Efficacy comparable to CER.[7] Significant improvement in total cholesterol, LDL-C, and TG in men and women with T2D over 12 months. Efficacy comparable to CER.[25] Significant improvement in LDL-C, TG, cholesterol, and blood pressure over 6 months in premenopausal women with overweight or obesity. Efficacy comparable to CER.[13]	**18-hour fast**: In overweight men in a proof-of-concept study, eating within a 6-hour window, with food intake skewed toward earlier in the day, significantly improved morning blood pressure but had no effects on arterial stiffness or serum lipids compared with matched food intake consumed over a 12-hour window over 5 weeks with no weight loss.[15] **16-hour fast**: Significant reduction in systolic blood pressure in men and women with obesity over 12 weeks with ad lib eating (no defined caloric restriction during 8-hour eating window).[34]	3 cycles of a 5-day FMD (5 days per month) reduced blood pressure, total cholesterol, LDL-C, and HDL-C over 3 months in generally healthy adult participants
Cognitive/brain health	**Preclinical**: Improvement in learning and memory and enhancement in neurogenesis, synaptic plasticity, and neuronal stress resistance in mice over 11 months. No improvement in mice fed with high-fat diet.[42] **Preclinical**: Prevention of cognitive deficits over 1 year in a mouse model of Alzheimer's disease.[43]			**14-hour fast**: No effects on cognitive function over 28 days in lean healthy men.[44]	**Preclinical**: FMD cycles improved performance in hippocampal-dependent short- and long-term memory in aged rodents; increased hippocampal neurogenesis and extended lifespan.[45] **Clinical**: 3 FMD cycles improved metabolic biomarkers associated with age-related cognitive decline in generally healthy adults in a pilot trial.[45]

Conclusions

From the research to date, IF protocols appear to be as beneficial as standard caloric restriction. Most studies use either ad libitum diets or the CER as control groups, making it harder to determine whether one IF protocol is more advantageous than another. Taking into account that all IF protocols investigated have shown comparable metabolic benefits, it is suggested that choosing a protocol that can best fit an individual's lifestyle will likely increase compliance and long-term success.

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