

The Safety and Efficacy of Intermittent Fasting for Weight Loss

Antoine Aoun, MD, PhD
Charbel Ghanem, MS
Natacha Hamod, MS
Sabine Sawaya, MS

Intermittent fasting (IF) diets have recently gained popularity as a weight loss and antiaging method that attracts celebrity endorsements and public interest. Despite the growing use of IF, the debate over its safety and efficacy is still ongoing. Defined IF regimens include 5 different types: alternate-day fasting, periodic fasting, time-restricted feeding, less clearly defined IF (fast mimicking diet, juice fasting), and religious fasts. Our literature review highlights the effect of IF essentially on body weight and cardiometabolic risk factors. Intermittent fasting may be effective for weight loss and may improve cardiovascular and metabolic health, although the long-term sustainability of these effects has not been studied. While data on the safety of IF are sparse, the most frequent adverse effects (hunger, irritability, and impaired cognition) may dissipate within a month of the fasting period. Intermittent fasting is not recommended for pregnant or lactating women, children or adolescents during maturation, the elderly or underweight people, and individuals vulnerable to eating disorders. *Nutr Today*. 2020;55(6):270–277

attracted celebrity endorsements and public interest.¹ Evidence shows that IF may have health benefits associated with triggering a metabolic switch from glucose to ketone-based energy sources.²

History

Intermittent fasting is a term used to describe periods of intended self-discipline or abstinence from food and drink consumption. Intermittent fasting has been used in various versions since ancient times all over the world.¹ Historically, it was used to promote physical and spiritual health benefits including cleansing and healing the body. For instance, the ancient Egyptians, Indians, and Greeks used fasting as a curative protocol, withholding food until the diseased individual exhibited signs of improvement. The world's largest religions have their own versions of fasting that vary in patterns (continuous vs intermittent), duration, and general conditions where a certain food or a group of foods might be restricted. Today, IF is also used for reducing body weight and for health reasons.

Physiology of Fasting

Fasting consists of different stages³: (1) a first stage when the primary fuel source is glucose and body fat storage is activated, lasting around 4 hours⁴; (2) a second stage lasting for up to 18 hours when glucagon is secreted and the body uses the liver's glucose reserves (glycogen) as a fuel source^{5,6}; (3) a third stage transitioning progressively to other fuel sources such as fat, lactic acid, and alanine, when the liver's glucose reserves are depleted after 12 to 36 hours of continued fasting^{4,7,8}; (4) a final stage (metabolic switch) when the mobilization of fat in the form of free fatty acids metabolized into fatty acid–derived ketones provides energy.^{4,6,9–13}

Organic Hunger, Hedonic Hunger, and Appetite

Before introducing the different types of IF, let us clarify the differences between hunger and appetite.¹⁴ Hunger (also known as organic hunger) is the actual physiological urge to eat. It stems from a complex hormonal and neural control system manifested in physiological signs such as stomach growling where the digestive system prepares itself, in anticipation, for the ingestion of foods. In contrast, appetite is the desire to eat and stems from the psychological

With the increasing prevalence of obesity and weight gain worldwide, people are in a constant search for various effective treatments that lead to weight loss. Recently, intermittent fasting (IF) diets have gained popularity as a weight loss method and have

Antoine Aoun, MD, PhD, is an associate professor of nutrition, Faculty of Nursing and Health Sciences, and university physician, Office of Student Affairs, Notre Dame University-Louaize, Zouk Mosbeh, Lebanon. Dr. Aoun's major research interests include eating behaviors and nutritional supplementation.

Charbel Ghanem, MS, Notre Dame University-Louaize, Zouk Mosbeh, Lebanon. Mr. Ghanem's major research interests include nutrition and metabolic disorders.

Natacha Hamod, MS, Notre Dame University-Louaize, Zouk Mosbeh, Lebanon. Ms. Hamod's major research interests include nutrition and mental disorders.

Sabine Sawaya, MS, Notre Dame University-Louaize, Zouk Mosbeh, Lebanon. Ms. Sawaya's major research interests include eating behaviors and habits.

This article was financed from the authors' own funds.

The authors have no conflicts of interest to disclose.

Correspondence: Antoine Aoun, MD, PhD, Associate Professor of Nutrition, Faculty of Nursing and Health Sciences, and University Physician, Office of Student Affairs, Notre Dame University-Louaize, PO Box 72, Zouk Mikael, Zouk Mosbeh, Lebanon (aaoun@ndu.edu.lb).

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DOI: 10.1097/NT.0000000000000443

inclination toward ingestion of particular food. The ability of an individual to discern one from the other plays an important role in the ability to discipline one's food consumption. Moreover, the inability to properly distinguish between the two has been proposed as one of the numerous factors contributing to overeating and consequently weight gain.

The middle ground between hunger and appetite is known as hedonic hunger,¹⁴ which is the drive to consume pleasure-inducing food despite the lack of caloric deficit and physiological need to eat accompanying organic hunger. The distortion between hedonic and organic hunger is a hallmark in the vicious cycle of weight gain in individuals with obesity. Hedonic hunger stems from complex internal and external factors involving the type and quantity of food consumed, the mood prior and during food consumption, and the hormonal regulation of leptin and ghrelin. The fact that some forms of bariatric surgery were able to decrease the intensity of hedonic hunger implies the presence of a physiological mechanism behind this type of hunger that remains to be fully elucidated.

Types of IF Diets

Intermittent fasting (also sometimes called intermittent energy restriction) diets include 5 different types: alternate-day fasting, periodic fasting, time-restricted feeding, less clearly defined IF (fast mimicking diet, juice fasting), and religious fasts. Ad libitum feeding is defined as food intake based on the eater's usual eating habits with no time or calorie restriction.^{15,16} Continuous energy restriction (CER) is when participants consume a reduced daily caloric intake (nonintermittent, with a minimum of 25% reduction in caloric intake) to achieve weight loss.

Despite the growing popularity of IF, the debate about its efficacy and safety is ongoing. For instance, in the United States, the American Heart Association states that IF may produce weight loss, reduce insulin resistance, and lower the risk of cardiometabolic diseases, although its long-term sustainability is unknown.¹⁷ The National Institute on Aging recommends against IF because of uncertainties about its effectiveness and safety, particularly for the elderly.¹⁸ Our literature review aims to examine whether IF is an effective and safe method for losing weight and attaining health benefits.

METHODS

Our study was carried out in the PubMed and ProQuest database (language limited to English) in April 2020, with no limitation of the publication period (but with emphasis on the most recent human studies). The keyword combinations used were as follows: "fasting" and "weight loss" (n = 43 articles), "types of IF" and "weight loss" (n = 34 articles), "fasting" and "health" (n = 31 articles), and "IF" and "effects" (n = 33 articles). Of the 141 articles, 37 were

common to several combinations, and 16 had no direct correlation with the subject. Finally, we included 86 articles related to the efficacy and safety of IF for weight loss (51 original studies and 35 review articles).

Effects of IF on Weight Loss and Cardiometabolic Risk Factors

The different types of fasting are claimed to have many advantages and disadvantages. Some are summarized in Table 1. Fasting, in its different types (involving alternate-day fasting and periodic fasting), may exert a homeostatic regulatory effect on blood glucose and lipid profiles.⁴⁵ In addition, it may possibly inhibit inflammatory processes that are mediated by a decrease in gut permeability and the enrichment of the gut microflora, resulting in the prevention of exaggerated immune reactions.⁴⁵ A study assessing a 3-week IF diet (consisting of an alternate-day fasting) on overweight men and women showed a remarkable decrease in insulin response and an improvement of glucose uptake and insulin sensitivity in overweight men, whereas overweight women showed an impaired glucose uptake and an exacerbation of insulin resistance in skeletal muscle.⁴⁶ These 2 effects were attributed to higher fluctuations of free fatty acids within the first 36-hour fast.⁴⁶

Clinical trials show that fasting (involving periodic fasting and time-restricted feeding) may decrease the risk of coronary artery disease, reduce atherosclerosis, and improve cardiovascular risk factors.^{47,48}

In other studies, IF (consisting of time-restricted feeding) resulted in changes in body weight (weight loss of 7 kg on average) similar to CER.^{38,49} Furthermore, a study conducted on men and women with obesity showed favorable changes in terms of nutrition and eating behaviors when both groups (periodic fasting vs CER) underwent either of these diets.⁵⁰

Another study evaluated the effect of IF (consisting of a time-restricted feeding with 20-hour fast) on insulin resistance, over a period of 2 weeks, in men with overweight and obesity. It showed an enhancement in insulin-mediated glucose uptake and insulin-induced inhibition of adipose tissue lipolysis. However, these 2 effects were associated with the increase in adiponectin levels observed after a 20-hour fast.⁵¹ A different study, conducted over a period of 2 weeks, showed no association between the IF regimen (involving time-restricted feeding) and changes in peripheral glucose uptake or hepatic insulin sensitivity.⁵²

A study showed that IF (involving Ramadan fasting), if followed rigorously, might ameliorate the lipid profile of healthy men and women suffering from obesity and dyslipidemia, by reducing total cholesterol, low-density lipoprotein cholesterol, and triglycerides and increasing high-density lipoprotein cholesterol levels.²⁴

From a physiological standpoint, fasting may induce a protective effect on the beta cells of the pancreas by

TABLE 1 The Main Types of Intermittent Fasting

Type of Diet ^{18,19}	Diet Description	Relevant Effects
Alternate-day fasting <ul style="list-style-type: none"> ▪ Complete alternate-day fasting, where no calories are consumed on fast days ▪ Modified alternate-day fasting, which allows the consumption of up to 25% of daily calorie needs on fasting days 	Fasting is done every other day. On those days, the calorie intake is only 25% of the normal daily calorie consumption, and on the other days, the individual follows a regular dietary plan	Does not affect lean body mass, ^{5,20} although 1 review found a small decrease ²¹ Improves cardiovascular and metabolic biomarkers, just like a calorie restriction diet, in people who are overweight, obese or have a metabolic syndrome ^{6,12,13,16,22} More effective when combined with exercise ²³ Decreases LDL-C, total cholesterol, and triglycerides and increases HDL-C. ²⁴ May decrease insulin resistance ^{25–28} A safe weight-loss strategy; no increased risk of disordered eating ^{25–28}
Periodic fasting (5:2 diet)	Fasting is applied 2 d/wk for a duration of 24 h. On those 2 nonconsecutive days, the person can consume around 500–700 calories or 25% of regular daily caloric intake	Decrease in weight and HbA _{1c} level similar to CR ^{29–31} Decreases fasting glucose, insulin, insulin resistance, liver steatosis and inflammatory markers ^{1,11,32} No effect ³³ or beneficial effect ³² on lipid profile Decreases visceral fat, adipocyte size, leptin, and resistin and increases adiponectin ¹ Corrects hypertension ³² Safe in T2D ¹
Time-restricted feeding (16:8 diet)	Abstention from eating for a 16-h period and ingestion of food in the remaining 8 h of the day. Considered the most popular IF ³⁴	More effective than CR for weight loss and glycemic control in T2D ³⁵ Glucose and lipid homeostasis ³⁶ Associated with reduction of body weight, total cholesterol, triglycerides, insulin, glucose, interleukin 6, and tumor necrosis factor- α in prediabetic men. ²³ Other studies showed significant decrease in body weight, glucose, triglycerides, and LDL-C and increase in HDL-C ³⁴ Feasible in older adults and leads to weight loss. ³⁷ Sleep improvements ³⁸
Fast mimicking diet	Applies a 120-h low calorie nonfasting ketogenic diet once a month	Decreases body mass index, fasting glucose, dyslipidemia, IGF-1 and blood pressure ³⁹
Juice fasting (10-d juice fast)	Consuming only juices and broths for 10 consecutive days each month ^a	Health claims not supported by scientific evidence
Religious fasts		
<ul style="list-style-type: none"> ▪ Ramadan fast 	Abstain from consuming food and drink from sunrise to sunset during the month of Ramadan	Decreases weight, fat mass and fat-free mass in overweight and obese individuals but not in normal weight individuals ⁴⁰

(continues)

TABLE 1 The Main Types of Intermittent Fasting, Continued

Type of Diet ^{18,19}	Diet Description	Relevant Effects
▪ Greek orthodox fasts	Abstain from consuming dairy products, eggs, and meat for 40 d during the Nativity fast, for 48 d during the lent fast and for 15 d during the Assumption fast	Decreases weight, total cholesterol, and LDL-C; conflicting findings on blood pressure and glycemia ^{21,22,41,42}
▪ Daniel fast	Involving a vegetarian diet and excluding refined foods, white flour, preservatives, additives, sweeteners, flavorings, caffeine, and alcohol. It is observed for 10–40 d	Decreases total cholesterol, LDL-C, HDL-C, systolic and diastolic blood pressure ⁴³ Good compliance to the fast (>98%) ⁴³ Positive impact on mood and better satiety ⁴³ No significant change in body weight, body fat, Insulin, HOMA-IR, and C-reactive protein ⁴³
▪ Jewish fast (Yom Kippur and others)	Fasting from sunset until the emergence of stars the following day (25 h). The observer does not eat or drink	Studies not available

Abbreviations: CR, calorie restriction; HbA_{1c}, hemoglobin A1c; IF, intermittent fasting; T2D, type 2 diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulinlike growth factor 1; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

^aJuice fasting may have several adverse effects: metabolic disorders in patients with undiagnosed diabetes or hypoglycemia; dizziness or fainting due to sudden lowering of blood pressure; diarrhea, which may result in dehydration and an imbalance of electrolytes in the body; and protein or calcium deficiencies from unsupervised long-term juice fasts.⁴⁴

decreasing beta cell failure, promoting and up-regulating the pancreatic regeneration marker NEUROG3.⁵³

A meta-analysis investigating the effectiveness of IF (all types of regimens included) on body mass index (BMI) and metabolic markers found that it improved fasting blood glucose and insulin resistance by decreasing BMI and serum leptin concentrations while increasing adiponectin. These glucose-lowering effects were observed in patients with diabetes and prediabetes but not in healthy individuals.⁵⁴

Two recent meta-analyses concluded that IF (all types of regimens included) was as effective as CER for weight loss.^{13,16}

The health benefits of fasting can be ascribed to both the temporary restriction of food and the long-term effect of weight loss.

Recent studies have shown that fasting and exercise exhibit synergistic effect (one potentiates the other) leading to greater weight loss when combined.⁵⁵

The relationship between fasting and cancer remains highly speculative; a small number of studies hypothesize that IF may enable tumor suppression in glioblastoma patients, thus extending survival.⁵⁶ Other studies hypothesized that fasting, along with chemotherapy, enhances survival, decreases tumor development, and limits the spread of tumors. The assumed rationale may be that fasting induced a hibernation-like state in normal cells and an apoptosis in cancerous cells.⁵⁷ No studies investigating the

link between fasting and cancer recurrence have been conducted.⁵⁸

A few small-scale clinical studies suggest that IF may reduce chemotherapy adverse effects.^{59,60}

Also, IF may have a minor beneficial effect on chronic pain and mood disorders,^{61–63} and it does not affect bone health.⁶⁴

In conclusion, there is some evidence that IF produces weight loss comparable to a CER diet.^{13,16,65–68} Preliminary evidence indicates that IF may be effective for weight loss, may decrease insulin resistance and fasting insulin, and may improve cardiovascular and metabolic health, although the long-term sustainability of these effects has not been studied.^{11,17} Other benefits are not yet clearly established.

Possible Adverse Effects of IF In Nonobese People

The Minnesota Starvation Experiment of 1944–1945 during World War II was undertaken to metabolically stress 30 healthy normal-weight men over a 24-week period by utilizing a hypocaloric 2-meal-a-day diet that resulted in 25% weight loss per subject during the experiment's duration. The diet consisted of foods that mirrored the diet consumed in Europe directly after World War II. The starvation induced significant increases in depression, hypochondriasis,

and less frequently severe emotional distress and even self-mutilation.⁶⁹

Two studies have tested the metabolic effects of IF on nonobese subjects over a period of 14 to 21 days under rigorous conditions. Subjects were required to consume high dietary intake on nonfasting days. Hunger persisted with IF, and subjects commented on having difficulty sustaining daily activities.⁷⁰ Once the lean subjects began to eat again, they consumed a large quantity of food (hyperphagia) to make up for previous deficits.⁷⁰ In normal weight individuals, short-term studies on IF showed negative effects on adipose stores and lipolysis, with fluctuations in free fatty acids and skeletal muscle insulin resistance.⁷¹ Furthermore, single bursts of fasting, lasting from 24 to 48 hours, in normal-weight subjects were associated with modest elevations in hepatic and intramyocellular triglyceride levels, which do not appear within a 12-hour overnight fast.⁷¹ The outcome of a weekly continuous fast on hepatic and intramyocellular triglycerides has not been assessed over long-term periods or in patients with obesity.

In Obese People

Clinical studies found that short-term IF produced minor adverse effects, such as continuous feelings of hunger, irritability, and impaired cognition, although these effects appeared to dissipate within a month of the fasting period.¹¹ However, the data are sparse, as most studies did not analyze adverse effects specifically.^{16,46,67,72} A 2018 systematic review found no major adverse effects¹⁶; however, IF is

not recommended for pregnant or breastfeeding women, children and adolescents during maturation, or individuals vulnerable to eating disorders.⁷³

Tolerance of a diet is a major determinant of its potential effectiveness and maintenance of benefits obtained, such as weight loss or biomarker improvement.⁶⁷ A 2019 review found that dropout rates for IF varied widely from 2% to 38%, and from 0% to 50% for a CER diet.¹⁶

In addition to weight loss and weight maintenance, IF should ideally decrease total body fat stores and conserve fat-free mass (FFM) stores while maintaining resting energy expenditure (REE). Studies have shown a 5% increase in REE during the first period of starvation, resulting from expanded energy cost of recycled fatty acid, storage of glucose, and gluconeogenesis in patients with or without obesity.⁷⁴

In addition to diets, FFM and REE changes depend on the extent of physical activity and possibly also protein intake. Intermittent fasting induced minimal losses of FFM in subjects with overweight or obesity when overall protein intake was high (up to 1–1.2 g/kg) on non-energy-restricted days.⁷⁵

Other Possible Adverse Effects

Intermittent fasting has been linked to impaired sleep quality.¹ Athletic performance does not appear to benefit from IF.⁷⁶ Overnight fasting before exercise increases lipolysis, but reduces performance in prolonged exercise (>60 minutes)^{77,78} (Table 2).

TABLE 2 Possible Effects of Intermittent Fasting on Health

Advantages	Disadvantages
Weight loss ^{1,31}	Hunger ¹¹
Insulin sensitization ^{1,29,30,45}	Irritability or impaired cognition ¹¹
Protection of the beta cells of the pancreas ⁵³	Hypoglycemia ¹¹
Enhanced glycemic control ^{1,32,45,46}	Fainting ¹¹
Blood pressure control ^{32,46}	Undernutrition ¹¹
Lipid profile improvement ^{24,32,46}	Hyperphagia (postfasting) ⁷⁰
Tumor suppression ^{56,57}	Difficulty in sustaining daily activity ⁷⁰
Enhancement of chemotherapy effects ^{59,60}	Loss of fat-free mass ⁷⁵
Reduction in chemotherapy adverse effects ^{59,60}	Decrease in athletic performance ^{76–78}
Chronic pain improvement ^{61–63}	Decrease in resting energy expenditure ⁷⁴
Mood disorders improvement ^{61–63}	Alteration (improvement in few studies) in sleep quality ¹
Neutral effect on bone (no demineralization) ⁶⁴	Unsafe in pregnant or lactating women, children or adolescents, the elderly or underweight people, and individuals vulnerable to eating disorders ⁷³

Intermittent fasting has not yet been studied in children, adolescents, the elderly, or underweight people and could be harmful in all these populations.^{13,16,18,79} Also, IF is not recommended for the lean, for individuals vulnerable to eating disorders, and for pregnant or lactating women.¹⁸

IF and Weight Loss in Summary

The available trials (2–12 weeks in duration) concluded that IF resulted in weight loss (1%–13%) regardless of changes in overall caloric intake and decreased BMI (4.3% on average).⁸⁰ Symptoms such as hunger remained stable or decreased, and no major adverse effects were reported. Intermittent fasting may improve glycemic control, but it also increases the risk of hypoglycemia. The studies (8–52 weeks) on IF that used CER as a comparator found similar weight loss (4.6%–13%) in both groups.^{20,22,70,81,82}

CONCLUSION

There are several types of IF, and they sometimes with different consequences on health. The effects of IF on weight loss and cardiovascular diseases are well documented. Regarding the weight loss effect, IF does not offer any distinct advantages when compared with CER. However, for some individuals, the IF regimen may be easier to follow than other weight loss diets. Solid data are lacking regarding the impact of IF on other health behaviors, such as sleep and physical activity. There are insufficient data to determine the optimal fasting regimen, in its various dimensions or components, such as the length of the fasting interval, the number of fasting days per week, the degree of energy restriction needed on fasting days, and recommendations for dietary behavior on nonfasting days. Large-scale randomized trials of IF regimens should last for at least a year to properly assess whether behavioral and metabolic changes are sustainable and whether they have long-term effects on biomarkers of aging and longevity.

Acknowledgments

The authors thank Dr Charbel El Amm (American University of Beirut, Lebanon), Mr Andres Rodriguez, and Dr Sibelle Al Hayek (University of Kansas, United States), who helped in editing and revising the manuscript.

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