Physiology and Benefits of Intermittent Fasting

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Periods of voluntary abstinence from food and drink (fasting) has been practiced since earliest antiquity by peoples around the globe. Books on ethnology and religion describe a remarkable variety of fasting forms and practices.[1] Many religious groups incorporate periods of fasting into their rituals, including Muslims who fast during the month of Ramadan from dawn to dusk, and Christians, Jews, Buddhist, and Hindus who traditionally fast on specified weekdays or calendar year days.

Though fasting has been practiced for millennia, only recently have studies shown its role in adaptive cellular responses that reduce oxidative damage and inflammation, optimize energy metabolism, and bolster cellular protection. Fasting extends longevity, in part, by reprogramming metabolic and stress resistance pathways. In rodents intermittent or periodic fasting protects against diabetes, cancers, heart disease, and neurodegeneration, while in humans it helps reduce obesity, hypertension, asthma, and rheumatoid arthritis. Thus, fasting has the potential to delay aging and help prevent and treat diseases while minimizing the side effects caused by chronic dietary interventions.

Types of Intermittent Fasting

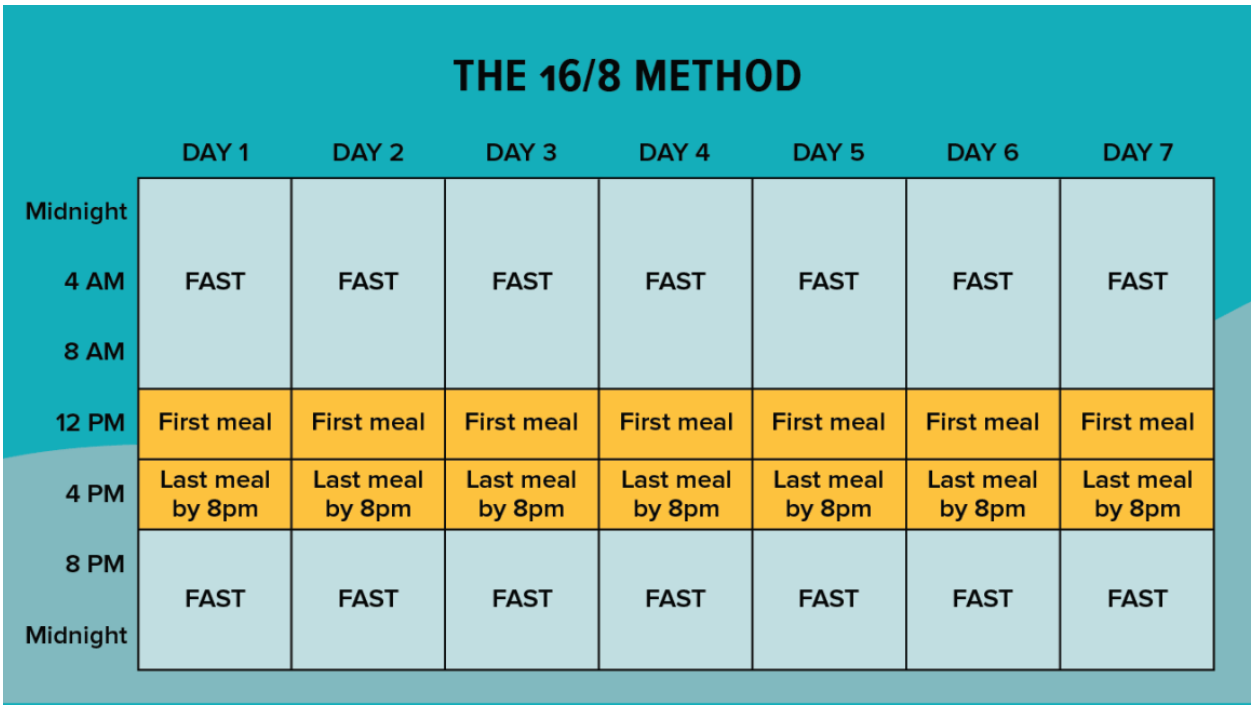
A popular form of fasting is known as intermittent fasting (IF; reduced meal frequency). The fundamentals of any intermittent fasting routine revolve around a period of not eating (the fasted state) and eating (the fed state). There are different types of IF; one method of IF involves the 16/8-time frame. This method, also known as the Leangains protocol, advocates fasting every day for 14 to 16 hours and restricting the daily "eating window" to 8-10 hours. This method was popularized by Martin Berkhan who is a personal trainer and a nutritionist.

Within the eating window, two, three, or more meals may be consumed. The Leangains method also incorporates exercise into the fasting period. When in a fasted state, the body is already burning fat for energy.

A number of animals and some human studies have shown that alternating fasting and eating times improves cellular health, potentially by activating an age-old adaptation to food shortage cycles called metabolic switches. Such a switch occurs when cells use up their stores of rapidly accessible, sugar-based fuel, and begin converting fat into energy in a slower metabolic process.

Fasting leads to pronounced metabolic changes. The shift from carbohydrates and glucose to fatty acids and ketones as the main source of cellular fuel for the body and brain seems to be a crucial factor. It has recently been referred to as intermittent metabolic switching and glucose-to-ketone switch. The reverse step–ketone-to-glucose switch–happens upon refeeding. The glucose to ketone switch includes reduction in blood glucose, insulin and IGF-1 levels, depletion or reduction of glycogen stores, and an increase in lipolysis (the breakdown of fats and other lipids by hydrolysis to release fatty acids) and ketogenesis.

Additionally, those who want to lose weight the healthy way should exercise as well. Physical activity promotes the development of muscle mass, for which a high amount of energy is used. Regular physical activity boosts the metabolism as well as fat burning processes. Walking, jogging or strength training at the gym is all compatible with intermittent fasting. By exercising, there is an increase in the body's rate of fat burning, hence why the Leangains methods advises working out in a fasted state for 1 hour– ideally 1 hour prior to the first meal, 3-4 days per week.

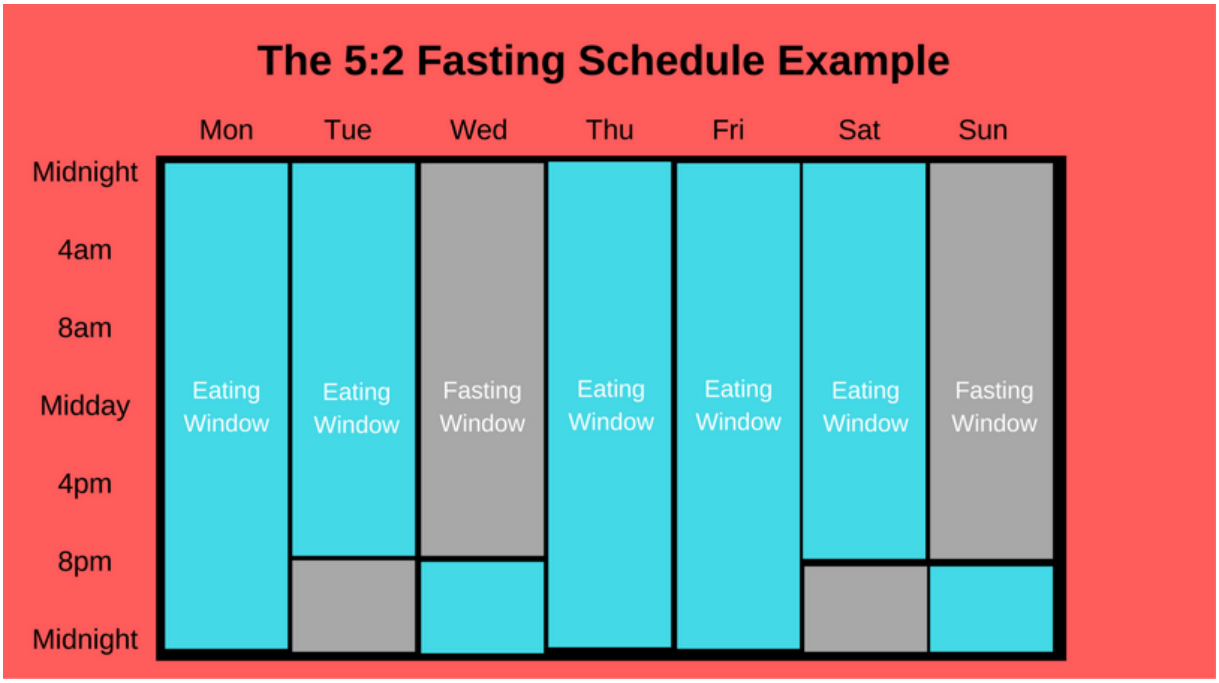


Another intermittent fasting method is the 5:2 diet that involves eating normally 5 days of the week while restricting calories to 500-600 for two days out of the week. This diet is also called '**The Fast Diet**' and was popularized by British journalist Michael Mosley. On the fasting days, it's recommended that women eat 500 calories and men eat 600 calories. For example, you might eat normally every day of the week except Mondays and Thursdays. For those two days, you eat two small meals (250 calories per meal for women and 300 calories for men). As critics correctly point out, there are no studies testing the 5:2 diet itself, but there are plenty of studies on the benefits of intermittent fasting. No matter what method of IF is used it is vitally important to always stay hydrated with water.

To achieve all the health benefits of IF, such as fat loss, increased metabolic rate, lower blood sugar levels, boost in the immune system and others, it is necessary to restrict consumption of caloric foods or drinks during the fasting period. Consuming non-caloric beverages will not break the fast. This is because non-caloric beverages do not cause the release of insulin, and consequently, do not interfere with fat burning and autophagy (cellular cleanup).

Non-caloric beverages include:

- Spring water
- Sparkling water
- Mineral water
- Plain black coffee
- Herbal tea



As with all eating programs, there are some drawbacks and side effects to IF. Intermittent fasting may not work for everyone's daily schedule, especially those who have abnormal or long working hours or extremely active lifestyles that require eating more frequently. There are people with certain health conditions who should avoid time-restricted eating.

- Eating disorders: Anyone who has an eating disorder should avoid any type of intermittent fasting routine. Intermittent fasting is healthy, but intermittent fasting can potentially turn into a form of abuse for someone with an eating disorder.
- Pregnant and breastfeeding mothers: Pregnant and breastfeeding mothers or people with high caloric needs would also do well to avoid the restricted calorie plan of intermittent fasting.

Studies in both humans and animals have shown that many of the health benefits of intermittent fasting are not simply the result of reduced free-radical production or weight loss. Instead, intermittent fasting elicits evolutionarily conserved, adaptive cellular responses that are integrated between and within organs in a manner that improves glucose regulation, increases stress resistance, and suppresses inflammation. During fasting, cells activate pathways that enhance intrinsic defenses against oxidative and metabolic stress and those that remove or repair damaged molecules.[2,]

Weight Loss

The food we eat is broken down enzymatically in our gastrointestinal tract and eventually ends up as molecules in our bloodstream. Carbohydrates, especially sugars and refined grains, are rapidly broken down into sugar, which cells use for energy. If cells do not use it all, it is stored in fat cells - as fat. But sugar can only enter cells with insulin, a hormone made in the pancreas. Insulin brings sugar into the fat cells and keeps it there.

Between meals, if no snacks are consumed, insulin levels will go down and fat cells can then be metabolized and used as energy. We lose weight if we let insulin levels go down. The whole idea of IF is to allow insulin levels to decrease low enough to allow fat metabolism for a greater length of time.

For many people, intermittent fasting schedules such as Leangains provide an advantage for weight loss. It more difficult to eat an abundant amount of food when eating within restricted feeding periods. This causes an overall decrease in calorie intake, which over time, leads to a more consistent caloric deficit, driving greater weight loss.

No matter which dieting method is used to reduce body fat, the goal is to achieve a caloric deficit. The same goal applies to intermittent fasting. According to many guides, it seems as if the caloric value is completely insignificant during the phase. However, too much food will always be turned into fat and become apparent in the form of unpleasing fat deposits. Intermittent fasting only works if one is eating mindfully during the phases of food intake. That means that the individual should not over-eat, but consume normal portion sizes, and consume healthy food whenever possible.

Fasting Physiology and Adaptive Responses

Fasting results in ketogenesis, which is the biochemical process by which organisms breakdown fatty acids and ketogenic amino acids to create ketone bodies. Additionally, fasting promotes potent changes in metabolic pathways and cellular processes such as stress resistance, lipolysis, and autophagy. Simply speaking, autophagy is the body’s way of cleaning out damaged cells, in order to regenerate newer, healthier cells. Thus, IF is detoxifying and regenerative.

IF modifies brain neurochemistry and neuronal network activity in ways that optimize brain function and peripheral energy metabolism. Four brain regions that are particularly important in adaptive responses to IF include the hippocampus (cognitive processing), striatum (control of body movements), hypothalamus (control of food intake and body temperature), and the

brainstem (control of cardiovascular and digestive systems). The brain communicates with all the peripheral organs involved in energy metabolism.

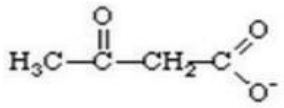
IF also enhances parasympathetic activity (mediated by the neurotransmitter acetylcholine) in the autonomic neurons that innervate the gut, heart, and arteries, resulting in improved gut motility and reduced heart rate and blood pressure. Lipolysis and the generation of ketone bodies also occur by depleting glycogen from the liver cells, eventually leading to reduced body fat. IF enhances insulin sensitivity of muscle and liver cells and reduces IGF-1 production. Levels of oxidative stress and inflammation are reduced throughout the body and brain in response to IF.

Thus, in changing metabolism, fasting can elicit numerous health benefits that, in some cases, are as effective as those of approved drugs such as the reduction of seizures and seizure-associated brain damage,[4, 5] and the amelioration of rheumatoid arthritis.[6]

Ketone bodies

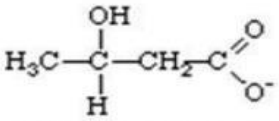
Liver mitochondria have the capacity to convert acetyl CoA derived from fatty acid oxidation into ketone bodies which are:

1- Acetoacetic acid



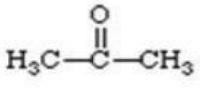
Acetoacetate

2- β-hydroxy butyric acid



D-β-Hydroxybutyrate

3- Acetone



Acetone

Functions of ketone bodies:

1-Used as source of energy. They are reconverted into acetyl CoA which is oxidized in Kreb's cycle to give energy.

2- In prolonged fasting and starvation, ketone bodies can be used as source of energy by most tissues except liver.
N.B. In fasting, most tissues get energy from oxidation of both ketone bodies and fatty acids, but the brain gets its energy from oxidation of ketone bodies. Brain never oxidizes fatty acids.

In humans and most mammals, the liver serves as the main reservoir of glucose, which is stored in the form of glycogen. Depending upon their level of physical activity, 12 to 24 hours of fasting typically results in a 20% or greater decrease in serum glucose and hepatic liver glycogen depletion, followed by a transition to a metabolic mode in which non-hepatic glucose, fat-derived ketone bodies, and free fatty acids are used as energy sources. Whereas, most tissues

can utilize fatty acids for energy, during prolonged periods of fasting, the brain relies on the ketone bodies b-hydroxybutyrate and acetoacetate, in addition to glucose, for energy consumption.

Depending on body weight and composition, the ketone bodies, free fatty acids, and gluconeogenesis allow the majority of human beings to survive 30 or more days in the absence of any food and allow certain species, such as king penguins, to survive for over 5-months without food.[7]

Fasting and the Metabolic Syndrome

Evidence is also mounting that intermittent fasting can modify risk factors associated with obesity and diabetes. Metabolic syndrome (MS), defined as abdominal adiposity, combined with insulin resistance, elevated triglycerides, and/or hypertension, greatly increases the risk of cardiovascular disease, diabetes, stroke, and Alzheimer's disease. Rats and mice maintained under the usual ad libitum feeding condition develop an MS-like phenotype as they age. MS can also be induced in younger animals by feeding them a diet high in fat and simple sugars.[8]

IF can prevent and reverse all aspects of the MS in rodents: abdominal fat, inflammation, and blood pressure are reduced; insulin sensitivity is increased; and the functional capacities of the nervous, neuromuscular, and cardiovascular systems are improved.[9, 10]

Additionally, a 2005 human study found that intermittent fasting increases insulin-mediated glucose uptake rates.[11] Preliminary findings also show promise for the use of IF as an alternative to caloric restriction for weight loss and type 2 diabetes risk reduction in overweight and obese populations.[12]

Fasting and the Aging Process

Clinical and epidemiological data are consistent with an ability of fasting to retard the aging process and numerous age-related diseases. Major factors implicated in aging whose generation are accelerated by gluttonous lifestyles and slowed by fasting in humans include the following:

(1) oxidative damage to proteins, DNA, and lipids;

(2) inflammation;

(3) accumulation of dysfunctional proteins and organelles; and

(4) elevated glucose, insulin, and IGF-I, although IGF-1 decreases with aging and its severe deficiency can be associated with certain pathologies. [13, 14]

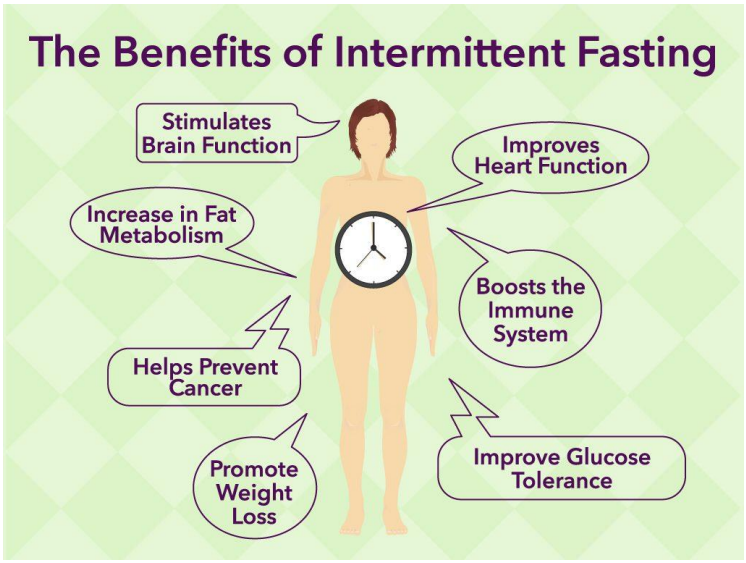
Fasting and Cancer

Caloric restriction has been shown in numerous studies to have anti-cancer, anti-tumorous properties. [15, 16, 17] However, caloric restriction may be difficult to apply in certain cases of cancer. Thus, an alternative is intermittent fasting. IF can have positive effects in cancer prevention and treatment. In mice, alternate day fasting caused a major reduction in the incidence of lymphomas[18], and fasting for 1 day per week delayed spontaneous tumorigenesis in p53-deficient mice.[19] Periodic fasting for 2–3 days was shown to protect mice from a variety of chemotherapy drugs, an effect called differential stress resistance to reflect the inability of cancer cells to become protected because oncogenes negatively regulate stress resistance, and prevent cancer cells from becoming protected.[20]

Conclusion

Intermittent fasting is a simple health intervention which can have profound benefits that go beyond weight loss. By simply eating within a defined window of time each day, several anti-aging pathways in the body are activated. One general mechanism of action of fasting is that it triggers adaptive cellular stress responses, which result in an enhanced ability to cope with more severe stress and counteract disease processes. In addition, by protecting cells from DNA damage, suppressing cell growth, and enhancing apoptosis of damaged cells, fasting could retard and/or prevent the formation and growth of cancers.

Human and animal studies have documented robust and replicable effects of fasting on health indicators including greater insulin sensitivity and reduced levels of blood pressure, body fat, IGF-1, insulin, glucose, atherogenic lipids, and inflammation. Fasting regimens can ameliorate disease processes and functional outcomes in animal model disorders including cancer, myocardial infarction, diabetes, stroke, AD, and PD.



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