



Review Article

The science of intermittent fasting: Mechanisms and health effects

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Abstract

In recent years, life has gradually shifted towards a more sedentary and convenient lifestyle. This shift is one of the major contributing factors for widespread health related problems. The World Health Organization (WHO) also highlights the global increase in non-communicable and metabolic disorders in the world. This is largely attributed to unhealthy dietary intake, sedentary lifestyle, lack of physical activity etc. One of the major health problems is obesity and overweight, which is no longer confined to high-income countries, but low-income and middle-income countries are also experiencing the same trend.

Intermittent Fasting (IF) is emerging as one promising strategy for weight management and overall health. Intermittent fasting can be done in many ways, like Intermittent Energy Restriction (IER) and Time-Restricted Fasting (TRF). There are various animal and human studies suggesting that Time-Restricted Fasting (TRF) has more pronounced health benefits. The results depicted weight loss, increased insulin sensitivity, improved cognitive function, a change in gut microbe composition, tissue repair, and reduced oxidative stress and inflammatory markers.

These effects are the result of key biological mechanisms of Intermittent Fasting (IF) such as metabolic switching of glucose to fat, modulated circadian rhythm pattern, and gut-brain axis. In various studies, it is claimed that intermittent fasting in combination with continuous energy restriction was found to mask the independent effect of intermittent fasting. According to various studies, intermittent fasting alone has the potential to reduce weight and other metabolic problems. Most of the studies are based on animal models and need more data related to human trials. This narrative review explains the evidence based underlying mechanisms of intermittent fasting along with its various health benefits.

Keywords gut brain axis, insulin-sensitivity, metabolic diseases, non-communicable diseases, obesity

Introduction

The human body is a complex system that is dependent on well-balanced food for working efficiently. The food should be balanced in terms of quality as well as quantity. The global shift towards modernization has resulted in more packaged and convenient foods. In the hustle of saving time and energy, people prioritize ease and convenience over the nutritional quality of food.

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Regular consumption of unhealthy foods, low physical activity, and sedentary lifestyle are the major contributing factors for various health problems such as metabolic problems, non-communicable diseases, obesity etc. Obesity and being overweight are the leading causes for diseases like insulin resistance, diabetes, cardiovascular diseases etc. In the last few years, obesity and overweight have emerged as one of the significant public health concerns, as they can contribute to various other health issues.

Concerning metabolic diseases, weight management for obtaining an ideal weight is one of the basic preventive measures for improving health conditions. Scientific studies suggest that Intermittent Fasting (IF) stands out as a very effective way for reducing body weight. In the last few years, Intermittent Fasting (IF) has been trending for weight management over a short span of duration. In Intermittent Fasting (IF), there is either complete abstinence or periodic restriction of meals in a day. It usually follows a cycle of periods of unrestricted eating and restricted fasting, which makes it a flexible and easy option for weight management [1]. According to Longo et al., [2], intermittent fasting improved weight reduction by metabolic switching of the body from glucose to ketone utilization. This has also been shown to enhance the weight reduction process, along with enhancing brain functioning. Intermittent Fasting (IF) can vary from Time Restricted Fasting (TRF), Modified Fasting, and Intermittent Energy Restriction (IER).

Intermittent Energy Restriction (IER)

Intermittent Energy Restriction (IER) is the type of Intermittent Fasting (IF) in which there is periodic fasting. Intermittent Energy Restriction is common in practice, and calories are restricted from 75-100% but only for a short duration and alternate normal diet [3]. IER is further categorized as a twice-weekly fast, which follows a fixed pattern of fasting for 2 days followed by 5 feeding days [4]. Alternate Day Fasting (ADF) is a form of fasting in which fasting is done for one day, followed by eating on the other day. Religious Fasting is a practice in which an individual voluntarily restricts food for a specific period as a part of culture or devotion. Time-related IER enhances weight loss by restricting calorie intake, which in turn reduces compensatory metabolic responses like reduction of resting energy expenditure [5].

Time-Restricted Fasting (TRF)

TRF operates with the body's circadian cycle. The alternate cycle of feeding and fasting is called "fasting physiology". Fasting physiology is triggered earlier as feeding time is restricted, thereby achieving the purpose of increasing energy consumption [4]. TRF improves metabolism through altering lipid and amino acid metabolite rhythmicity, without perturbing clock gene expression [6]. The most common form of TRF is 16:8, in which all energy intakes are controlled in 8 h and the fasting is performed during the remaining 16 h [7].

Modified Fasting

Modified fasting regimens are characterized by a substantial reduction in energy intake, typically limited to 20–25% of estimated daily energy requirements on regularly scheduled fasting days. According to Mosley and Spencer [8], modified fasting has periods of severe calorie restriction rather than complete restriction of food.

The most extensively studied form of intermittent fasting in both humans and animal models is Alternate Day Fasting (ADF) [9]. In a study comparing an 85% energy restriction on alternate fasting days with ad libitum chow feeding, the energy-restricted regimen resulted in reductions in visceral fat and leptin levels, along with increased adiponectin concentrations. Additional studies by this research group further demonstrated that such fasting regimens in mice are associated with decreased adipocyte size, reduced cell proliferation, and lower levels of insulin-like growth factor-1 (IGF-1) [10-13].



Alternate-day type of Intermittent Fasting (IF) is extensively studied in humans as well as animal models [9]. In animal models, the alternate-day fasting has shown effective results for managing weight and fasting glucose levels [12b]. Moreover, in other animal studies, the alternate day fasting has also significantly reduced the total cholesterol and triglycerides levels in plasma, hepatic steatosis, and suppressed inflammatory gene expression. It also modulated cancer-related risk factors and proliferation of the cells [14-16].

Mechanism of Intermittent Fasting (IF)

The period of fasting in Intermittent Fasting (IF) has a significant effect on metabolism [17]. Intermittent Fasting produces systemic effects like caloric restrictions, improving insulin resistance, reducing visceral fat, and addressing problems like dyslipidemia, inflammation, and achieving weight loss. Additionally reported benefits include improved blood lipid profile, osteoarthritis, chronic wounds healing, and thrombophlebitis [18].

Flipping of metabolic switch

One of the major mechanisms behind these responses is the flipping of the Metabolic Switch. The metabolic switch can be defined as the body's mechanism of naturally switching the primary energy source i.e., glucose coming from glycogenolysis, to fatty acids or fat derived ketones. This transition is characterized by fatty acid mobilization and oxidation with increased ketone body production. It allows the body to adapt to a period of limited food, resulting in lipolysis and ultimately weight reduction. This flipping of the metabolic switch can also be activated during sustained physical activity. This switch typically occurs after approximately 12-36 hours following the last meal. It depends on the initial liver glycogen content, the composition of the preceding meal, and an individual's amount of energy expenditure during the fast [18].

After exhaustion of glycogen stores, the body starts lipolysis for energy production, in which the stored triglycerides present in adipose tissues are converted to glycerol and free fatty acids (FFAs). These free fatty acids are then transferred to the liver. These free fatty acids are utilized to produce acetyl-CoA by the process of β -oxidation. The acetyl-coA then converted to ketone bodies such as acetoacetate (AcAc) and β -hydroxybutyrate (BHB) [7]. The acetoacetate (AcAc) and β -hydroxybutyrate (BHB) produced in the liver are then utilized by the brain for energy during starvation, which are again metabolized back to acetyl-CoA and HMG-CoA. HMG-CoA is a metabolic intermediate in the production of hormones, cholesterol, and isoprenoids, which is synthesized from acetyl-CoA. The ketogenesis caused by Intermittent Fasting results in the increased expression of BDNF. BDNF regulates energy at the cellular level in the body by boosting metabolic health and promoting negative energy balance, aiding in weight loss. The BDNF is a protein responsible for neuron growth and differentiation, which ultimately supports synaptic plasticity, neuro-modulation, mitochondrial biogenesis, memory, etc. It is significant for brain development and also reduces the level linked to neurological conditions in animal models [7]. The following flow chart explains flipping the metabolic switch (Figure 1).

During the fed conditions, the levels of circulating ketone bodies remain low ($<0.5\text{mM}$), which usually cannot be detected easily [19]. However, during fasting, ketone body levels begin to rise, reaching approximately $0.2\text{-}0.5\text{mM}$ within 8 to 12 hours and increasing further to about $1\text{-}2\text{mM}$ by 8 hours [20].

During fasting periods, activity of the mammalian target of rapamycin (mTOR) pathway is reduced, resulting in global inhibition of protein synthesis and enhanced recycling of dysfunctional proteins through autophagy [21]. Autophagy plays a critical role in the body's ability to cope with oxidative stress [22, 23]. Suppression of the mTOR pathway further leads to improvements in antioxidant defences, enhanced DNA repair mechanisms, and increased stimulation of brain-derived neurotrophic factors (BDNF) [24].

This way, intermittent fasting promotes the regular activation of the metabolic switch, resulting in lower glucose availability and sustained elevation in circulating ketone bodies [7].

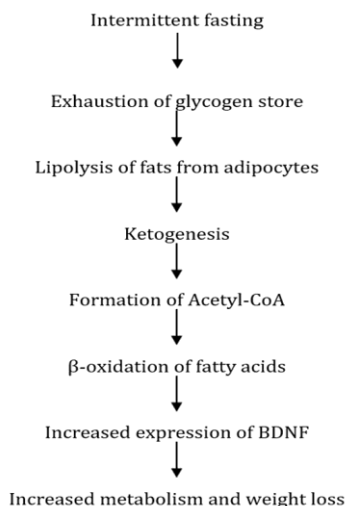


Figure 1. Flow chart explains flipping the metabolic switch

Circadian clock mechanism

Organisms have evolved endogenous circadian timing systems that coordinate physiological processes, including hormonal secretion patterns, in synchrony with environmental day-night oscillations [25]. This cycle can generally be divided into two phases: time awake (light phase) and time asleep (dark phase). From an evolutionary perspective, the light phase is designed for activity and eating, whereas the dark phase is intended for rest and recovery.

The suprachiasmatic nucleus (SCN) is a primary regulator of the circadian clock (light-dark cycle) in humans. Time-restricted fasting (TRF) has been seen to affect the circadian-regulated cycle by acting on the Mechanistic Target of Rapamycin (mTOR) signaling pathway [7, 26-27]. Time-restricted fasting (TRF) supports physiological and metabolic rhythm, helping align anabolic and catabolic activities and activity-rest pattern within the body [5].

Gut microbiome and Gut-brain axis

Another key pathway by which Intermittent Fasting (IF) supports brain health and cognitive functioning is the microbiota-gut-brain axis (MGBA). Human gut hosts trillions of microorganisms which are collectively called the gut microbiota. Higher microbial diversity correlates with favourable metabolic outcomes such as increased insulin sensitivity [28]. The gut biome composition is relevant for proper cognitive functioning. There are various interconnected mechanisms through which the gut microbiome modulates functioning of the brain [29]. The growing research evidence indicates that gut microbiome composition directly affects brain functioning through the neuro-endocrine and immune system, which together form the microbiota-gut-brain axis (MGBA) [29-30].

According to Muller et al., [31], the gut microbiota acts as a biological filter and regulator for detecting a wide range of chemical signals. These detected chemical signals can be distributed systematically to promote the health of the host. The gut microbiota can work bidirectionally with the central nervous system through interconnected neuro-endocrine and immunological pathways. This mechanism also involves activation of sympathetic neurons as well as parasympathetic neurons present within the gastrointestinal tract, regulation of the immune system, neurotransmitters, and gut derived biproducts [32-34].



The gut microbiome also produces a wide range of secondary metabolites that directly affect brain functioning and cognition. Some common examples of these metabolites produced are neuromodulators, anti-inflammatory mediators, pro-inflammatory mediators, and other compounds that support cellular energy metabolism [35-37]. These metabolites also function to maintain the blood-brain-barrier (BBB) integrity and neurodevelopment.

Impact of Intermittent fasting on human health

Improve heart health and brain performance

Various animal studies demonstrate that both intermittent fasting and calorie restriction have positive effects on heart and brain health. In rats following either a reduced-calorie diet or an intermittent fasting schedule, resting heart rate (HR) and blood pressure (BP) dropped noticeably compared to those in the control group. In addition, rats fed an IF diet exhibit improved cardiovascular responses to stress, characterized by reduced increases in BP and HR during immobilization stress and faster recovery to baseline levels once the stress is removed [38]. Various animal studies suggest that intermittent fasting has neuroprotective effects. It was also observed that IF can also reduce the accumulation of beta-amyloid (A β) plaques, which are responsible for slowing down the cognitive ability [39]. IF enhances the expression of BDNF, as it is a crucial protein that supports the survival of existing neurons, promotes the production of new neurons, and regulates overall brain functioning. In animal models, it has been evident that IF enhances the survival of newly generated neurons derived from stem cells in the hippocampus of mice, a brain region essential for learning and memory. IF has been effective against parkinson's disease, alzheimer's disease, multiple sclerosis, autism spectrum disorder, epilepsy, and other neurological problems in animal models [40].

Weight management

IF is emerging as a promising dietary strategy for weight management and treating obesity. Evidence from various clinical trials indicates that IF consistently induces weight loss ranging from modest to clinically meaningful reductions in baseline body mass, with reported losses of approximately 0.8-13.0%. Randomized control trials (RCTs) comparing IF with continuous calorie restriction demonstrate comparable efficacy, which suggests that IF has weight management effects [41]. Most available evidence on weight loss focuses on the combined effects of calorie restriction and intermittent fasting, while the independent effects of intermittent fasting alone have not been extensively studied. However, research on alternate-day fasting indicates significant benefits, including reductions in body weight (-3 to -7%), body fat (-3 to -5.5 kg), total serum cholesterol (-10 to -21%), and triglycerides (-14 to -42%), along with improvements in glucose regulation [42-43].

Improvement in insulin sensitivity

Intermittent fasting (IF) results in significant short-term improvements in insulin resistance and glycemic control in individuals with type 2 diabetes. Fasting and physical activity of an individual regulates the expression of GLUT (Glucose transporters) isoforms, particularly GLUT 4, which is sensitive to insulin and has a role in the transportation of glucose to muscles and adipocytes. Intermittent Fasting increases the expression of GLUT 4 and thereby improves insulin sensitivity [44]. Moreover, IF promotes weight loss by utilizing the fat stores present in the body and thus improves insulin sensitivity.

Insulin sensitivity influences the activation of IRS-1 and IRS-2. The levels of IRS-1 and IRS-2 also vary during fed and fasting states, as Insulin receptor substrate (IRS-1) is responsible for glycogenesis and lipogenesis during the fed state, and Insulin receptor substrate (IRS-2) is responsible for gluconeogenesis during the fasting state. IRS-2 is responsible for energy metabolism during the fasting state. When there is insulin resistance, the IRS-1 and IRS-2 don't get activated, which leads to impaired metabolism.



Randomized and pilot studies demonstrate reductions in fasting glucose of approximately 0.8–1.1 mmol L⁻¹ and decreases in HbA1c (Glycosylated haemoglobin) of about 0.7 percentage points, indicating improved insulin sensitivity during IF interventions [45, 46, 47]. Various other studies also suggest that IF is effective against increased oral glucose insulin sensitivity, decreased C-peptide levels, lower fasting glucose levels, and decreased glucagon levels.

Different IF approaches like fasting twice a week or sticking to a daily 16–17 hour fasting resulted in less need for diabetes medications, pointing to better metabolic management. However, when compared with continuous calorie restriction, IF didn't produce better results for weight management and for glycemic outcome [45, 48]. The positive effect of IF on glycemic control and insulin resistance decreased as soon as IF was discontinued, highlighting adherence to a strict schedule to sustain its long-term health benefit [48-49].

Reduced risk of cardiovascular disease

Varady et al., [50] conducted several studies examining the effects of modified alternate-day fasting on cardiovascular risk factors in overweight and obese individuals. One study reported that two months of alternate-day fasting resulted in reductions in resting heart rate, as well as decreased circulating levels of glucose, insulin, and homocysteine [51]. Another study demonstrated that the same duration of alternate-day fasting significantly reduced fat mass, total cholesterol, LDL cholesterol, and triglyceride levels [50]. However, only a limited number of studies have directly examined the relationship between intermittent fasting and cardiovascular disease outcomes. A meta-analysis done by Kibret et al., [52] also demonstrated that alternate day fasting and time restricted fasting offer significant cardiometabolic benefits. Modified alternate day fasting and time restricted fasting showed significant effectiveness in reducing weight, waist circumference, and both systolic and diastolic blood pressure. These methods were also impactful in preserving fat free mass and improving plasma blood glucose. This further illustrates how IF interventions can improve blood pressure and thereby reduce CVD risk.

Anti-inflammatory function

Intermittent fasting (IF) promotes weight loss, which in turn reduces macrophages in adipose tissue while enhancing overall inflammatory profiles and insulin sensitivity [53]. Multiple clinical studies indicate that IF decreases levels of pro-inflammatory markers like C-reactive protein (CRP), IL-6, TNF- α , and interferon- γ , especially among people with obesity [54-56]. In a systematic review of 18 randomized controlled trials, IF consistently lowered CRP, though it showed no notable effects on IL-6 or TNF- α relative to control groups [57]. There are also contradictory findings across studies. Some studies suggest that IF potentially boosts macrophage accumulation in adipose tissue because of increased lipolysis in fasting states, particularly in overweight or obese women [58].

Conclusion

Intermittent fasting is becoming popular since it is easy to adapt and fits well with both human physiology and modern lifestyle. Instead of just focusing on reducing calories, IF is based on structured periods of fasting and feeding. IF focuses on both the timing and pattern of food intake, which promotes metabolic adaptation. Findings from animal models and human studies revealed that IF affects several physiological pathways positively and thus contributes to better health outcomes. There are several benefits linked to IF, like helping in metabolic regulation, cellular repair, neurological function, and better cardiovascular health. The central mechanism that lies behind the positive effect of IF is metabolic change from glucose utilization to fatty acid and ketone metabolism.

This metabolic shift leads to improvement in insulin sensitivity, reduction in oxidative stress, and an increase in the production of ketone bodies, which serve as an efficient alternative fuel for the brain. Ketone utilization is linked to elevated levels of brain-derived neurotrophic factor (BDNF), a



protein essential for neuronal survival, synaptic adaptability, and cognitive performance. Moreover, IF suppresses activation of the mTOR signaling pathway and hence activates autophagy, increasing cellular resilience to stress and promoting tissue repair and regeneration. IF regulates the circadian cycle, especially through time-restricted fasting (TRF). By aligning eating and fasting periods with the body's internal biological clock, TRF supports improved metabolic efficiency without disturbing the expression of clock-related genes. Additionally, IF also plays an important role in influencing the composition of gut microbiota, which is closely connected with better communication along the gut-brain axis, metabolic control, and immune function. The restoration of microbial rhythmic patterns through TRF may further contribute to better cognitive benefits and overall brain health.

Among the different types of intermittent fasting, alternate-day fasting (ADF) has been shown to exert particularly strong effects on body weight regulation, lipid metabolism, and insulin responsiveness. Research findings indicate meaningful reductions in body fat, total cholesterol levels, triglycerides, and markers of inflammation, which together contribute to a lower risk of cardiovascular disease and type 2 diabetes. Although many studies have explained that IF in combination with continuous calorie restriction, growing attention is now being focused on understanding the independent metabolic effects of IF itself. However, despite encouraging results, much of the available evidence on underlying mechanisms and long-term outcomes is still based on animal models. There is a clear need for large-scale, rigorously designed human clinical trials to determine optimal fasting patterns and their long-term effects on the body. Moreover, the effects of IF on a specific population are needed to come up with specific recommendations.

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