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Benefits of Intermittent Fasting: Role In Neurological, Metabolic and Cardiovascular Health

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ABSTRACT

Intermittent fasting (IF) is an eating pattern that alternates between periods of eating and fasting, offering a range of benefits that impact the body's key systems. For the nervous system, IF enhances brain health by promoting the production of brain-derived neurotrophic factor (BDNF), improving cognitive function, and offering neuroprotection against diseases like Alzheimer's. It also reduces oxidative stress and inflammation, safeguarding neurons from damage. In the cardiovascular system, intermittent fasting helps lower blood pressure, reduce cholesterol and triglyceride levels, and decrease inflammation, all of which contribute to better heart health and a reduced risk of cardiovascular disease. From a metabolic perspective, IF improves insulin sensitivity, supports fat burning, and triggers autophagy, a vital process for cellular repair. It also boosts human growth hormone (HGH), which aids in muscle preservation and metabolic function. Regarding weight loss, intermittent fasting promotes fat loss, particularly visceral fat, by reducing overall calorie intake and enhancing fat oxidation. It also helps preserve lean muscle mass, making it a highly effective and sustainable approach for managing weight and improving overall health. In essence, intermittent fasting has a holistic effect, benefiting the nervous system, cardiovascular health, metabolism, and weight management, contributing to enhanced well-being and longevity.

Keywords: Intermittent fasting, metabolism, cardiovascular health, neurotransmitters.

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INTRODUCTION

The relationship between food and health is deeply significant because the nutrients and quality of what we eat have far-reaching effects on our physical, mental, and emotional well-being. Physically, food provides the energy and nutrients necessary for the body to perform vital functions, such as cell repair, muscle growth, and immune defence, delivers essential vitamins, minerals, and antioxidants that protect against chronic diseases such as diabetes, cardiovascular disease(1), and certain cancers by reducing inflammation and supporting organ health. Food has a powerful impact on brain function and mood regulation. Nutrients like omega-3 fatty acids, improve cognitive function and may reduce the risk of depression, while antioxidants in foods combat oxidative stress, which is linked to aging and neurodegenerative conditions(2). Conversely, poor dietary choices, such as diets high in processed foods, added sugars, and unhealthy fats, contribute to obesity, metabolic disorders, and mood disorders, exacerbating the risk of lifestyle-related illnesses. By understanding the profound interplay between food and health, individuals can make informed choices that align with their unique needs and goals for long-term well-being. The development of dietary guidelines, and research on the diet-disease relationship, such as how high-fat or high-sugar diets increase the risk of heart disease and diabetes. In recent decades, as globalization and urbanization altered food systems, there has been a growing focus on combating lifestyle-related conditions (3). At the same time, sustainability and personalized nutrition have gained prominence, emphasizing eco-friendly diets and tailored approaches based on genetics and individual health needs. These developments highlight an enduring yet ever-changing connection between food and health, deeply intertwined with human progress and well-being. The relationship between intermittent fasting and health is rooted in ancient practices, cultural traditions, and evolving scientific understanding. fasting also had the incidental benefit of promoting physical health by giving the body a break from constant digestion(4). Similarly, traditional healing systems, such as Ayurveda, integrated fasting as a way to balance bodily energies and improve overall vitality.

Studies showed that periodic fasting could improve metabolic health, support weight management, and potentially extend lifespan by promoting processes like autophagy the body's way of cleaning out damaged cells and regenerating new ones. Researchers also linked intermittent fasting to reduced inflammation, improved insulin sensitivity, and a lower risk of chronic diseases like diabetes, cardiovascular diseases, and neurodegenerative conditions. Modern variations of intermittent fasting, such as the 16:8 method or alternate-day fasting, have become popular as tools for weight loss and metabolic health(5). This resurgence reflects a blend

of ancient wisdom and contemporary science, emphasizing fasting not just as a spiritual or cultural practice but also as a scientifically backed strategy for enhancing physical and mental well-being.

Fasting and Heart Health

Increasing evidence from animal and human studies suggests that intermittent fasting (IF) can reduce the risk of cardiovascular disease (6) and enhance myocardial function and resilience (7). IF has been shown to affect pathways regulating cyclic GMP signalling(8), lipid and amino acid metabolism(5, 8-10), cell adhesion, cell death, and inflammation in the heart(11), reduce cardiovascular risk factors and protect the heart against ischemic injury(10).Proteome and phosphoproteome profiling of heart tissues obtained from mice showed that the short intermittent fasting (IF) regimens (12- or 16-hour) linked positively with pathway modifications, although longer IF regimens (every other day) exhibited an inverse connection with metabolic activities such as fatty acid oxidation and immunological responses (8). Recent investigations indicates that intermittent fasting (IF) and calorie restriction (CR) might assist obese patients lose weight and lessen their cardiovascular risk (12). IF combined with CR led to significant reductions in body weight, fat mass, and visceral fat compared to CR alone. The IFCR group lost 3.9 ± 1.4 kg vs 2.5 ± 0.6 kg in the CR group(13). The inclusion of liquid meal replacements to the IFCR protocol led to greater weight loss and reduced heart disease risk factors including as LDL cholesterol, triglycerides, and tiny LDL particles(14). There are studies depicting the synergistic effects of IF and CR on metabolic health in obese women(15). The study demonstrates that intermittent fasting with calorie restriction using liquid meals (IFCR-L) significantly reduces coronary heart disease (CHD) risk factors. Participants experienced a 19% reduction in LDL cholesterol and a 20% decrease in triglycerides, alongside increased LDL peak particle size. These lipid improvements correlated with reduced waist circumference and lower levels of pro-atherogenic adipokines like leptin and TNF-alpha. Compared to the food-based diet (IFCR-F), IFCR-L showed superior lipid modulation, emphasizing its effectiveness in managing CHD risk through dietary interventions. Adenosine monophosphate-activated protein kinase (AMPK) is activated during intermittent fasting (16) and plays a crucial role in altering right ventricular (RV) lipid metabolism and microtubule dynamics.

Intermittent fasting enhances the structural characteristics of mitochondria and peroxisomes, increases the levels of electron transport chain proteins, and restores the t-tubule structure to its original state in experimental models of pulmonary arterial hypertension (PAH). These modifications are associated with improved right ventricular (RV) function, indicating that

intermittent fasting (IF) may serve as a novel therapeutic approach to treat RV dysfunction in RV dysfunction in PAH(17), a condition currently lacking effective treatments(18). In rats, intermittent fasting before or after myocardial infarction (MI) decreases left ventricular (LV) dilatation and myocyte hypertrophy. When intermittent fasting is initiated prior to MI, its advantages are more obvious than when it is initiated after to MI. After MI, rats' overall mortality was decreased by intermittent fasting. When intermittent fasting was started before to MI, it resulted in superior diastolic function evolution, a smaller MI, and a preponderance of concentric over eccentric remodelling. Pro-angiogenic and cell survival cascades were increased by intermittent fasting, which was started two weeks after MI. After MI, rats' myocardial fibrosis and foetal gene expression were not affected by intermittent fasting (19).

Intermittent fasting (IF) has been shown to significantly improve conditions associated with high-fat diet (HFD)-induced obesity cardiomyopathy. In a study conducted on male C57BL/6J mice, IF was implemented after 13 weeks of HFD feeding. The results indicated that IF intervention led to notable improvements in cardiac function and structure, as well as in serum lipid metabolism disorders caused by the HFD (20). Intermittent fasting (IF) has been shown to exert beneficial metabolic effects on blood pressure and cardiac structure by modulating the local renin-angiotensin system (RAS) in the heart, particularly in mice fed high-fat or high-fructose diets. Demonstrated that IF significantly reduced body weight, systolic blood pressure, blood glucose, total cholesterol, and triacylglycerol levels in mice subjected to an IF regimen after an 8-week period of dietary alteration. The mechanism behind these improvements is linked to a favourable shift in the RAS. Specifically, IF promotes the ACE2/MAS receptor axis while suppressing the renin/ACE/AT1 axis, which is associated with hypertension. This modulation leads to beneficial left ventricular remodelling, characterized by reduced left ventricular mass and thickness, regardless of the diet type (21). The study demonstrates that intermittent fasting (IF) effectively alleviates atherosclerosis and enhances plaque stability for the first time. Mechanistically, IF reduces monocyte adhesion and infiltration into the endothelium by lowering circulating levels of CCL2 and Ly6Chigh monocytes. Additionally, IF significantly mitigates high-fat diet (HFD)-induced hypercholesterolemia by decreasing both cholesterol intake and synthesis in the liver. The findings suggest that monitoring circulating monocytes and CCL2 levels should be prioritized as key endpoints in atherosclerosis research, alongside traditional inflammatory markers such as C-reactive protein and IL-1β. The study concludes that IF could serve as a promising non-pharmaceutical therapy for atherosclerosis, with potential clinical applications in managing cardiovascular diseases (22).

Diverse Mechanisms of Intermittent Fasting on CVS

Intermittent fasting (IF) induces significant molecular adaptations in the heart, enhancing its resilience against ischemic injury by modifying the pathways related to cyclic GMP signalling, lipid metabolism, and inflammation, with effects varying by fasting duration, enhancing structural proteins and signalling pathways were observed, particularly in longer fasting regimens. Insulin resistance is decreased and fat oxidation is enhanced when IF initiates a metabolic shift from glucose to the use of fatty acids and ketones. Metabolic parameters are improved when IF and CR work together to positively affect hormones such as insulin, growth hormone (GH), and insulin-like growth factor 1 (IGF-1). While IF maintained metabolic benefits without rigorous calorie control, participants experienced considerable weight loss during CR, indicating that a flexible eating pattern facilitates adherence. AMP-activated protein kinase (AMPK) is activated by IF, which promotes fatty acid oxidation and improves mitochondrial and peroxisomal function in the RV, which is essential for energy production; AMP-activated protein kinase (AMPK) is activated by IF, which improves lipid metabolism and mitochondrial function in the RV, counteracting dysregulation associated with PAH; the activation leads to increased protein abundance in the electron transport chain, promoting efficient energy utilization; IF normalizes microtubule density and t-tubule structure, mitigating dysregulation associated with right ventricular failure; echocardiographic assessments revealed enhanced RV systolic and diastolic function, attributed to decreased cardio myocyte hypertrophy and fibrosis; and IF changes the composition of the gut microbiota, increasing beneficial bacteria like Lactobacillus, which may contribute to improved metabolic profiles and decreased lipotoxicity. Cardiac myocyte hypertrophy, which is essential for preserving heart function after injury, is dramatically reduced by IF started either before or after MI. Better overall cardiac performance was shown by echocardiographic evaluations that revealed decreased dilatation and enhanced left ventricular (LV) function. The overall structural integrity of the heart improved, indicating that IF mitigates unfavourable remodelling processes, even if myocardial fibrosis and fetal gene expression were not significantly changed. IF increased the levels of mRNA linked to fatty acid metabolism and decreased those linked to fatty acid absorption and synthesis. This suggests that heart tissues are moving toward better lipid metabolism. The intervention reduced levels of m6A RNA methylation, which is associated with lipid metabolism and obesity, pointing to a possible mechanism by which IF protects the heart. Cardiovascular health benefits from IF's reduction of local RAS activation in the left ventricle, which favours the ACE2/MAS receptor axis over the renin/ACE/AT1 axis. Significant drops in body weight and systolic blood pressure were the

outcomes of the fasting regimen, which enhanced heart function. By preventing hepatic cholesterol synthesis, which is essential for lowering the development of atherosclerotic plaque, IF dramatically reduces serum total and LDL cholesterol levels. In order to decrease monocyte adherence to the endothelium and the ensuing inflammation, IF lowers the numbers of circulating Ly6C high monocytes and the expression of adhesion molecules (VCAM-1 and ICAM). By increasing the amount of collagen and smooth muscle cells in plaques, the fasting diet improves their stability and decreases necrotic core areas.

FASTING AND BRAIN HEALTH

Twenty-eight people signed up in all, 14 of whom had a metabolic condition and 14 of whom were healthy. For four weeks, the fasting regimen required a daily fast of more than 14 hours. A week after returning to a regular diet, at the conclusion of the fourth week, and before to the fasting phase, BDNF levels were assessed. The findings showed a mean paired difference of -98.5 ng/ml (P = 0.0006) for BDNF levels at the conclusion of the fasting phase, indicating a substantial overall drop.(23) Significantly, those with metabolic syndrome had lower BDNF levels than healthy patients; mean paired differences were -27.6 ng/ml and -169.5 ng/ml, respectively (P = 0.003), which indicates that circulating BDNF levels are decreased by intermittent fasting diet. Thus, BDNF may have a role beyond its neurotrophic capabilities, possibly indicating inflammatory and metabolic states in people with metabolic syndrome. It also underlines the intricate link between fasting, BDNF levels, and metabolic health (24)one important dietary method for weight loss, especially for obese people, is intermittent fasting (IMF). The metabolic and neurological processes that underlie the efficacy of IMF have been investigated in recent research, with an emphasis on how it affects body weight, body composition, and metabolic health. The results show that in addition to helping obese mice lose weight and improve their metabolic parameters, intermittent fasting causes notable neurochemical alterations that may be a factor in these outcomes (25). The In contrast to controls on an ad libitum high-fat diet, the study showed that intermittent fasting (IMF) protocols, whether paired with a low-fat diet (IMF-LFD) or a high-fat diet (IMF-HFD), led to significant weight loss, with the IMF-HFD group losing roughly 13% and the IMF-LFD group losing roughly 18% of body weight. Significant reductions in body fat, ranging from 40% to 52%, were achieved with all dietary treatments. In contrast to the high-fat and IMF-HFD groups, the IMF-LFD group notably displayed an increase in lean mass of roughly 12% to 13%. Furthermore, norepinephrine level in the anterior areas of the medial hypothalamus in the IMF groups was significantly higher, indicating increased sympathetic nervous system activity. These results

demonstrate how intermittent fasting can preserve or enhance lean mass, encourage fat loss, and alter neurochemical pathways that may support metabolic health and energy expenditure.

An assessment of the effect of three months of IF on the development of the hippocampus in mice. The findings demonstrated that three months of IF markedly enhanced the hippocampus's Notch signalling pathway activity, neurotrophic factor BDNF, and downstream cellular transcription factor p-CREB. Furthermore, there was a rise in the expression of the neural stem cell marker Nestin and the postsynaptic marker PSD95. These results imply that by triggering the Notch 1 signalling pathway, IF may promote hippocampus neurogenesis.(26)PTEN is especially important for synaptic plasticity and neuronal growth in the central nervous system (CNS). Male mice with neuronal PTEN haplo insufficiency have been shown to be affected by intermittent fasting (IF). The research on intermittent fasting (IF) in Drosophila melanogaster highlights its potential to mitigate the progressive decline of the nervous system associated with aging. This decline is characterized by protein aggregate formation and the subtle dys regulation of multiple functional pathways. Previous studies have indicated that IF enhances longevity, maintains adult behaviours, and reduces protein aggregates by promoting autophagic functions in the aging brain.(27)Interestingly, IF successfully restored this memory loss, indicating that IF can reveal behavioural traits that PTEN-deficient models might conceal. Increased orexin A (OXA) neuron activation in the lateral hypothalamus and increased OXA expression in the lateral hypothalamus and spinal cord may be linked to the positive effects of IF (28)The antinociceptive effects of IF were abolished by blocking spinal orexin 1 receptors, suggesting that the orexin pathway is essential for mediating the observed cognitive advantages. One interesting approach to therapeutic therapies for enhancing cognitive performance in people with PTEN-related impairments may be the regulation of orexin signalling during IF. To fully investigate IF's potential to improve cognitive outcomes in diverse neurodevelopmental situations, more study is required(29). In animal models of intracerebral haemorrhage (ICH), intermittent fasting (IF) has demonstrated encouraging outcomes in reducing neuroinflammation and neurological impairments. Following ICH, IF reduced neurological impairments in both the acute and chronic stages(11). In terms of morphology, IF improved the removal of hematomas, decreased acute brain oedema, and lessened chronic striatal atrophy. On days 1, 3, and 7 following ICH, IF enhanced Nissl+ neurons and decreased TUNEL+ cells. IF decreased inflammatory releases (IL-1β and TNF-α) and inhibited CD16+Iba-1+ microglia activation at day 3. Microglia-specific Sirt3 deletion reduced the effects of IF, in part because it inhibited the Nrf2/HO-1 signalling pathway. IF decreased proinflammatory factors and elevated Iba-1+ microglia that expressed

Arg1 on day 7. By inhibiting inflammatory responses through the Sirt3/Nrf2/HO-1 pathway in microglia, intermittent fasting prevents ICH.

It is unclear how intermittent fasting (IF) affects neurovascular diseases brought on by chronic cerebral hypoperfusion (CCH), yet it has neuroprotective benefits on a number of illness states, including stroke. In order to examine the impact of IF on CCH-induced neurovascular pathologies, measurements of leaky micro vessels, blood-brain barrier (BBB) permeability, tight junction protein expression, extracellular matrix components, and white matter changes were made in male C57BL/6NTac mice that were given either ad libitum feeding (AL) or IF (16 hours of fasting per day) for four months. According to the study, by reducing neurovascular damage, metalloproteinase and oxidative stress-associated pathways, and cell death in the brain after CCH, IF may be a useful strategy for avoiding or inhibiting the development of neurovascular diseases in VCI and VaD. • IF reduced the rise in matrix metalloproteinase (MMP)-2 and its upstream activator MT1-MMP that was brought on by CCH. These proteins are implicated in the rupture of the blood-brain barrier and the degradation of extracellular matrix. IF raised the antioxidant indicators glutathione and superoxide dismutase and decreased the CCH-induced rise in the oxidative stress marker malondialdehyde.

In Drosophila melanogaster, intermittent fasting (IF) demonstrates the potential to slow down the aging-related progressive degradation of the neural system, which can be marked by the creation of protein aggregates and the subtle dysregulation of several functional pathways. According to earlier research, IF promotes autophagic processes in the aging brain, which prolongs life, preserves adult behaviours, and lowers protein aggregates. Notably, transcriptional drift-variance was higher in middle-aged tissues, especially in parts linked to central nervous system proteolytic pathways. Thus it is evident that intermittent fasting has been shown to exert beneficial effects on aging Drosophila, particularly regarding neuronal health and function. IF may be a useful dietary intervention to prolong life and maintain cognitive function in aged creatures by encouraging autophagy and modifying gene expression profiles. The fundamental processes and possible uses of IF in neurodegenerative disorders require more investigation.

Alzheimer's disease-induced increases in tail skin temperature were avoided by intermittent fasting. Abdominal fat accumulation was reduced by intermittent fasting. Without altering energy expenditure, intermittent fasting reduced food consumption. Alzheimer's disease enhanced the oxidation of glucose, while intermittent fasting increased the oxidation of fat as a fuel source. Despite the fact that both Alzheimer's disease and intermittent fasting worsen insulin resistance when fasting, intermittent fasting raised insulin production and lowered serum glucose

levels following oral glucose challenge (8). In rats with Alzheimer's disease, intermittent fasting reversed memory loss more effectively than ad libitum feeding. When compared to ad libitum meals, intermittent fasting improved the liver impairment index and dyslipidaemia.

Investigations wherein neurons (SH-SY5Y) were exposed to various media for 16 hours, including normal (N), calorie-restricted (CR), fasting (PF), and glucose-free (G0). The PF model showed more marked increases in mitochondrial activity and lower levels of lactate and lactate dehydrogenase (LDH). Regardless of the availability of glucose, neurons efficiently used ketones. (9)

Diverse Mechanisms of Intermittent Fasting on CVS

One important neurotrophin that controls energy balance, neurogenesis, and neuroplasticity is BDNF(30). It has a role in glucose metabolism and appetite control, both of which are essential for preserving metabolic health (31). According to the study's hypothesis, BDNF levels may be impacted by intermittent fasting, which could provide a treatment option for metabolic syndrome (32). Changes in BDNF levels during fasting were found to be positively correlated with changes in tumour necrosis factor-alpha (TNF-α) levels (30). This implies that the association between BDNF and intermittent fasting may be mediated by inflammation, identifying BDNF as a biomarker for endothelial dysfunction and inflammation in addition to its neurotrophic properties.(33)

The hypothalamus has higher norepinephrine levels when intermittent fasting is followed. One neurotransmitter that is essential for controlling thermogenesis and energy expenditure is norepinephrine. Increased lipolysis, or the breakdown of fat, and fat oxidation are two benefits of enhanced norepinephrine signalling that can aid in fat reduction while maintaining lean muscle composition. (34) Expression of Neuropeptide Y (NPY): The study discovered that IF causes the hypothalamus to express more neuropeptide Y. An orexigenic peptide called NPY increases hunger and food consumption. But when paired with calorie restriction, its elevated expression during fasting may have a dual purpose by encouraging fat mobilization and energy expenditure. (35) This effect is influenced by the hormonal alterations brought on by IF, such as elevated norepinephrine and modified NPY signalling. (36)

The equilibrium between energy intake and expenditure is impacted by intermittent fasting. The body adjusts to use stored fat while reducing muscle loss by promoting the use of fat for energy during fasting times. This adaptation is especially helpful in models of diet-induced obesity, because consuming too many calories causes fat to accumulate. (37) A neuropeptide called orexin controls appetite, arousal, and alertness. It also has a major impact on how pain is

modulated. After intermittent fasting, there was an increase in orexin expression in the spinal cord and lateral hypothalamus, indicating that orexin signalling is essential for the antinociceptive effects of fasting. The increased activity of orexin neurons, which probably contributes to analgesic effects, is responsible for the decrease in pain perception. Research indicates that orexin signalling occurs at the spinal level. The Notch 1 signalling pathway's activation is one of the main mechanisms that has been found. (38) Neural stem cell maintenance and cell differentiation depend on this mechanism. In the hippocampus of mice exposed to IF, the study discovered elevated levels of Notch 1, NICD1 (Notch intracellular domain), and HES5 (a downstream target of Notch signalling). This implies that IF enhances Notch signalling, which supports the survival and growth of neural progenitor cells, hence stimulating neurogenic processes. Increased phosphorylation of CREB (p-CREB), a transcription factor that controls genes involved in neuronal survival and development, was also seen in the study. Long-term potentiation (LTP), a process that underlies memory and learning, depends on CREB activation, which is connected to BDNF production. The hippocampus showed increased expression levels of neuronal markers following three months of IF, including NeuN (a marker for mature neurons) and Nestin (a sign for neural stem cells). This suggests that IF facilitates both the maturation of existing neurons as well as their recruitment. Intermittent fasting may induce long-term adaptations in brain plasticity, enhancing both neurogenesis and cognitive functions associated with the hippocampus(39)**.** PTEN (phosphatase and tensin homolog) is a tumour suppressor gene that regulates various cellular processes, including cell growth and survival. In PTEN haplo-insufficient mice, reduced levels of PTEN lead to hyperactivation of the PI3K/AKT signalling pathway, which is associated with increased neuronal growth but can also contribute to cognitive deficits.(40) Intermittent fasting appears to help restore a more balanced signalling environment, potentially normalizing the hyperactive pathways that impair cognitive function. IF treatment mitigated transcriptional drift-variance (TD), which is associated with the dysregulation of functional pathways, including stress response, metabolism, and neural functions. This suggests that IF can restore a more youthful transcriptional profile in aging tissues, promoting cellular health and function.(41) Increased autophagic activity helps clear protein aggregates that accumulate over time, thereby maintaining cellular proteostasis and preventing neurodegeneration. This enhanced autophagy is linked to improved neuronal health and function.(42) By improving mitochondrial efficiency and reducing oxidative damage, IF supports neuronal survival and function, which are often compromised during aging. IF helps regulate physiological processes such as sleep-wake cycles, which are critical for cognitive

health. This synchronization can improve overall behaviour and cognitive function in aging Drosophila.(27) Sirt3, located primarily in mitochondria, is crucial for regulating cellular processes such as apoptosis and autophagy, particularly under oxidative stress conditions. In the context of ICH, Sirt3 plays a protective role by modulating microglial activation and reducing the release of pro-inflammatory cytokines like IL-1β and TNF-α. This modulation helps to alleviate neuroinflammation and neurological deficits associated with ICH.(43) Specifically, elevated levels of Nrf2 lead to increased production of HO-1, an enzyme that contributes to anti-inflammatory responses and cellular protection during ICH. Research indicates that IF reduces the activation of M1-type microglia, which are associated with pro-inflammatory responses, while promoting M2-type microglia that support tissue repair and anti-inflammatory processes. This shift is crucial for minimizing neuronal injury and improving neurological outcomes following ICH. Intermittent fasting protected against the deterioration of these metabolic parameters but exacerbated bone mineral density loss and insulin resistance at fasting in Alzheimer's disease-induced oestrogen-deficient rats. Time-restricted feeding schedules, a form of IF, have been shown to restore normal circadian patterns in animal models, leading to improved sleep quality and cognitive performance. Studies indicate that caloric restriction through IF reduces the levels of this toxic protein, thereby mitigating neurodegeneration and preserving cognitive function. This reduction is thought to occur through enhanced autophagy, a cellular process that clears damaged proteins and organelles.(44)Intermittent fasting promotes metabolic adaptations that enhance energy utilization. It increases insulin sensitivity and encourages the use of ketone bodies as an alternative energy source during fasting periods(45). IF leads to improved energy metabolism by enhancing the efficiency of ATP production in neurons. During fasting periods, the body shifts from glucose to fat as a primary energy source, increasing the production of ketone bodies, which are beneficial for neuronal energy supply. This metabolic shift not only provides an alternative energy source but also helps reduce insulin resistance and improve overall metabolic health (45). Prolonged IF has been associated with decreased oxidative stress in neurons. Lower levels of oxidative stress contribute to better mitochondrial function and neuronal survival.(46) Intermittent fasting induces mild metabolic stress that triggers adaptive stress responses in neurons. These responses include the activation of autophagy, a process that clears damaged cellular components and promotes cellular repair mechanisms(47). Chronic cerebral hypoperfusion (CCH) is a significant contributor to vascular cognitive impairment. IF has been found to protect against neurovascular damage caused by CCH. It does this by maintaining the structural integrity of the blood-brain barrier (BBB) and

reducing microvascular leakage, which is essential for preventing neuronal damage and preserving cognitive function (48).IF significantly decreases oxidative stress levels in the brain. This reduction is mediated through the upregulation of antioxidant defence mechanisms, including the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates the expression of antioxidant proteins. By lowering oxidative stress, IF helps protect neurons from damage and apoptosis, thereby supporting overall brain health(46). IF exerts anti-inflammatory effects by suppressing the activation of microglia, the primary immune cells in the central nervous system. This suppression reduces the release of pro-inflammatory cytokines that contribute to neuronal injury and cognitive decline. By modulating neuroinflammatory responses, IF helps mitigate the adverse effects associated with chronic cerebral hypoperfusion(49). Intermittent fasting enhances the expression of neuroprotective proteins that support neuronal survival and function. These proteins help in repairing cellular damage and promoting resilience against stressors that could lead to cognitive impairment.

INTERMITTENT FASTING AND HUMAN METABOLIC HEALTH

Intermittent fasting (IF) has shown potential benefits in improving metabolic health and reducing obesity-related conditions based on studies in rodents and humans. Alternate Day Fasting (ADF), Modified Fasting (5:2 Diet), and Time-Restricted Feeding are all popular intermittent fasting strategies that support weight loss and metabolic health. ADF involves fasting every other day, leading to weight loss and reductions in glucose and insulin levels, though hunger on eating days can be a challenge. The 5:2 Diet, a form of modified fasting, restricts energy intake on two non-consecutive days each week, contributing to weight loss and various metabolic improvements. Time-Restricted Feeding, where eating is confined to a specific time window each day, has been shown to improve metabolic profiles and promote fat loss, supporting overall health. Each of these methods offers a unique approach to fasting, with benefits in weight management and metabolic regulation. (50)

Alternate-day fasting (ADF) has been shown to be a safe and tolerable dietary strategy for weight loss, producing similar outcomes in weight, body composition, lipids, and insulin sensitivity compared to moderate daily caloric restriction (CR) over an 8-week period. ADF resulted in a greater energy deficit of approximately 376 kcal/day compared to CR, yet weight loss was only marginally greater (ADF: -8.2 kg vs. CR: -7.1 kg). Notably, ADF did not lead to increased weight regain after 24 weeks, making it a viable option for those struggling with daily CR adherence. (51) Research indicates that alternate day fasting (ADF) is more effective than daily calorie restriction (CR) in reducing insulin resistance among adults at risk for diabetes. In a

study, ADF resulted in a significant reduction of 53% in HOMA-IR, compared to just 17% with CR, despite similar weight loss between the two diets. Neither ADF nor CR significantly impacted other metabolic risk factors, such as plasma lipids or blood pressure. This suggests ADF may offer unique metabolic benefits for insulin-resistant individuals. (52)

The combined high-protein, intermittent fasting, low-calorie (HP-IF-LC) diet effectively induces significant weight loss, improves BMI, lowers cholesterol, and enhances cardiovascular health in obese individuals. This diet is associated with reduced blood lipid levels and improved arterial compliance, contributing to long-term health benefits. A 12-week intervention showed marked improvements in resting heart rate and blood pressure, supporting its efficacy in managing obesity-related health risks. Additionally, adherence to the HP-IF diet may help minimize weight regain post-intervention. (53)**.** Intermittent fasting (IF) has shown potential benefits for metabolism and longevity, even in healthy individuals. Studies suggest that IF may enhance sirtuin activity, particularly SIRT3, which is associated with protective cellular pathways. This effect can be partially inhibited by antioxidant supplementation. Research indicates that IF can improve metabolic health, reduce oxidative stress, and promote longevity through mechanisms like autophagy and improved mitochondrial function. Therefore, IF is considered acceptable and beneficial for healthy individuals, supporting metabolic health and longevity. (54)

Intermittent fasting could be beneficial for overweight individuals to improve body composition by decreasing fat mass. In 27 trials, intermittent fasting resulted in weight loss ranging from 0.8% to 13.0% of baseline body weight, regardless of changes in overall caloric intake. A small 2018 study found people with obesity who followed the 16:8 fasting regimen for three months lost almost 3% of their body weight. Intermittent fasting may help maintain muscle mass in resistance trained subjects. Weight training during intermittent fasting may help maintain muscle, even when losing fat. Intermittent fasting could decrease GLP-1 levels and improve health-related biomarkers such as glucose and insulin levels. The 16:8 diet can decrease fat mass while preserving muscle, leading to “lean gains”. (55)

A two-year follow-up study comparing intermittent fasting (IF) to caloric restriction (CR) in obese subjects revealed that while CR resulted in a consistent weight loss of approximately 1250 grams monthly, IF led to a reduced rate of 473 grams monthly. Both methods positively impacted metabolic parameters, including BMI, glucose, and insulin levels. However, IF showed increased urinary acetoacetate levels, indicating enhanced lipid catabolism. Overall, CR was more effective for weight loss, while IF may offer benefits for health and cellular resistance without caloric restriction. (56)

Diverse Mechanisms of Intermittent Fasting on Metabolism

Intermittent Fasting (IF) and Alternate Day Fasting (ADF) offer a range of metabolic health benefits, primarily by creating energy deficits and aligning eating patterns with the body's natural circadian rhythms. IF can enhance metabolic health by improving insulin sensitivity, reducing fasting insulin levels, and promoting weight loss, which can lower the risk of obesity and type 2 diabetes. Additionally, IF can improve gut microbiota composition, reduce inflammation, and lead to healthier lipid profiles by lowering triglycerides and LDL cholesterol. ADF, which alternates between fasting and eating days, creates a more substantial energy deficit, improving insulin sensitivity and supporting weight loss with less impact on resting metabolic rate compared to continuous caloric restriction (CR). Both IF and ADF may improve cardiovascular health by enhancing arterial compliance and promoting better endothelial function. IF, in particular, is associated with gene expression changes that promote longevity, including upregulation of sirtuins, which help reduce oxidative stress and improve mitochondrial function.

Both IF and ADF promote fat loss while preserving lean muscle mass, especially when combined with exercise and adequate protein intake. This dual benefit enhances overall body composition, reducing visceral fat and improving vascular health. Furthermore, IF stimulates autophagy, a cellular repair process that clears damaged proteins and organelles, supporting cellular resilience and metabolic flexibility. These fasting strategies also contribute to reduced oxidative stress, activating antioxidant defences and reducing markers of inflammation. Studies indicate that IF improves metabolic adaptations, boosts insulin sensitivity, and helps with glucose metabolism, making it particularly beneficial for individuals at risk for type 2 diabetes. Through these mechanisms, IF and ADF not only support weight management but also foster long-term health benefits, including enhanced longevity and improved metabolic function.

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