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Intermittent Fasting: A Potential Bridge for Metabolic Health and Quality of Life

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Abstract

In contemporary societies, individuals usually consume meals at least thrice daily. Nevertheless, excessive consumption of food in this manner can frequently result in metabolic health problems such as insulin resistance and excessive accumulation of visceral fat, particularly when combined with a sedentary way of life. Over time, animals, including humans, have adapted to survive in environments where food was scarce. These adjustments enabled them to operate at a high level physically and mentally even when deprived of nourishment. Intermittent fasting (IF) involves eating patterns where people refrain from consuming energy for extended periods, typically lasting from 16 to 48 hours, followed by regular food intake on a recurring basis. We refer to this as periodic fasting (PF), which involves fasting or following diets that imitate fasting for durations ranging from 2 to 21 or more days. Laboratory investigations on rodents and mice have demonstrated that both IF and PF have notable positive impacts on various aspects of well-being. Significantly, they can also counteract disease processes and enhance overall function in experimental models of a broad range of age-related disorders, including diabetes, cardiovascular disease, cancer, Alzheimer's disease, Parkinson's disease, and stroke.

Research on IF (e.g., restricting energy by 60% for 2 days a week or every other day), alternate-day fasting (ADF) (e.g., following a 5-day diet with 750-1100 kcal), and time-restricted eating (TRE) (limiting food intake to 8 hours or less per day) in both normal and overweight individuals has shown positive effects on weight loss and various health markers such as insulin resistance and risk factors for heart disease. Mitochondrial health, DNA repair, and autophagy are enhanced through IF by activating cellular stress response pathways. Furthermore, ADF stimulates stem cell-mediated regeneration and has long-lasting metabolic impacts. To evaluate the effectiveness of IF in promoting overall wellness and managing age-related ailments, further randomized controlled clinical trials are necessary. These investigations should compare IF with ADF and continuous energy restriction, while maintaining comparable energy consumption levels.

Keywords: Intermittent Fasting, Ketone bodies, Obesity, Diabetes, Cardiovascular disease, Blood pressure, Alzheimer's disease

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Introduction

The ability of organisms to acquire nourishment is crucial for their survival and reproductive success. Hence, animals have developed various adaptations, both in behavior and physiology, to endure periods of food scarcity or absence [1-3]. In the absence of food for extended durations, certain organisms enter a state of dormancy. For example, yeast goes through a period of stability, nematodes experience a state of repose, and ground squirrels and some bears go into hibernation. Mammals have organs such as the liver and adipose tissue that act as energy reserves, enabling them to withstand periods of fasting or starvation for varying lengths of time depending on the species. It is worth noting that the metabolic, endocrine, and nervous systems have evolved in a way that allows for high levels of physical and mental performance during fasting. In this article, we explore research on IF diets, which involve extended periods of time (e.g., 16-48 hours) with minimal or no food intake, interspersed with regular periods of eating [4]. The term PF is utilized to differentiate between studies that involve frequent short-term fasting and studies that involve less frequent but longer-lasting fasting. It refers to IF with fasting periods that range from 2 days to 21 days or more, or what is known as "fasting mimicking diets." The phrase time-restricted feeding (TRF) describes a pattern of eating where the consumption of food is limited to a daily window of 8 hours or less [5-6]. Research conducted on laboratory animals has revealed the underlying cellular and molecular mechanisms by which individuals respond to fasting, resulting in enhanced overall fitness, increased resistance to injury, and protection against a wide array of diseases. Recent randomized controlled trials conducted on human participants have shown the possibility of IF, including diets that mimic certain aspects of FMDs, in humans. Moreover, these studies have indicated that IF improves various health indicators in both individuals who are in good health and those with specific chronic conditions [7].

This paper focuses on examining the impacts of IF, such as PF and FMD, on both animals and humans. Examples of specific IF diets include complete fasting every second day; reducing energy intake by 70% every other day; consuming only 500–700 calories for two consecutive days per week; and limiting food consumption to a 6–8-hour window daily, also known as "TRF". Instances of PF consist of a 4–5-day FMD, 2–5 days of fasting with only water, and a 7-day FMD.

The majority of IF studies with animals have primarily utilized either alternate day fasting or TRF, while most randomized controlled trials with humans have involved either a 60–75% reduction in energy intake (500–800 kcal) on alternate days or for two consecutive days per week. Comparing multiple IF regimens within the same study is a rarity, thus no definitive conclusions can be drawn regarding the superiority of one regimen over another in terms of enhancing health and disease resistance [8-11].

While the specific outcomes may vary depending on the type of IF pattern and the species under examination, all of the IF regimens mentioned in the previous paragraph led to a number of essential metabolic changes that characterize a fasting period. These changes include maintaining blood glucose levels within the lower normal range, depleting or reducing glycogen stores, mobilizing fatty acids, and producing ketones, lowering levels of circulating leptin, and often increasing adiponectin levels. During the fasting period of IF diets, there are also behavioral changes such as heightened alertness and improved mental acuity. The subsequent sections will cover the change in metabolic process towards utilizing ketones for fuel, as well as the adaptive reactions of the brain and autonomic nervous system in times of food scarcity. These factors play a crucial part in the positive influence of IF on physical well-being and disease prevention [12, 13]. Since overall caloric intake is typically decreased during IF, it is essential to determine how physiological responses to IF are affected by overall caloric restriction (CR). Some studies have directly compared groups practicing either IF or diets with the same calorie content, and we will outline the resemblances and variations observed in those instances. However, we will not delve into the extensive research on CR, as it has already been extensively covered elsewhere [14]. Nevertheless, it is worth mentioning that the most commonly utilized approach for daily caloric restriction in studies involving rodents (restricted daily feeding) is essentially a form of IF/TRF. In this method, the animals are individually housed, and the average amount of food they consume each day when given unrestricted access to food is considered their ad libitum food intake. Subsequently, the animals are randomly assigned to either the ad libitum control group or the CR group, with the latter receiving a designated percentage (usually 60–80%) of their normal ad libitum intake (i.e., 20–40% CR). Animals on CR typically receive their daily food ration or, in some cases, their thrice-weekly ration in a single feeding [15]. However, under these circumstances, animals on CR often consume their entire food allocation within a few hours of receiving it, resulting in IF for extended periods (e.g., 16–20 hours when fed daily, or 36 hours or more when fed thrice weekly). The extent to which IF and CR contribute to the reported increase in lifespan and health benefits observed in studies on standard CR in laboratory research has not been thoroughly explored, creating a significant gap in knowledge in this field. In this article, our main focus will be on IF, while acknowledging the role of periodic fasting or fasting mimicking diets (PF/FMDs) in terms of longevity and disease prevention in both laboratory animals and humans.

The six stages of fasting are included.

Stage 1: 8-14 hours

- Stable blood sugar levels
- Using up stored sugar and sugar in the blood
- At 10 hours—the muscles use about 50% glucose and 50% fat (you're starting to transition to fat-burning)

Stage 2: 14-24 hours

- Starting to get into ketosis.
- Fewer cravings
- More energy
- Improved mood
- Improved cognitive function.

Stage 3: 24-36 hours

- Full ketosis and fat burning
- The liver is making ketones.
- Decreased appetite.
- Decreased ghrelin.
- Increased BDNF (new brain cells)

Stage 4: 36-48 hours

- Autophagy
- Kill cancer cells.
- Decreased oxidative stress.
- Decreased misfolded proteins.
- Increased memory

Stage 5: 48-60 hours

- Insulin sensitivity super boost
- More autophagy
- Less inflammation
- Atrophy healing
- Protein sparing

Stage 6: 60-72 hours

- Immune system regeneration
- Spike in immune stem cells
- A 2014 study demonstrated that a 72 hour fast led to a complete rejuvenation of the immune system, and people on chemotherapy had less damage.

According to White, 16:8 is the most popular method. However, there are plenty of other options available (Figure 1). You fast every day for 16 hours and restrict your daily eating window to eight hours when you follow the 16:8 method of IF. Most people follow this schedule by eating nothing after dinner and skipping breakfast. The best time to eat is between noon and 8:00pm [16].

Figure 1: The 16:8 diet.

Intermittent Fasting and Health Indicators in Laboratory Animals

Comparisons between a control group that is fed freely and a group that practices IF are commonly conducted in animal studies [17]. In some cases, a group practicing daily CR is also included. It is worth noting that control laboratory rats and mice are typically sedentary, similar to the stereotypical human "couch potato", due to their ad libitum feeding and unstimulating environment [18]. This aspect should be considered when extrapolating data from IF studies in animals to humans, especially when looking at the potential effects of IF on individuals of normal weight. The two primary IF regimens used in laboratory rodents are ADF and TRF [19]. Rats and mice following an ADF regimen generally exhibit reduced body weights in comparison to the controls that have unrestricted access to food. The decrease in body weight can vary from 5% to 10% up to 25-30%, depending on the specific animal strain. The initial indication of potential health benefits associated with IF emerged from research studies in which rats following an ADF diet from a young age lived approximately twice as long as rats following an ad libitum diet. Implementing ADF during middle age extended the lifespan of rats by 30-40% when compared to those with unrestricted feeding, and regular physical activity further amplified this extension of life [20]. ADF also aids in the preservation of cognitive function and sensory-motor function during the aging process in rodents. The anti-aging impact of IF appears to be conserved across various species, as IF enhances lifespan even in simpler organisms like nematodes [21].

Different effects of IF on body composition and energy metabolism have been documented. ADF, a form of IF, leads to a reduction in fat levels, particularly visceral fat, and an increase in lean mass in rats or mice. Animals following an ADF regimen typically exhibit a greater proportion of lean mass to fat mass when compared to animals following CR diets with a 30-40% reduction [22]. In a specific investigation, mice following an ADF diet displayed similar body weights to freely fed mice, yet still demonstrated notable enhancements in glucose metabolism (reduced glucose and insulin levels) and heightened mobilization of fatty acids (increased β-hydroxybutyrate levels) [23]. These improvements were on par with, or even exceeded, the improvements observed in mice following a 40% CR diet. On fasting days, body temperature is notably lower than on feeding days. IF has been proven to enhance insulin sensitivity and improve glucose tolerance in both animal and human studies. In mice with hyperphagia and obesity caused by brain-derived neurotrophic factor (BDNF) haploinsufficiency, ADF reverses insulin resistance and reduces circulating levels of insulin and leptin. IF also promotes glucose regulation and insulin sensitivity in long-lived Ames Dwarf mice and growth hormone receptor mutant mice, thereby demonstrating the positive effects of IF in animals that maintain a low body weight as they age. Interestingly, unlike CR, SIRT1 may not play a major role in the physiological adaptations to ADF. However, while most studies on IF in rodents have shown various health benefits and protection against diseases (refer to below), there have been reports of negative effects of IF in certain rodent models. For instance, one study found that rats maintained on an ADF diet for one month had improved glucose tolerance, whereas rats maintained on ADF for 8 months had impaired glucose tolerance. Despite having a lower body weight, the rats on IF in the latter study exhibited glucose intolerance, although the reason behind this was not determined. Additionally, it has been reported that IF has detrimental effects on glucose metabolism in hypercholesterolemic (low-density lipoprotein receptor-deficient) mice, in contrast to the clear positive effects of ADF on lipid and glucose metabolism in wild-type rodents and human subjects [24-25].

Animal studies on IF have revealed various alterations in circulating hormones. Leptin and insulin levels decrease, while adiponectin levels increase in animals following an ADF diet. In response to ADF, rats experience a significant increase in corticosterone levels. However, unlike chronic uncontrollable stress, corticosterone does not have a detrimental effect on neurons in the brains of animals on ADF. Interestingly, chronic uncontrollable stress reduces the expression of the mineralocorticoid receptor in hippocampal neurons, increasing the vulnerability of these neurons to excitotoxic and metabolic stress. Conversely, IF decreases the expression of the glucocorticoid receptor while sustaining mineralocorticoid receptor expression, which is expected to enhance synaptic plasticity and boost neuronal stress resistance [26]. Furthermore, ADF has been found to impact sex hormones and gonadal function in rats. Testosterone levels increase in males but not in females following ADF, and significant changes in gene expression occur in the gonads of males compared to females [27].

The cardiovascular systems of rats and mice respond similarly to IF when they are trained to exercise aerobically. ADF results in a significant decrease in the resting heart rate and blood pressure of rats after a week, and these decreases continue for two weeks afterward [28]. It does not matter if you are fasting or feeding, these reductions persist. Rats' heart rates revert to pre-ADF diet levels after 1-2 weeks if they are returned to an ad libitum diet, suggesting that IF affects cardiovascular health only during the IF period. As a result of increased parasympathetic tone during IF, cholinergic neurons in the brain stem are stimulated, which leads to a decrease in heart rate. Although rats on ADF are moderately calorie restricted (10-20%) during IF, the impact on heart rate during IF cannot be attributed solely to caloric restriction, as mice on a 40% caloric restriction still experience greater heart rate reductions. Both exercise and IF have been shown to enhance BDNF signaling, and BDNF can decrease heart rate by boosting cholinergic neurons in the brainstem [29-31]. This suggests that exercise and IF both stimulate BDNF signaling, which increases cholinergic neuron activity in the brainstem, resulting in a decrease in resting heart rate and blood pressure, as well as an increase in heart rate variability. In rats with uncontrollable stress, IF has also been shown to enhance cardiovascular stress adaptation. Exercise and intermittent bioenergetic challenge have similar effects on heart rate and blood pressure, suggesting that both promote optimal cardiovascular health [32, 33].

The potential impact of IF on animal behavior and circadian rhythms can have implications for overall health and lifespan. The circadian regulation of energy metabolism, demonstrated by the rhythmic fluctuations of key hormones such as insulin, leptin, corticosterone, and adiponectin, can be influenced by the timing of meals. IF can modify certain behavioral aspects controlled by these rhythms, such as activity levels. For example, when animals are given food for only a few hours at a specific time each day, they tend to display increased activity in the hour or two before their feeding time. The effects of IF on the circadian regulation of energy metabolism and behavior may be due to alterations in the fundamental molecular mechanisms of the "clock" in peripheral tissues and/or the central control centers in the hypothalamic suprachiasmatic nucleus. In the case of ADF, it is suggested that the suprachiasmatic nucleus governs metabolic and behavioral rhythms when food is provided or withheld during the daytime, while the peripheral clock takes over when food is applied or withdrawn during the nighttime. In addition to affecting the hypothalamus and peripheral tissues, there is emerging evidence indicating that exercise and IF can impact the physiology of mitochondria in neurons within the hippocampus and other brain regions. This is accomplished through mechanisms involving increased generation of new mitochondria and enhanced ability to withstand

mitochondrial stress, facilitated by BDNF, PGC-1α (a master regulator of genes involved in generating new mitochondria), and sirtuin 3 (SIRT3; a mitochondrial protein deacetylase that reduces oxidative stress and cell death). These metabolic adaptations in neurons may contribute to the improvement in cognitive function observed in rodents maintained on ADF compared to those allowed to eat freely [34-35].

The available data from animal studies indicate that involuntary IF has been a fundamental challenge for animals throughout evolution, and this has resulted in the brain and other organ systems responding adaptively to IF in ways that improve the individual's ability to perform and protect themselves from illness and injury [36].

3.1. Intermittent Fasting and Age-Related Diseases in Animal Models

3.1.1. Diabetes

In simple terms, IF has the capability to hinder and treat type 2 diabetes in rodent models. For example, when sand rats are provided with a diet high in fat, they experience insulin resistance and diabetes. However, their condition improves when they are placed on a TRF diet, where they only eat during an 8-hour period each day and fast for 16 hours. Likewise, C57BL/6 mice on a high-fat diet develop hyperinsulinemia, obesity, and systemic inflammation. But these negative effects are prevented when their food intake is limited to an 8-hour window each day [37]. It's worth noting that the anti-diabetic impact of TRF in mice is not solely due to reducing calorie intake, as the mice on the 8-hour/day diet consume the same amount of food as the control mice with unrestricted access. Mice with low levels of BDNF and mice lacking BDNF experience overeating, insulin resistance, and diabetes, similar to mice lacking leptin and mice with mutated leptin receptors. However, treating mice with BDNF through daily intraperitoneal injections reverses their obesity and diabetes [38]. In the case of diabetic mice with reduced BDNF levels, their circulating levels of glucose, insulin, and leptin decrease, and their glucose tolerance normalizes when they are placed on an ADF diet. Interestingly, IF can also improve insulin deficiency and glucose intolerance in a rat model of type 1 diabetes by preserving pancreatic β-cells. Although it hasn't been fully confirmed yet, it is highly probable that IF boosts the resistance of cells to stress, which in turn safeguards β-cells. This has been observed in studies conducted on other cell types, such as myocardial cells and neurons [39-42].

As a result of increased insulin receptor signaling sensitivity, IF prevents and reverses diabetes by increasing glucose uptake by muscle and liver cells, and perhaps other cell types as well. As another signaling pathway may be affected by IF, other changes may include reduced mTOR signaling; mitochondrial function may be improved; mitochondrial biogenesis may be stimulated; and CREB, BDNF and autophagy pathways may be up regulated. Inflammation of multiple organ systems occurs in diabetes, and IF can suppress inflammation, which may contribute to the anti-diabetic effects of IF.

3.1.2. Cardiovascular Disease

Remarkable cardioprotective effects have been observed in experiments involving rats and mice. In a simulation of a heart attack, rats that had been adhering to an ADF regimen for 3 months prior to the heart attack experienced a smaller extent of heart tissue damage and a decline in the number of cells undergoing programmed cell death in the high-risk area by around 75% compared to the rats that had been fed freely. Further analysis using echocardiography after the heart attack revealed that rats on a regular diet experienced alterations in the structure of the left ventricle and an enlargement of the damaged area, whereas these changes were not detected in rats on the ADF regimen. Similarly, ADF shielded the hearts of mice from damage caused by a heart attack. However, when autophagy was impaired in mice, ADF did not confer the same protective effects. In fact, ADF worsened heart damage in mice with impaired autophagy, indicating that the beneficial effects of ADF are mediated through the stimulation of autophagy. Another study reported that IF significantly enhanced the survival rate and recovery of heart function in rats when initiated 2 weeks after a heart attack induced by blockage of the left coronary artery. While over 75% of the rats on an ADF regimen survived during the 8-week period following the heart attack, less than 25% of the rats on a normal unrestricted diet survived. The mechanism of IF's action in this study was suggested to involve hormesis and adaptive cellular stress responses, as levels of HIF-1α, BDNF, and VEGF were significantly elevated in the myocardial tissue of rats on the IF regimen compared to those on the control regimen. When initiated in 2-month-old rats, ADF protected the heart against inflammation, oxidative stress, and fibrosis associated with aging. ADF also prevented age-related increases in the activity of ERK1/2 and PBK7 kinases, as well as altered STAT3 transcription factor activity [43-45]. The beneficial effects of IF on cardiac function during aging appear to be conserved across species, as it was discovered that TRF can mitigate the decline in cardiac function during aging in fruit flies. On the contrary, another study reported that when rats were maintained on an ADF regimen for 6 months, they exhibited diminished heart relaxation and signs of reduced cardiac capacity [46]. However, the interpretation of these findings is uncertain because the rats on the ADF regimen weighed considerably less than those on the unrestricted diet, and thus may require less cardiac output to support their needs while leading a sedentary lifestyle in laboratory cages [47].

Hypertension, low heart rate variability, insulin resistance, and hyperlipidemia are factors that increase the risk of cardiovascular disease and stroke in humans. Laboratory rodents show that IF can lower blood pressure, increase heart rate variability, and improve insulin resistance [48]. The drop in blood pressure may be linked to better vasodilation in vascular endothelial cells. Rats on ADF have higher heart rate variability, possibly due to increased activity of brain stem cholinergic cardiovagal neurons. Animals on ADF and TRF diets experience lower levels of circulating cholesterol and triglycerides. TRF also helps protect against obesity and metabolic syndrome caused by atherogenic diets like high fat + glucose and high fructose diets. TRF's effects are associated with reduced hepatic triglyceride content, lower circulating leptin and triglycerides, and decreased proinflammatory cytokines in adipose tissue. Moreover, mice on TRF perform better in physical tests like the rotarod test and treadmill endurance test compared to mice with ad libitum feeding. This suggests that IF can enhance physical fitness. Importantly, these tests were conducted during the feeding phase of the compressed (9 hour) daily feeding period. This indicates that the mice's improved motor and endurance performance was not solely due to their feeding state.

3.1.3 Neurological disorders

Alzheimer's disease (AD), Parkinson's disease (PD), and stroke are commonly associated with increasing age. The deterioration and demise of neurons in these conditions are thought to be caused by impaired function of mitochondria, oxidative harm, compromised lysosomes, and dysregulated calcium balance within cells. Additionally, the excessive excitability of neurons, known as excitotoxicity, is believed to contribute to their decline. In the past, experimental models of neurodegenerative disorders relied on the use of neurotoxins that specifically induced degeneration of particular neuronal populations affected in corresponding human diseases. For example, PD models involved the administration of neurotoxins such as MPTP, 6-hydroxydopamine,

and rotenone, which inhibit mitochondrial complex I and lead to degeneration of dopaminergic neurons. Likewise, models relevant to AD included the creation of hippocampal lesions using excitotoxins like kainic acid and domoic acid, which activate glutamate receptors [49]. Moreover, inhibitors of succinate dehydrogenase (Complex II in the mitochondrial electron transport chain), such as 3-nitropropionic acid (3NPA) and malonate, selectively induce the death of striatal medium spiny neurons, which are the neurons primarily affected in Huntington's disease (HD). Starting in the 1990s, investigations were initiated to explore the potential of IF, which is known to counteract aging processes, in providing protection to neurons in animal models of neurodegenerative disorders [50]. This is particularly significant considering that aging is the primary risk factor for these conditions.

Prior to the administration of kainic acid to rats, ADF improves learning and memory impairments and prevents degeneration of hippocampal neurons. Moreover, rats following ADF exhibit reduced motor dysfunction and striatal neuron degeneration compared to rats on 3NPA and malonate, indicating that ADF could potentially serve as a treatment for patients with HD. In a study involving PD models, mice maintained on ADF for several months showed enhanced functional outcomes and decreased loss of dopaminergic neurons, suggesting that mice are more resistant to MPTP [51]. Rhesus monkeys maintained on a CR diet for 6 months experienced less motor impairment and depletion of striatal dopamine. In the same study, the levels of two neurotrophic factors known to protect dopaminergic neurons against MPTP (BDNF and glial cell line-derived neurotrophic factor) were elevated in the lesioned striatum of CR monkeys compared to those on the control diet. Various transgenic mouse models of AD have been created, which exhibit age-related accumulation of Aβ with or without Tau pathology, as well as associated learning and memory deficits. These "AD mice" express familial AD mutations in the β-amyloid precursor protein (APP) alone or in combination with a familial AD presenilin 1 mutation. Aβ is produced from APP through sequential enzymatic cleavages by β- and γ-secretases, with presenilin 1 serving as the enzymatic subunit of the γ-secretase enzyme complex. When 3xTgAD mice (which express APP, presenilin 1, and Tau mutations) were maintained for 1 year on either a 40% CR or ADF diet starting at 5 months of age, they did not develop the cognitive impairment observed in 3xTgAD mice fed ad libitum. Interestingly, while levels of Aβ and Tau accumulation were reduced in the brains of 3xTgAD mice on the caloric restriction diet, they remained unchanged in 3xTgAD mice on the ADF diet, suggesting that IF can protect neurons from dysfunction even in the presence of Aβ and Tau pathologies. Other studies have also demonstrated that caloric restriction can attenuate Aβ pathology in the brains of mice with APP mutations. The mechanisms by which IF protects against synaptic dysfunction and cognitive deficits in mouse models of AD are currently unknown, but they may involve reductions in oxidative stress, preservation of mitochondrial function, and increased signaling of neurotrophic factors and autophagy. This is because IF induces expression of antioxidant enzymes and neurotrophic factors such as BDNF and FGF2, BDNF stimulates the production of new mitochondria, IF up-regulates autophagy, and neurotrophic factors and interventions that enhance mitochondrial bioenergetics and autophagy can protect neurons in experimental models of AD [52].

Familial PD can be caused by mutations in α-synuclein. Various strains of transgenic mice, whether expressing wild type or mutant human α-synuclein, exhibit a gradual build-up of α-synuclein in neurons, resulting in motor dysfunction and eventual death. Mice that express the mutant form of α-synuclein (A53T) demonstrate impaired heart rate regulation, characterized by an elevated resting heart rate due to the accumulation of α-synuclein aggregates in the brainstem and reduced cardiovagal tone. The autonomic deficit in these mutant mice was reversed by maintaining them on an ADF, while a high fat diet exacerbated the deficit. Furthermore, a high fat diet hastened the onset of motor dysfunction and brainstem pathology in another strain of α-synuclein mutant mice, which was associated with decreased activity of kinases known to be involved in neurotrophic factor signaling [53]. In addition to promoting neurotrophic factor/BDNF signaling, IF may counteract PD-related pathological processes by stimulating autophagy. In fact, inhibiting mTOR with rapamycin, which boosts autophagy, reduced oxidative stress and synaptic damage, and improved motor function in a mouse model of PD based on α-synuclein accumulation.

The level of BDNF is decreased in the striatum and cortex of mice with the huntingtin mutation, leading to insulin resistance in the periphery and gradual degeneration of neurons in the striatum and cortex. ADF, when initiated prior to the onset of motor dysfunction in huntingtin mutant mice, raises BDNF levels in the brain, normalizes glucose metabolism, and significantly postpones the emergence of neurodegeneration and motor dysfunction. Despite its proven benefits in animal models of AD, PD, and HD, ADF has been shown to have no positive effects and instead exacerbates motor dysfunction in a transgenic mouse model of amyotrophic lateral sclerosis (ALS), where the mice have an overexpression of a mutant form of Cu/Zn superoxide dismutase that is responsible for familial ALS in humans. One possible reason for the lack of benefit in the ALS model is that the neurons affected in ALS (lower and upper motor neurons) are incapable of adaptively responding to the metabolic challenge presented by fasting.

When initiated before ischemic injury, ADF reduces brain damage and improves function in animal stroke models. There are a lot of ways IF protects brain cells from stroke, but we don't know how it works at the molecular and cellular level [54]. In addition to neurotrophic factors (BDNF and FGF2), antioxidant enzymes (heme oxygenase 1), and protein chaperones (HSP70 and GRP78), they upregulate. In addition, IF may also reduce inflammation in stroke models, as evidenced by lower levels of proinflammatory cytokines (TNF, IL1, and IL6), and suppression of the 'inflammasome'. In an animal model of systemic inflammation, IF has been found to reduce cerebral oxidative stress and cognitive impairment caused by lipopolysaccharide. In stroke models, it's been shown that lowering leptin levels and increasing ketones helps protect the brain. It's still unclear if IF helps animals recover from strokes. We need this information to figure out if IF can help humans as well. In animal studies, IF improved outcomes after traumatic nerve damage and peripheral neuropathy. ADF improved outcomes and reduced spinal cord damage in rats with incomplete cervical spinal cord injury and thoracic contusion injury. It also helped when ADF was started after thoracic contusion spinal cord injury. In a mouse model of spinal cord injury, however, ADF started after the injury didn't really make much of a difference. There's still a lot we don't know about why ADF works in rats but not mice, so more research is needed [55]. Traumatic brain injury is also a major killer, especially in young people. Even though IF hasn't been studied in animal models of traumatic brain injury, calorie restriction 4 months before the injury (limited daily feeding with a 30% reduction in calorie intake) reduced brain damage, improved cognitive function, and increased BDNF levels in the affected brain areas.

It is unclear why ADF is effective in rats, but not mice, and further investigation is necessary. Traumatic brain injuries contribute significantly to disability and mortality, particularly among young and active individuals, similar to spinal cord injuries. However, it has been observed that CR (daily restricted feeding with a 30% reduction in calorie intake) has the effects of IF on animal models of traumatic brain injury. As soon as the program is started four months before the

injury, brain damage is reduced, cognitive deficits improve, and BDNF levels rise in the affected cerebral cortex and hippocampus. IF has been shown to enhance peripheral nerve health and immunity to illnesses, according to recent research. In a mouse model of the demyelinating neuropathic condition Charcot-Marie-Tooth type 1A (Trembler mice), ADF improved motor performance, increased myelination, and decreased PMP22 protein aggregate accumulation. According to additional research, IF promotes peripheral nerve health and disease resistance by upregulating autophagy and related mechanisms for protein quality control.

3.1.4. Cancer

Lately, a bunch of studies in animal models have shown that PF lasting 2 or more days can be just as good as chemotherapy in slowing down the progression of a wide range of cancers. But the real kicker is that it can protect normal cells from the nasty effects of chemotherapy drugs while making cancer cells more sensitive to the treatment.

A super strict diet that mimics PF and starts in middle age can really do a number on tumor incidence, not to mention putting off when tumors start and reducing the number of places with tumor-like lesions. It's like it's saying, "Hey, metastatic cancers, you better watch out!". We've gone into more detail about the role of PF and FMDs in cancer prevention and treatment elsewhere [56]. But for now, let's focus on IF and cancer. We've looked into IF in murine cancer models, mostly for cancer prevention. A study on the effects of ADF on the survival of 3–4-month-old tumor-free and tumor-bearing Fisher rats. Turns out, 50% of the ADF rats made it to day 10, compared to only 12.5% of the rats on the control diet. And get this, the study had both a tumor prevention and a tumor treatment part. They started the ADF a week before the rats got injected with ascites tumor cells. All that to say, it's kind of hard to figure out exactly how it works.

A further study demonstrated that mice with accelerated cancer death phenotypes undergoing one day of fasting per week survived significantly longer than mice on ad libitum diets. Only 8% of insulin-like growth factor 1 (IGF-1) levels were reduced by the one-day IF diet, which may explain its limited effectiveness.

With all the new research on those high-calorie FMDs and their effects on mice and humans, it's important to compare them directly with other fasting diets like ADF, the 5:2 diet, and TRF. We've seen how combining PF or FMDs with chemotherapy can really pack a punch and even lead to cancer-free survival in mice. But we need to be cautious about the potential toxicity when combining fasting diets with chemotherapy, especially on the feeding days [57]. It's possible that this could increase the growth of different cell types and promote the development of secondary tumors. We should also consider how IF diets might affect the metabolism of chemotherapy drugs, as this could impact their effectiveness against cancer cells.

The majority of investigations on IF in humans have focused on examining whether IF could serve as a potential approach to decrease weight and rectify unfavorable metabolic parameters in obese and overweight individuals (Figure 2). This holds significance as the challenges of sustaining continuous energy restriction (CER) for long-term weight management are widely recognized. Johnson et al. conducted the initial trial on IF for weight reduction in a group of 10 obese subjects with asthma. The trial involved alternate days of an 85% energy-restricted low carbohydrate diet plan. Results from this study indicated favorable reductions in serum cholesterol and triglycerides, as well as markers of oxidative stress (8-isoprostane, nitrotyrosine, protein carbonyls, and 4-hydroxynonenal adducts) and inflammation (serum tumor necrosis factor-α) [58]. Ketone levels in the bloodstream were also found to be elevated during the fasting days. Although this study demonstrated the feasibility of IF in obese subjects, the absence of a CER comparison group prevents us from distinguishing whether the benefits were a result of overall energy restriction and weight loss or a specific effect of the IF regimen. The most extensively studied IF schedule has been alternate days of 70% CR, which is a modified version of ADF. Several studies on ADF, as summarized in recent reviews, have shown positive outcomes such as reductions in weight (−3 to −7%), body fat (3 −5.5 kg), total serum cholesterol (−10 to −21%), and triglycerides (−14 to −42), along with improvements in glucose homeostasis. However, the lack of a CER control group in the majority of these studies once again prevents us from determining whether these effects are due to the overall energy restriction and weight loss or a specific effect of the IF regimen.

Up until now, only a small number of published randomized controlled trials have examined if IF could be as good as or better than an isocaloric CER for managing weight and metabolic risk in overweight or obese individuals. These trials have tested different IF plans, including: having 2 consecutive days of a 55-70% CR every week, having 4 days of 50% CR each week, following an alternating pattern of 3-7 days with 70%, 60%, 45%, and 10% CR per week, and having alternating days of a 70% CR and ad libitum eating. These studies were relatively small in scale and all of them reported similar weight loss outcomes for IF and CER. In this particular study, there wasn't a significant difference in weight loss between the groups, but there was a greater reduction in body fat with two different low carbohydrate IF plans compared to CER over a span of 4 months [59, 60]. A low carbohydrate, low energy diet (70 percent carbohydrate, 600 calories, 40 grams carbohydrate) and a less restrictive low carbohydrate diet (55 percent carbohydrate, 1000 calories, 40 grams carbohydrate) with monounsaturated fats and protein ad libitum were both included in both IF regimens. A Mediterranean-style diet was followed for five days (45% carbs, 30% fat, 15% monounsaturated fatty acids, 8% polyunsaturated fatty acids, and 7% saturated fatty acids). A Mediterranean diet with 25% CER was compared to them. It's unlikely that any differences in adherence and reductions in adiposity can be attributed to differences in carbohydrate intake between the diet groups (41% and 37% of energy for the two IF diets, compared to 47% for the CER diet).

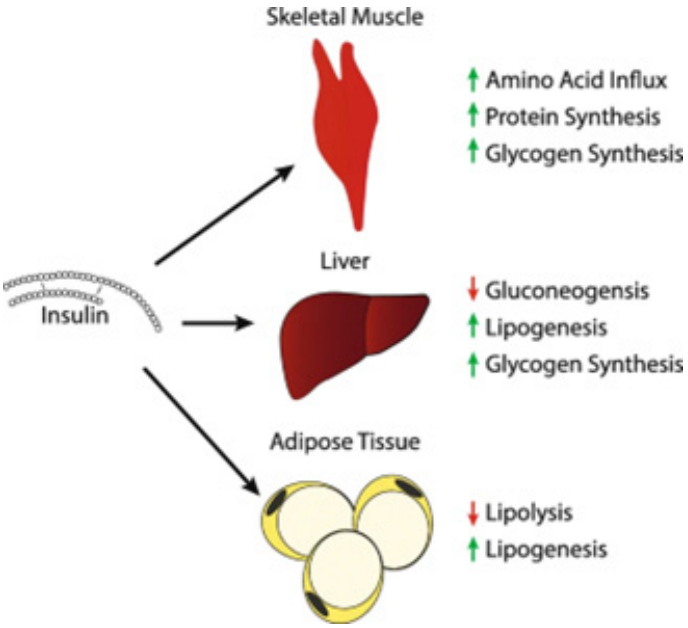

Figure 2: Effects of Insulin on Various Tissues [63]

Dropping out from the selected studies ranged from 0 to 40%, which was pretty much the same for both the IF and CER groups. The studies that looked at adherence to IF days showed that people did a good job sticking to it, achieving 65-75% of the potential IF days during the trial period. And here's the important part: when people weren't on the diet, they didn't try to make up for it by eating a ton. None of the trials showed any excessive eating on the non-dieting days. In fact, the two Manchester trials found that people actually ate less on those days, by about 23-32%. So, on those days, the energy restriction was similar to what was planned for the women on the CER diet. In our 2013 study, we found that the two-day low carbohydrate IF diet resulted in greater fat loss compared to CER. This seems to be because people stuck to the restricted days and naturally ate less on the non-restricted days.

The primary goal of weight loss diets is to maximize the reduction of body fat while minimizing the loss of fat-free mass (FFM). This is important in order to maintain physical function, prevent declines in resting energy expenditure, and avoid weight gain. Advocates of IF diets argue that they can help preserve FFM, enabling our hunter-gatherer ancestors to survive periods of food scarcity. However, there is limited evidence to support this claim due to the relatively small size of IF trials, which may not have sufficient statistical power to demonstrate changes in FFM. Studies comparing weight loss among overweight and obese individuals suggest that both IF and CER lead to similar losses of FFM, with the protein content of the diet playing a significant role, rather than the specific pattern of energy restriction. This finding is well-established for CER diets. In our initial IF trial, we observed comparable weight loss as FFM with both IF and CER approaches (both 20%), when the diets provided a protein intake of 0.9 g per kg of body weight. Our 2013 trial reported equal losses of FFM (both 30% of weight lost) with a standard protein (1.0 g protein/kg body weight) IF compared to a standard protein CER (1.0 g protein/kg body weight), but a greater preservation of FFM (20% of weight loss) with a higher protein IF (1.2 g protein/kg weight) ($p<0.05$). Studies of ADF have reported the proportion of weight lost as FFM to be as low as 10% in obese women and as high as 30% amongst non-obese subjects. Subsequent studies have shown that exercise helps to retain FFM amongst subjects undergoing IF which is well documented with CER. In fact, a study demonstrating the effects of TRF (8 hour feeding period every day) on young adult men with resistance training demonstrated that fat mass was lost while lean mass was retained, and muscle endurance improved [61]. At least some IF diets do not adversely affect physical performance and can even enhance it. These results are consistent with those of TRF in mice.

Although the effects of IF versus CER in the studies mentioned above have piqued interest, these studies have been relatively short-term (lasting no more than 6 months). The true measure of a successful weight loss diet lies in its ability to sustain weight loss over the long term. The success rate of maintaining weight loss with CER (defined as maintaining a weight loss of more than 10% for at least 12 months) varies between 20% and 50%, depending on the level of ongoing support. In a recent study, obese individuals were randomly assigned to either zero-calorie ADF or daily CER (with a caloric intake 400 calories below their baseline) for a period of 2 months, followed by 6 months of unsupervised follow-up. During the 2-month intervention, both groups experienced weight and fat loss. However, at the 6-month follow-up, changes in lean mass and fat mass from the baseline were more favorable among the subjects in the ADF group. It's worth noting that this latter study is the only published data on weight loss maintenance with IF, creating a significant gap in the existing evidence. There is currently no data on the potential of IF regimens to prevent weight gain in individuals with a normal weight. Strategies to prevent weight gain in individuals with a normal weight are crucial for public health, as adult weight gain is a major public health concern associated with the risk of various non-communicable diseases such as cancer, diabetes, cardiovascular diseases, and dementia. Reports of persistent hunger with IF and difficulties in carrying out daily activities during restricted days of IF in non-obese individuals suggest limited compliance and potential effectiveness of these specific regimens in this population. However, other patterns of IF, such as one day of calorie restriction per week, may be better tolerated and should be explored in non-obese individuals [62]. Lastly, in addition to controlled studies on IF in human subjects, there have been numerous studies on health indicators in individuals who fast from dawn until dusk during the month of Ramadan. Overall, it seems that many individuals lose weight during Ramadan and experience improvements in certain health indicators. However, these studies are generally not well-controlled due to the significant variation in daily fasting periods (ranging from 9 to 20 hours) based on the geographical location of the subjects.

These studies have sparked interest in comparing IF to CER, but they're short-term (only lasted up to 6 months). The real measure of a successful weight loss diet lies in its ability to keep the weight off for a long time. The success rate of maintaining weight loss with CER (meaning keeping off more than 10% of weight for at least a year) ranges from 20% to 50%, depending on the level of ongoing support. In a recent study, obese people were randomly split into two groups: one group followed ADF with zero-calorie intake, and the other group followed daily CER (eating 400 calories less than their usual intake) for 2 months, and then they were left on their own for the next 6 months. Both groups lost weight and fat during the 2-month period. However, after 6 months, the ADF group showed better improvements in lean mass and fat mass compared to their starting point. It's worth mentioning that this study is the only published data on weight loss maintenance with IF, which leaves a big gap in the existing evidence. Currently, there is no data on whether IF can help prevent weight gain in people who have a normal weight. Preventing weight gain in people with a normal weight is important for public health, as gaining weight as an adult is a major concern linked to the risk of various diseases like cancer, diabetes, heart disease, and dementia. Reports of feeling hungry during IF and having difficulties doing daily activities on restricted days of IF in non-obese individuals suggest that these specific regimens may not be very effective or easy to stick to for this population. However, other patterns of IF, like restricting calories for one day per week, may be better tolerated and should be explored in non-obese individuals. Lastly, in addition to controlled studies on IF in humans, there have been many studies on health indicators in people who fast from sunrise to sunset during Ramadan. Overall, it seems that many people lose weight during Ramadan and see improvements in certain health indicators. However, these studies are generally not well-controlled because the fasting periods vary greatly (from 9 to 20 hours) based on where the subjects are located.

3.2. Intermittent Fasting and Age-Related Diseases in Humans

3.2.1. Type 2 Diabetes

Limited information exists regarding the impact of IF compared to CER on glucose regulation in overweight/obese individuals with type 2 diabetes. The effects of incorporating periods of IF into a standard 25% CER diet, with either 75% energy restriction for 5 days per week every 5 weeks or 1 day per week for 15 weeks. As expected, additional periods of energy restriction led to greater weight loss. The intervention of 5 days per week every 5 weeks resulted in the most significant improvement in HbA1c levels, regardless of weight loss, suggesting a potential insulin-sensitizing effect specific to this pattern of IF combined with CER. The effects of ADF (24-hour total fasting and 24-hour unrestricted feeding)

on 16 normal and overweight men and women. Peripheral insulin sensitivity, measured by glucose uptake during a test meal, was evaluated the morning after a fasting day, following a 36-hour fast. Interestingly, insulin sensitivity increased in men but decreased in women [63]. The decrease observed in women may be related to higher levels of free fatty acids during fasting, which is likely a normal physiological adaptation rather than a cause for concern. Therefore, IF has been found to have varying effects on peripheral and hepatic insulin sensitivity, which may differ between obese and normal weight individuals and may be influenced by gender. Further research utilizing more reliable measures of insulin sensitivity, such as the insulin clamp or other techniques, is necessary.

3.2.2. Cardiovascular Disease

Varady and her team [2, 17] conducted a series of experiments to assess the impact of ADF on cardiovascular risk factors in individuals who are overweight or obese. In one particular study, they implemented ADF for a duration of 2 months, which led to a decline in resting heart rate, as well as decreased levels of glucose, insulin, and homocysteine in the blood. These changes have favorable implications for minimizing the risk of cardiovascular disease. Another study discovered that adhering to a 2-month ADF regimen resulted in a reduction in fat mass, total cholesterol, LDL cholesterol, and triglyceride concentrations. Nevertheless, there is a scarcity of studies comparing the effects of IF and CER on indicators of cardiovascular risk [64]. Randomized comparisons between IF and CER have demonstrated similar decreases in blood pressure and triglycerides. Additionally, these comparisons have revealed an enlargement in LDL particle size. Hill et al. observed a more significant decrease in serum cholesterol with IF (14%) when compared to CER (6%).

3.2.3. Intermittent Fasting and Cancer

We don't have any data on how IF affects cancer rates in humans. Keeping your weight under control is probably going to lower the risk of thirteen different types of cancer that are connected to obesity. However, we don't know how managing your weight after being diagnosed with obesity-related cancer affects the outcome [65]. Some indirect evidence suggests that IF might lower the risk of cancer, based on its impact on certain biomarkers associated with cancer risk. These biomarkers include insulin, cytokines, leptin, and adiponectin, which are believed to play a role in how obesity and excessive energy intake contribute to cancer development and growth in humans.

The impact of IF on overall and available IGF-1 in human trials has shown variation. This is due to the fact that, unlike animal trials, the levels of total IGF-1 and active IGF-1 (measured through IGF-binding proteins 1, 2, and 3) in circulation are not reliable indicators of the effects of energy restriction and weight loss in humans. Additionally, they do not accurately correspond to IGF-1 bioactivity at the tissue level. However, both IF and CER increased the levels of IGF binding protein 1 (by 26% and 28%, respectively) and IGFBP-2 (by 22% and 36%, respectively), while not affecting serum bioavailable IGF-1 (measured after feeding days and ultrafiltered).

Numerous human studies have yielded varying outcomes regarding IGF-1. In contrast to animal studies, the levels of total IGF-1 and active IGF-1 (assessed via IGF-binding proteins 1, 2, and 3) in the bloodstream do not consistently indicate the impact of energy restriction and weight loss on humans. These measurements fail to provide insights into the tissue-level functioning of IGF-1 [66]. Our own investigation discovered no alteration in the overall levels of circulating IGF-1, despite achieving weight loss through either IF or CER. However, both IF and CER did elevate the levels of IGF binding protein 1 (by 26% and 28%, respectively) and IGFBP-2 (by 22% and 36%, respectively). Interestingly, the bioavailable IGF-1 in the blood (measured using ultrafiltration) remained constant after days of consuming meals.

Higher leptin production and lower adiponectin production in adipose tissue are associated with increased adiposity. This is thought to impact cancer development and progression by influencing insulin sensitivity, inflammation, cell proliferation, and apoptosis. Only overweight individuals experience a rise in adiponectin levels following significant weight loss (>10%) that involves reduction in body and visceral fat. Some studies on IF have revealed modest weight loss accompanied by a 30% increase in plasma adiponectin on fasting and feeding days, as well as reductions in weight (−4%) and body fat (−11%). Interestingly, our research suggests a potential greater elevation in adiponectin with IF compared to calorie restriction, despite similar reductions in weight and adiposity ($p = 0.08$) [67-69]. However, our subsequent study on IF found no change in adiponectin levels with either IF or calorie restriction. IF leads to significant and comparable reductions in leptin (40%) and the ratio of leptin to adiponectin, similar to calorie restriction. CR results in a decrease in circulating levels of C reactive protein by 2-3% for every 1% weight loss, while TNF-α and IL-6 are reduced by approximately 1-2% per 1% weight loss. The reductions in inflammatory markers observed with IF are similar to those seen with CR for a given weight loss [70]. Therefore, although the available biomarker data is limited, it indicates that IF produces similar changes in most cancer risk biomarkers as CR, except for insulin resistance and adiponectin, which necessitate further investigation using rigorous methodologies [Figure 3][70].

4. Conclusions and Future Directions

There are numerous physiological markers of well-being that show improvement in laboratory rats and mice that are on IF diets such as ADF and TRF. Some of the positive effects of IF include: decreased levels of insulin and leptin, which coincide with increased insulin and leptin sensitivity; lower body fat; higher ketone levels; reduced resting heart rate and blood pressure, along with increased heart rate variability (resulting from heightened parasympathetic tone); reduced inflammation; improved resistance of the brain and heart to stress (e.g., less tissue damage and better functional outcome in stroke and myocardial infarction models); and increased resistance to diabetes. IF has the potential to delay the onset and slow down the progression of neuronal dysfunction and degeneration in animal models of AD, PD, and HD. Emerging discoveries are uncovering the cellular and molecular mechanisms through which IF enhances the resilience of cells, tissues, and organs against stress and common diseases associated with aging and sedentary, indulgent lifestyles. Human studies that have measured various health markers at the beginning and after periods of IF lasting 2–6 months or more indicate that IF may provide protection against the metabolic syndrome and related conditions like diabetes and cardiovascular disease. Recent small trials involving IF in cancer patients and multiple sclerosis patients offer a strong foundation for conducting larger clinical trials in chronic age-related and obesity-related disorders.

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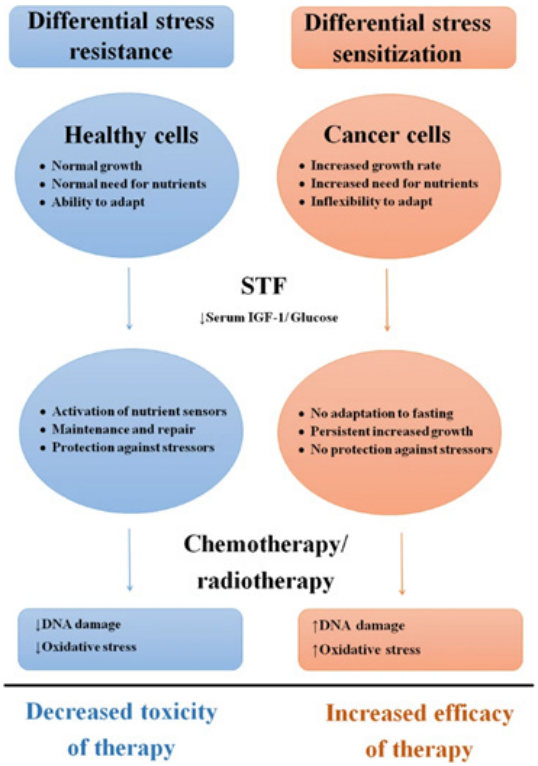

Figure 3: Differential effects of short-term fasting on healthy and cancer cells [70].

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