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Flipping the Metabolic Switch: Understanding and Applying Health Benefits of Fasting

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Abstract

Intermittent fasting (IF) is a term used to describe a variety of eating patterns in which no or few calories are consumed for time periods that can range from 12 hours to several days, on a recurring basis. Here we focus on the physiological responses of major organ systems, including the musculoskeletal system, to the onset of the metabolic switch – the point of negative energy balance at which liver glycogen stores are depleted and fatty acids are mobilized (typically beyond 12 hours after cessation of food intake). Emerging findings suggest the metabolic switch from glucose to fatty acid-derived ketones represents an evolutionarily conserved trigger point that shifts metabolism from lipid/cholesterol synthesis and fat storage to mobilization of fat through fatty acid oxidation and fatty-acid derived ketones, which serve to preserve muscle mass and function. Thus, IF regimens that induce the metabolic switch have the potential to improve body composition in overweight individuals. Moreover, IF regimens also induce the coordinated activation of signaling pathways that optimize physiological function, enhance performance, and slow aging and disease processes. Future randomized controlled IF trials should use biomarkers of the metabolic switch (e.g., plasma ketone levels) as a measure of compliance and the magnitude of negative energy balance during the fasting period.

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Introduction

Calorie restriction (CR), a reduction in caloric intake without malnutrition, has consistently been found to produce reductions in body weight and extend healthy life span across a variety of species,(1) including non-human primates.(2) Studies conducted in overweight humans indicate short-term CR (6-months) can significantly improve several cardiovascular risk factors, insulin-sensitivity, and mitochondrial function.(3) Thus, there is emerging evidence from human clinical trials to indicate in overweight adults, CR may have a number of beneficial effects, in addition to weight loss. Unfortunately, findings from obesity intervention trials over the past several decades indicate the vast majority of humans have significant difficulty sustaining daily CR for long periods of time.(4)

In recent years, intermittent fasting (IF) has gained popularity as an alternative to continuous CR and has shown promise in delivering similar benefits in terms of weight loss and cardiometabolic health.(5–9) In contrast to traditional caloric restriction paradigms, IF is a dietary approach that requires fasting for varying periods of time, typically for 12 hours or longer.(6, 10, 11) For example, alternate-day fasting (ADF) is a form of IF where individuals alternate between not consuming any calories for one day and eating without restriction the next.(8) Similarly, alternate-day modified fasting (ADMF) is a form of IF in which individuals alternate between consuming few calories one day (< 25% energy needs) and eating without restriction the next.(12) Table 1 defines the various terms used to describe different types of IF regimens discussed in this review.

Placing time restrictions on feeding has been shown to have broad systemic effects and trigger similar biological pathways as caloric restriction.(5) For example, IF regimens have been shown to improve cardio-metabolic risk factors (such as insulin resistance, dyslipidemia and inflammation cytokines),(13) decrease visceral fat mass,(6) and produce similar levels of weight loss as CR regimens.(8) In addition to the weight loss effects and metabolic improvements, several other beneficial effects of therapeutic fasting have been described including improvements in lipid profiles,(14) osteoarthritis,(15) healing of thrombophlebitis,(15) healing of refractory dermal ulcers, (16) and tolerance of elective surgery.(17)

One key mechanism responsible for many of these beneficial effects appears to be “flipping” of the metabolic switch. But what is this metabolic switch and how is it flipped? Here, we define the metabolic switch as the body’s preferential shift from utilization of glucose from glycogenolysis to fatty acids and fatty acid-derived ketones. The reason we use the word ‘preferential’ is because there is now a growing body of research to indicate ketones are the preferred fuel for both the brain and body during periods of fasting and extended exercise. (18, 19) Of relevance to weight management, this switch represents a shift from lipid synthesis and fat storage to mobilization of fat in the form of free fatty acids (FFAs) and fatty-acid derived ketones. For this reason, many experts have suggested IF regimens may

have potential in the treatment of obesity and related metabolic conditions, including metabolic syndrome and type 2 diabetes.(20)

The metabolic switch typically occurs in the third phase of fasting when glycogen stores in hepatocytes are depleted and accelerated adipose tissue lipolysis produces increased fatty acids and glycerol.(21) The metabolic switch typically occurs between 12 to 36 hours after cessation of food consumption depending on the liver glycogen content at the beginning of the fast, and on the amount of the individual's energy expenditure/exercise during the fast. The lipids in adipocytes (triacylglycerol and diacylglycerol) are then metabolized to FFAs, which are released into the blood (Figure 1). Simultaneously, other cell types may also begin generating ketones, with astrocytes in the brain being one notable example. FFAs are transported into hepatocytes where they are metabolized by β -oxidation to produce the ketones β -OHB and acetoacetate, which may in turn induce mitochondrial biogenesis.(22)

The ketones are transported in high amounts into cells with high metabolic activity (muscle cells and neurons) where they are metabolized to acetyl coenzyme A, which then enters the tricarboxylic acid (TCA) cycle to generate ATP. Through these physiological processes, ketones serve as an energy source to sustain the function of muscle and brain cells during fasting and extended periods of physical exertion/exercise.(21) Thus, it appears when the metabolic switch is flipped, the primary energy source for the body shifts from glucose to FFA derived from adipose tissue lipolysis and ketones, which serve to preserve muscle. In support of this, retention of lean mass is increased following IF regimens for weight loss as compared to continuous CR regimens in humans.(8) Additionally, in mice, the decline in muscle mass that occurs during normal aging is prevented by time restricted feeding (TRF) involving 40% caloric restriction.(23)

There are a few potential mechanisms through which a shift to fatty acid and ketone oxidation, relative to glucose oxidation, may serve to preserve muscle mass. Muscle cells store triglycerides in lipid droplets providing a local source of fatty acids that are utilized for β -oxidation and ketone generation during periods of prolonged fasting and extended exercise (see Nakamura et al., 2014 for review).(24) The transcriptional regulator PPAR- α induces the expression of genes that mediate fatty acid oxidation in muscle cells, and also regulates muscle cell mitochondrial biogenesis and glucose metabolism. PPAR- α gene targets that mediate a shift in muscle cell fuel preference from glucose to fatty acids during fasting and endurance exercise include the fatty acid translocase CD36, fatty acid binding protein 3, mitochondrial uncoupling protein 3, PGC-1 α , pyruvate kinase dehydrogenase 4 and forkhead box O1A. Mice with a muscle cell-specific knockout of the PPAR- α gene exhibit reduced numbers of oxidative fibers in their tibialis muscle,(25) whereas overexpression of PPAR- α results in increased numbers of oxidative fibers.(26) Mice lacking PGC-1 α only in skeletal muscle are exercise intolerant and their muscle cells do not exhibit functional adaptations to exercise.(27) The emerging evidence therefore suggests critical roles for metabolic switch-associated signaling pathways in both acute functional adaptations to bioenergetic challenges and the long-term increases in muscle growth and endurance capacity that accrue from intermittent metabolic switching.

Based on the findings described above, many experts have proposed IF regimens can improve body composition in overweight individuals; however, the effects of this dietary approach on body weight and body composition in humans are not currently well understood. In this paper, we briefly review the evolutionary underpinnings of optimal brain and body function in the fasted state and historical experience with fasting in humans. We then review the effects of different types of IF regimens on cellular, systemic, and performance-based outcomes from pre-clinical studies. In the final section, we review findings from human clinical trials that have tested the effects of IF regimens on changes in body composition, cardiometabolic health, and performance outcomes in humans.

Evolutionary Perspective

Many animals in the wild regularly experience extended time-periods with little or no food. For example, packs of wolves living in the Northern Rocky Mountains of the United States typically kill prey, such as deer, elk or bison only once every one or two weeks. Their success depends upon their brains and bodies functioning at a high level so they can work with their pack mates to ‘formulate’ and execute a strategy to capture and kill the prey animal.(28) In order to survive in such environments, animals have to possess the ability to quickly shift their metabolism from lipidogenesis (fat storage) to fat mobilization for energy through fatty acid β -oxidation. This metabolic flexibility enables individuals to store energy in the form of lipids in fat depots when food is available, and then perform at a high level during extended periods when food is not available.(29) Accordingly, those individuals whose brains and bodies performed optimally in a food deprived/fasted state would have a survival advantage.

Knowledge of early human evolution and data from recent studies of hunter-gatherer societies suggest humans evolved in environments where they intermittently experienced extended time-periods with little or no food.(30, 31) Indeed, one can reasonably hypothesize the superior cognitive capabilities of humans evolved as adaptations that enabled invention of tools and methods for hunting, animal domestication, agriculture and food storage, and processing.(32) To our knowledge, however, there have been no studies in which plasma ketone levels have been measured, or the frequency and duration of metabolic shifts determined, in current-day hunter-gatherers.

Fasting in Humans: Historical Perspective

Historically, fasting has been used as both a religious and a medical practice for thousands of years. Fasting for medical purposes has been suggested since the time of ancient Chinese, Greek and Roman physicians.(33) Throughout the millennia, many have recommended fasting for medical reasons. For example, Benjamin Franklin has been quoted as saying “The best of all medicines is resting and fasting.”(34) Similarly, Mark Twain wrote “A little starvation can really do more for the average sick man than can the best medicines and the best doctors. I do not mean a restricted diet; I mean total abstention from food for one or two days.”(35)

Initial scientific studies conducted in 1914 utilized fasting for the treatment of both type 1 and type 2 diabetes.(36),(37) Subsequently, numerous studies suggested fasting as a treatment for type 2 diabetes. Genuth(38) described a case report of a severely obese woman who had resolution of her diabetes following four weeks of fasting; significantly, her glucose tolerance remained normal for over a year after she regained the lost weight. Jackson et al. (39) found an improvement in glucose tolerance following 17–99 days of fasting, and the improvement in glucose and insulin metabolism was not related to the weight lost during the fast or the weight regained following the fast. Several additional studies found an improved insulin sensitivity and glucose tolerance in people with diabetes immediately following a fast.(40) (41–46)

These potential benefits, however, must be weighed against potential risks as there have also been numerous adverse effects reported in the medical literature from “therapeutic fasting.” These include: nausea and vomiting,(47) edema,(48) alopecia and motor neuropathy,(14) hyperuricemia and urate nephropathy,(49) irregular menses,(49) abnormal liver function tests and decreased bone density,(17) thiamine deficiency and Wernicke’s encephalopathy, (50, 51) and mild metabolic acidosis.(52) Additionally, several deaths have been reported during or immediately following therapeutic fasting with the etiologies including lactic acidosis, small bowel obstruction, renal failure, and cardiac arrhythmias.(53)

The adverse events described above have only occurred during or following extended fasts of several weeks or more, and have not been reported in trials of shorter more frequent fasts such as the ‘5:2’ diet, which consists of eating no more than 500 calories on two days per week (7) ADF diets, or IF diets.(8, 54) Thus, although therapeutic fasting has been popular as recently as the 1950s and 1960s,(21) the potential severity of adverse events following therapeutic fasting limited its use in traditional medicine and led to the development of protein sparing modified fasts that are still in use today. It is only over the last decade that scientific interest in the benefits of short-term fasting approaches, such as IF or ADF, in humans has returned, in part due to the positive findings found with IF in animal models (described below).

Adaptive Cellular and Molecular Responses to Fasting in Animal Models

Three IF protocols that have been most thoroughly studied in laboratory mice and rats are ADF, TRF (8 – 12 hour feeding window each day) and a very low calorie diet three consecutive days/week (4:3 IF). In addition, we include examples of IF studies in which rats or mice were maintained on 30–40% daily CR because they typically consume their entire daily food allotment within a 3 – 6 hour time window of receiving it, and thus fast for at least 18 hours/day.(55, 56) The observed reduction in body fat and elevation of ketone levels in these mice strongly indicates the metabolic switch occurs in animals on 30–40% CR.(57, 58)

An early study showed when rats are maintained on ADF beginning at 10 months of age, their average lifespan is increased by 30% compared to littermate rats fed ad libitum.(59) The ADF rats maintained a lower body weight and, when provided with running wheels, maintained a high level of daily running compared to control rats fed ad libitum. To our

knowledge, similar lifespan studies have not been performed on rodents on either TRF or 4:3 IF diets. All three IF eating patterns, however, produce elevations in circulating ketone levels, by amounts and for time periods that are determined by the IF regimen, indicating the metabolic switch is turned on intermittently.(60, 61) In this section, we compare and contrast results of analyses of blood and tissue samples for different organ systems of mice or rats maintained on one of these IF regimens in comparison with control animals fed ad libitum.

Circulating Biomarkers

Compared to control animals fed ad libitum, rats or mice maintained on ADF and/or IF exhibit reduced plasma glucose, insulin and leptin levels, and elevated ketone and adiponectin levels, which are most pronounced on the fasting days.(60, 62–64) Mice fed a high fat diet ad libitum develop obesity, elevated plasma glucose, insulin and leptin levels, and impaired glucose tolerance; TRF mostly normalizes these adverse effects of the high fat diet.(61, 65) Compared to mice fed ad libitum, mice on the 4:3 IF diet also exhibit reductions in plasma glucose levels and elevations of ketone levels, which are most pronounced at the end of the fasting period.(66) Interestingly, levels of insulin-like growth factor 1 (IGF-1) are reduced at the end of the three day fasting period in mice on the 4:3 diet, (66) whereas IGF-1 was not reduced, and even increased, in mice on the ADF diet.(60) In the 4:3 IF diet study the animals lost weight during the IF period, whereas in the ADF study the mice did not lose weight. The reduced IGF-1 levels may result from a long-term negative energy balance in animals on the 4:3 diet, whereas an elevation of IGF-1 levels in mice on ADF may mediate the maintenance of lean mass.

Liver

During the first several hours of food deprivation, and until liver glycogen stores are depleted, glycogenolysis in hepatocytes generates glucose for extrahepatic tissues.(21) The most thorough studies of molecular and biochemical responses of hepatic cells to IF are those of mice on TRF fed either a normal or a high fat diet.(61, 65) Early studies of TRF were aimed at understanding how the timing of food intake affects circadian rhythms.(67, 68) TRF (4 hour feeding period every day) normalized circadian rhythms, improved glucose regulation and reduced weight gain in mice.(68) Similarly, 8 hours/day TRF prevented high fat diet-induced obesity in mice,(65) and 9 hours/day TRF lowered glucose levels, increased insulin levels and insulin sensitivity in a rat model of type I diabetes.(69)

In mice fed a high fat diet, TRF normalizes the expression of genes involved in fatty acid metabolism (*Fasn*), β -oxidation (*Ppar γ*) and antioxidant defenses (*Sod1*) in the liver.(61) TRF accentuates diurnal rhythms in the expression of many different genes in liver cells including those encoding *Per2*, *Bmal1* and *Cry1*. TRF also completely prevents the adverse effects of a high fat diet on the circadian rhythm of phosphorylation CREB (cyclic AMP response element-binding protein), a transcription factor that plays a critical role in gluconeogenesis during fasting.(61) TRF also completely prevents the accumulation of lipids in the liver that occurs in mice maintained on a high fat diet.(61) Moreover, multiple markers of inflammation (TNF- α , IL-6 and IL-1 β) are reduced in livers of mice on TRF, and metabolomic analyses indicate multiple alterations in liver metabolites (palmitate, oleate and

palmitoleate), bioenergetic pathway molecules (glucose-6-phosphate, citrate and ophthalmate), and the antioxidant reduced glutathione, caused by a high fat diet are reversed by TRF.(61) However, IF diets have not always resulted in improvements in health indicators. For example, compared to young male rats fed a high fat diet ad libitum, those fed the same diet for only three hours each day for five weeks exhibited increased insulin resistance despite having reduced amounts of body fat.(70)

The transition in transcriptional programs that occurs in liver cells in response to the metabolic switch is regulated, in part, by sirtuins.(71) SIRT1 suppresses glucose production through inhibiting CRTC2 -mediated gluconeogenesis. Time-course analyses during the fasting period showed SIRT1 is activated during the metabolic switch from glycogenolysis to ketone production, which leads to deacetylation and degradation of CRTC2.(29) In addition, SIRT1 represses lipolysis and cholesterol synthesis by regulating the activity of cholesterol catabolic pathways.(29) SIRT1 acts as a positive regulator of liver oxidation of fatty acids. It increases the rate of fatty acid oxidation by deacetylating PGC-1 α .(72) and by activating peroxisome proliferators-activated receptor α (PPAR α). (73) PPAR α promotes fatty acid β oxidation in both the mitochondria and peroxisomes. In addition, SIRT1 interacts with the hepatocyte-derived hormone fibroblast growth factor 21 (FGF21) to coordinate an adaptive response to fasting by inducing ketogenesis, preventing hepatic steatosis and controlling energy expenditure.(74)

Overexpression of SIRT1 in mice, however, did not enhance the ability of ADF to decrease adiposity and increase insulin sensitivity,(75) suggesting there are additional pathways through which IF triggers the metabolic switch. Mitochondrial SIRT3 is critical for fatty acid oxidation and ketogenesis during fasting. It directly regulates the acetylation state and activity of mitochondrial enzymes involved in the metabolic switch including acetyl CoA synthetase 2, long chain acyl-CoA dehydrogenase, ornithine transcarbamoylase and a subunit of Complex 1 in the mitochondrial electron transport chain.(76–78) Mice lacking SIRT3 exhibit hallmarks of fatty-acid oxidation disorders during fasting such as reduced ATP levels and intolerance to cold exposure.(78) Shimazu et al. (2010)(79) found SIRT3 is also necessary for ketogenesis in the hepatocytes; they showed SIRT3 deacetylates mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2) which is the rate-limiting enzyme of β -hydroxybutyrate production during fasting. As a consequence, SIRT3 knockout mice have lower plasma ketone levels during fasting.

Muscle

Given that skeletal muscle is a major consumer of energy and utilizes ketones during prolonged fasting, there have been surprisingly few studies in which the effects of IF on muscle tissue have been evaluated at any level, from molecular and biochemical to functional. This is perhaps due to the emphasis on the metabolic responses of muscles to exercise, from which a vast literature has emerged. Several studies have reported changes in gene expression in muscles within 6–12 hours of the onset of food deprivation; the genes include FOXO1, PGC-1 α , MyoD and uncoupling protein 3.(80, 81) Interestingly, the decline in muscle mass that occurs during normal aging in mice is prevented by 40% CR/TRF, and this beneficial effect on muscle is associated with increased activity in the 2–3

hours prior to feeding and improved performance in agility tests.(23) When mice are maintained on a high-fat diet they become obese when fed ad libitum, but when maintained on ADF they do not become obese and retain muscle mass.(82) Moreover, mice on a low fat diet gain more muscle when on ADF compared to mice fed the same diet ad libitum.(82)

Accumulating evidence suggests some organ systems exhibit similar cellular and molecular responses to aerobic exercise and IF (e.g., suppression of mTOR, stimulation of autophagy, and mitochondrial biogenesis).(83, 84) It is therefore informative to briefly summarize major responses of muscle cells to exercise before reviewing effects of fasting on muscles. Acetylcholine released from presynaptic terminals of motor neurons activates nicotinic receptors on the muscle cell membrane resulting in membrane depolarization and Ca^{2+} influx through voltage-dependent channels and Ca^{2+} release from the endoplasmic (sarcoplasmic) reticulum. The Ca^{2+} then engages multiple downstream signals including kinases (e.g., CaMKII) and phosphatases (e.g., calcineurin), SIRT1 and SIRT3, reactive oxygen species, AMPK, and the transcription factors CREB, FOXO1, FOXO3 and PGC-1 α . (85) Similar to exercise, fasting for time-periods sufficient to flip the metabolic switch results in the activation of AMPK in muscle cells which, in turn, can activate SIRT1.(86) Consequently, gene expression programs and posttranslational modifications of extant proteins that promote mitochondrial biogenesis, autophagy and cellular stress resistance are activated, while mTOR and overall protein synthesis are suppressed.

IF and exercise stimulate mitochondrial biogenesis and mitochondrial stress resistance in muscle cells by mechanisms involving the second messenger Ca^{2+} and an increase of the AMP/ATP ratio. The elevation of cytoplasmic Ca^{2+} levels that mediates muscle contraction also activates Ca^{2+} /calmodulin-dependent protein kinase IV which, in turn, activates the transcription factor CREB. The increase in the AMP/ATP ratio activates AMPK. Both CREB and AMPK up-regulate expression of PGC-1 α , a master regulator of the transcription of multiple genes which encode proteins that mediate the division and growth of mitochondria.(87) As in liver cells, fasting induces the expression of SIRT3 in skeletal muscle cells, and SIRT3 knockout mice exhibit reduced activities of AMPK and CREB, and reduced expression of PGC-1 α .(88) SIRT3 also protects muscle cells against oxidative stress by deacetylating and activating SOD2. Data also suggest fasting stimulates autophagy in muscle cells by mechanisms involving AMPK-mediated inhibition of mTOR signaling and up-regulation of the autophagy-promoting proteins FOXO3a and ULK1.(89) AMPK also contributes to the increased sensitivity of muscle cells to insulin that occurs in response to IF and exercise. Thus, mice deficient in AMPK α 2 are resistant to the insulin-sensitizing effect of a TRF diet in which they are provided an amount of food equivalent to 60% of their ad libitum intake.(90) Moreover, mice with muscle-specific AMPK knockout exhibit hyperglycemia and impaired gluconeogenesis, which may result from impaired autophagy in muscle cells.(91)

Cardiovascular System

Studies of rats and mice have documented robust effects of IF and/or ADF on heart rate and blood pressure. In one study, transmitters were implanted in rats that enabled continuous monitoring of heart rate and blood pressure in their home cages.(92) After 48 hour baseline

recordings were acquired, the rats were assigned to either ad libitum control diet or an ADF diet and recordings were made at designated time periods during a six month period. In rats on the ADF diet, but not the ad libitum diet, resting heart rate and blood pressure decreased progressively during the first month of ADF and were thereafter maintained at the lower levels (350 beats/min in ad libitum (AL) rats versus 250 beats/min in ADF rats; mean blood pressure of 120 mm Hg in AL rats and 90 mm Hg in IF rats). Moreover, rats on ADF exhibited superior cardiovascular stress adaptation as indicated by reduced blood pressure and heart rate elevation during and after one hour of immobilization stress.(92) However, it was reported that male rats maintained on ADF for six months exhibit reduced cardiac reserve,(93) although it is unclear whether this is related to a pathological process or is associated with a long-term reduction in cardiac load due to the reduced blood pressure and heart rate in response to ADF.(63)

Heart rate variability is also increased in response to ADF, as a result of enhanced parasympathetic tone.(93) The effects of ADF on heart rate, blood pressure and heart rate variability are very similar to the effects of endurance training, suggesting similar underlying mechanisms.(94) Interestingly, the effects of IF on cardiovascular regulation result from BDNF-mediated enhancement of activity of cholinergic cardiovagal neurons in the brainstem dorsal motor nucleus of the vagus.(95) Because exercise is known to be a potent inducer of BDNF expression in the brain,(96) studies are needed to determine whether brainstem BDNF signaling also mediates the beneficial effects of endurance training on heart rate and blood pressure.

Central Nervous System

The decline in cognitive function with age is forestalled in mice maintained on 40% CR/TRF.(97, 98) For example, an early study showed 40% CR/TRF prevented age-related decrements in motor performance (rotarod test) and maze learning (14 unit T-maze) in mice.(99) Although the cellular and molecular mechanisms by which IF enhances cognitive and motor performance have not been established, the shift to ketone utilization appears to be one of the key biological mechanisms that prevents age-related reductions in brain white matter integrity, and preserves spatial memory.(97)

Emerging findings also suggest other possible mechanisms through which IF can maintain or even enhance cognitive function during aging. For example, both normal weight and obese mice maintained for three months on 40% CR/TRF exhibit an increased density of dendritic spines on hippocampal dentate granule neurons, and this increase in synapse numbers is correlated with an increased level of brain-derived neurotrophic factor (BDNF).(100) It is well known that BDNF plays fundamental roles in learning and memory and also mediates the anxiolytic and antidepressant effects of exercise and antidepressant drugs.(96, 101) BDNF signaling may play important roles in the enhancement of synaptic plasticity by IF, as well as in the production of new neurons from stem cells (neurogenesis) in the hippocampus.(102) Recent findings suggest β -OHB also has important signaling functions involving activation of transcription factors. In neurons, β -OHB induces the expression of BDNF, which, in turn stimulates mitochondrial biogenesis and the formation of new

synapses. In these ways, events triggered by the metabolic switch may play major roles in the optimization of performance of the brain and body by IF.

In addition to BDNF, studies have shown ADF increases the expression of fibroblast growth factor 2, heme oxygenase 1 and glucose regulated protein 78 in the cerebral cortex and striatum; these proteins are known to protect neurons against excitotoxic, metabolic and oxidative stress.(103) Studies of mice with a conditional knockout of CREB in the hippocampus and forebrain have demonstrated a critical role for this transcription factor as a mediator of the cognition-enhancing effects of IF (40% CR/TRF).(104) Additional findings suggest 50% CR/TRF can prevent age-related increases in DNA methylation, which may thereby sustain the expression/responsivity of genes involved in adaptive neuroplasticity and cognition.(105) Collectively, the available data suggest IF affects multiple transcription-coupled signaling pathways that result in bolstering of synaptic plasticity and neuronal stress resistance.

Recent studies of laboratory animals provide further support that cognitive function and physical performance are enhanced by IF. For example, when mice were maintained on an ADF diet for 6–8 months, their performance in two different learning and memory tests (an operant conditioning task and a novel object recognition task) was significantly improved compared to control mice fed daily.(106) Similarly, mice maintained on ADF for 11 months exhibited superior cognitive ability in the Barnes maze test of spatial memory.(107) Another study found when old rats (20 months old) were maintained on an ADF diet for three months their locomotor performance on a rotarod test, as well as their learning and memory performance on a water maze test, were significantly improved.(108) Thus, findings from pre-clinical trials suggest IF can improve cognitive and locomotor performance even when initiated late in life.

Numerous studies have shown ADF can protect neurons in the brain against dysfunction and degeneration in animal models of a range of different neurological disorders including epilepsy,(109) Alzheimer's disease,(110) and Parkinson's disease (111) and stroke (112). For example, mice maintained on ADF for three months prior to transient occlusion of the middle cerebral artery (an animal model of focal ischemic stroke) exhibit highly significant reductions in brain damage and neurological deficits, and a reduction in stroke-induced reactive neurogenesis.(112) The underlying mechanisms likely involve both activation of adaptive stress response signaling pathways in neurons by neurotrophic factors and neurotransmitters,(112) and circulating factors. It is well established that the ketone β -OHB can suppress epileptic seizures, and emerging findings suggest β -OHB may also play a role in the neuroprotective effects of IF in animal models of Alzheimer's and Parkinson's diseases and stroke. As evidence, it was reported that β -OHB stimulates transcription of the gene encoding BDNF in hippocampal neurons.(113) With regards to future translational studies it will be of considerable interest to determine whether IF is beneficial when initiated after the onset of symptoms in animal models first, and then in human patients.

Impact of Intermittent Fasting on Changes in Body Composition in Humans

Individuals with a typical Western eating pattern of three or more meals per day never flip the metabolic switch and thus their ketone levels remain continuously low. Additionally, as their insulin resistance increases with excess weight and diabetes, the time it takes to flip the switch is prolonged (Figure 2). The different IF eating patterns described in this article all flip the metabolic switch with varying frequencies and durations (Figure 2). Compared to an eating pattern in which food is consumed over long time intervals (typically 12 or more hours daily), IF eating patterns may result in a wide range of beneficial effects on health including improved glucose metabolism,(7, 10, 114–116) reduced inflammation,(117, 118) reduced blood pressure,(12, 75, 115, 119) improved cardiovascular health,(120–123) and increased resistance of cells to stress and disease in humans (Figure 3).(118, 124) These effects have been clearly established in animal studies as described above, but only some of these adaptations to IF have been investigated in humans, and then typically in overweight or obese subjects.

Many of the beneficial metabolic and health effects of IF described above may be driven by reductions in body weight and/or body fat. With caloric restriction, approximately one-fourth to one-third of the weight loss is known to be of lean tissue. In a study of 34 healthy men randomly assigned to either a normal control diet or daily TRF (16 hours of daily fasting) and followed for two months during which they maintained a standard resistance training program, the men in the TRF group showed a reduction in fat mass with retention of lean mass and maximal strength.(125) Although findings from the latter and several other previous studies suggest a smaller proportion of lean mass is lost following IF regimens compared to continuous CR for weight loss,(8, 54) there is a need for more research in this area as this approach may not be optimal for all adults and patient populations. This is also a particularly important question for older adults, due to the loss of muscle mass associated with both aging (sarcopenia) and in response to caloric restriction.(126, 127)

In order to gain a better understanding of the effects of IF regimens on changes in body composition, we reviewed the effects of both TRF and ADF regimens on body composition in humans based on findings from clinical trials completed over the past couple decades. Our preset inclusion criteria were the following: 1) interventional clinical trials, 2) sample sizes of at least 10 participants, 3) intervention periods of four weeks or longer, 4) inclusion of adult participants (>18 years), 5) objective measures of body weight and body composition pre- and post-intervention, and 6) article written in the English language. We identified these trials by searching PubMed using the following terms: “fasting” and/or “intermittent fasting” and/or “alternate day fasting” and/or “time restricted feeding” and/or “alternate day modified fasting.” Filters were set to allow only “clinical trials,” “human” studies, and “English” studies to be displayed.

For IF studies involving TRF, defined as fasting for periods of at least 12 hours but less than 24 hours, three of the four eligible studies reported significant reductions in body weight and fat mass. No significant changes in lean mass were reported for any study, which suggests the observed weight losses were primarily comprised of body fat. The magnitude of weight

loss, however, was relatively small (< 5.0 kg) in all studies. Table 2 presents findings from clinical trials that examined TRF.(122, 125, 128–130)

For IF studies involving ADMF or ADF, the vast majority (9 of 10) trials tested ADMF interventions with only one trial testing an ADF intervention. Significant reductions in body weight and fat mass were observed in 10 of the 10 eligible trials, and the magnitude of weight losses were quite large with half (5 of 10) of these trials reporting clinically meaningful reductions in body weight (> 5.0 kg). Noteworthy, the five trials that did not report a clinically meaningful weight reduction were of a short-term duration (8–12 weeks), and all five of these trials reported significant weight losses of 3.0 kg or more. The reported effects on lean mass were mixed with three of the 10 eligible trials reporting significant reductions in lean mass. Based on these findings, ADMF regimens appear to produce consistent reductions in body weight and body fat mass but have less consistent effects on changes in lean mass. Table 3 presents findings from clinical trials that examined ADMF and ADF regimens.(12, 54, 119, 131–135)

Impact of Intermittent Fasting on Changes in Cardio-Metabolic Health in Humans

In this section, we briefly review the emerging findings on the effects of IF on cardiometabolic outcomes, in humans. Metabolic syndrome, a combination of insulin resistance, hypertension and abdominal obesity, is a major risk factor for atherosclerotic heart disease and consequent myocardial infarction and heart failure.(136) Each of these defining features of the metabolic syndrome is mitigated by IF in rats and mice,(92, 93) and in models of type 2 (insulin resistance-mediated) diabetes.(63, 69, 137) An emerging literature indicates IF can also ameliorate many of the key features of the metabolic syndrome in humans by decreasing fasting glucose, fasting insulin, and insulin resistance.(8, 138)

In most studies, IF regimens have been shown to reduce overall fat mass and visceral fat both of which have been linked to increased diabetes risk.(139) IF regimens ranging in duration from 8 to 24 weeks have consistently been found to decrease insulin resistance.(12, 115, 118, 119, 122, 123, 131, 132, 134, 140) In line with this, many, but not all,(7) large-scale observational studies have also shown a reduced risk of diabetes in participants following an IF eating pattern. For example, in a study conducted by Horne and colleagues, (120) a series of patients in Utah undergoing coronary artery cauterization were surveyed for the practice of periodic fasting (a common religious practice in the Mormon Church) and for the presence of diabetes based on diagnosis and medication use. Participants who reported periodically fasting had a significantly lower odds ratio for having diabetes compared to those who did not report fasting regularly. In line with this, IF regimens (both TRF and ADMF) have been found to decrease fasting glucose levels by 3 to 6% in individuals with prediabetes.(12, 123, 134) IF regimens, however, do not appear to affect fasting glucose levels in healthy individuals.(141)

In most studies, IF regimens have been shown to reduce traditional cardiovascular risk factors. Reductions in total cholesterol typically range from 6 to 21%, with LDL cholesterol

decreasing by 7 to 32% following IF interventions.(12, 115, 118, 122, 123, 134) Similarly, IF regimens have also been shown to decrease triglyceride levels by between 16 to 42% in the majority of studies tested.(12, 115, 118, 119, 122, 123, 131, 132, 134, 140) Significant reductions in systolic (3 to 8%) and diastolic blood pressure (6 to 10%) have also been reported following 6 to 24 weeks of IF, though these changes appear to be driven by weight loss as significant reductions in blood pressure were only reported in studies in which participants lost 6% or more of their body weight.(12, 115, 123, 132)

Not all human trials, however, have demonstrated beneficial effects of TRF on cardiometabolic health indicators. For example, in a small study of middle-age adults, participants were provided three full meals of food corresponding to their estimated daily caloric intake within a 4-hour period (4 – 8 PM) each day for two months. Compared to when participants ate the same three meals spaced at typical breakfast lunch and dinner times, there were very few significant differences in health indicators during a two-month diet period.(129) Where significant, some changes were positive (reduced fat mass and HDL cholesterol) and some were negative (increased blood pressure and LDL cholesterol). When glucose tolerance tests were performed in the morning on the same participants, those on TRF exhibited poorer glucose tolerance compared to participants eating three regularly spaced meals.(128) The latter difference, however, was likely due to the fact the glucose tolerance test was performed within 12 hours of consumption of a full day's amount of calories as indicated by elevated glucose levels, but normal levels of insulin, leptin, ghrelin and adiponectin in the TRF group.(128)

Impact of Intermittent Fasting on Cognitive and Performance Outcomes in Humans

Human trials of IF that include cognitive and physical performance outcomes are unfortunately limited. Studies of cognition and mood during extended fasts, however, suggest few or no adverse effects, and improvements in performance in some cognitive domains including executive function have been reported.(142–144) In regards to physical performance, a recent randomized controlled trial of IF (20 hours of fasting 4 days/week) during one month of resistance training in men demonstrated superior improvements in upper and lower body endurance in the IF group compared to the control group.(130) Clearly, many additional controlled trials of long-term IF protocols in which brain function and physical performance are evaluated in human subjects are needed to confirm the evidence from evolutionary considerations and anthropological studies.

Future Directions

While our review suggests IF results in both weight and fat loss (even when caloric intake is not limited), as well as increased insulin sensitivity in overweight subjects, there remains an important need for randomized controlled trials (RCTs) of IF in normal weight subjects. Emerging findings indicate that IF when combined with resistance training can produce beneficial changes in body composition and strength in young, healthy males. Additional studies are needed to better understand the effects of combining IF with resistance training on body composition and strength outcomes in other populations.

There remains an important need for interventions that can improve unhealthy changes in body composition that occur during aging. Given the known loss of lean mass that occurs during both aging and continuous CR, IF regimens may be an effective approach to help older adults lose unhealthy weight while retaining larger amounts of lean mass.

When taken together with animal studies, the medical experience with fasting, glucose regulation and diabetes strongly suggests IF can be effective in preventing type 2 diabetes. Thus, RCTs of IF with end points that focus on disease outcomes and/or performance outcomes (e.g., endurance and cognition) should be pursued. The feasibility of such approaches should also be carefully evaluated in such trials, as individuals in some previous trials have reported high levels of hunger and potential discomfort on fasting days.(124, 140)

Of high relevance to the feasibility question, we suggest that future randomized controlled IF trials should use biomarkers of the metabolic switch (e.g., plasma ketone levels) as a measure of compliance and the magnitude of negative energy balance during the fasting period. It is critical for this switch to occur in order to shift metabolism from lipogenesis (fat storage) to fat mobilization for energy through fatty acid β -oxidation. Moreover, based on the growing body of research that indicates ketones are the preferred fuel for both the brain and body,(18) we hypothesize that once the metabolic switch occurs, both the tolerability and sustainability of IF regimens are greatly increased. Experimental studies, however, are needed to distinguish the effects of caloric restriction versus the metabolic switch induced by IF regimens on fat metabolism, hunger, and overall tolerability.

As the health benefits and therapeutic efficacies of IF in different disease conditions emerge from RCTs, it is important to understand the current barriers to widespread use of IF by the medical and nutrition community and to develop strategies for broad implementation. One argument against IF is that, despite the plethora of animal data, some human studies have failed to show such significant benefits of IF over CR.(54) Adherence to fasting interventions has been variable, some short-term studies have reported over 90% adherence, (54) whereas in a one year ADMF study the dropout rate was 38% vs 29% in the standard caloric restriction group.(135)

There are many reasons some individuals experience difficulties adhering to IF regimens, but most notably is the fact that very few studies ensured that “the switch” was truly flipped and ketosis was achieved. Although some individuals have difficulties in adherence, the majority of studies show similar dropout or non-adherence rates in the treatment and control groups. Finally, despite the many longer-term studies with very few adverse events, safety remains a potential concern. If findings of the research outlined above provide additional support for the metabolic benefits of IF, however, it is foreseeable in the near future that healthcare professionals may recommend IF regimens to patients who are overweight, insulin resistant, and/or hypertensive.

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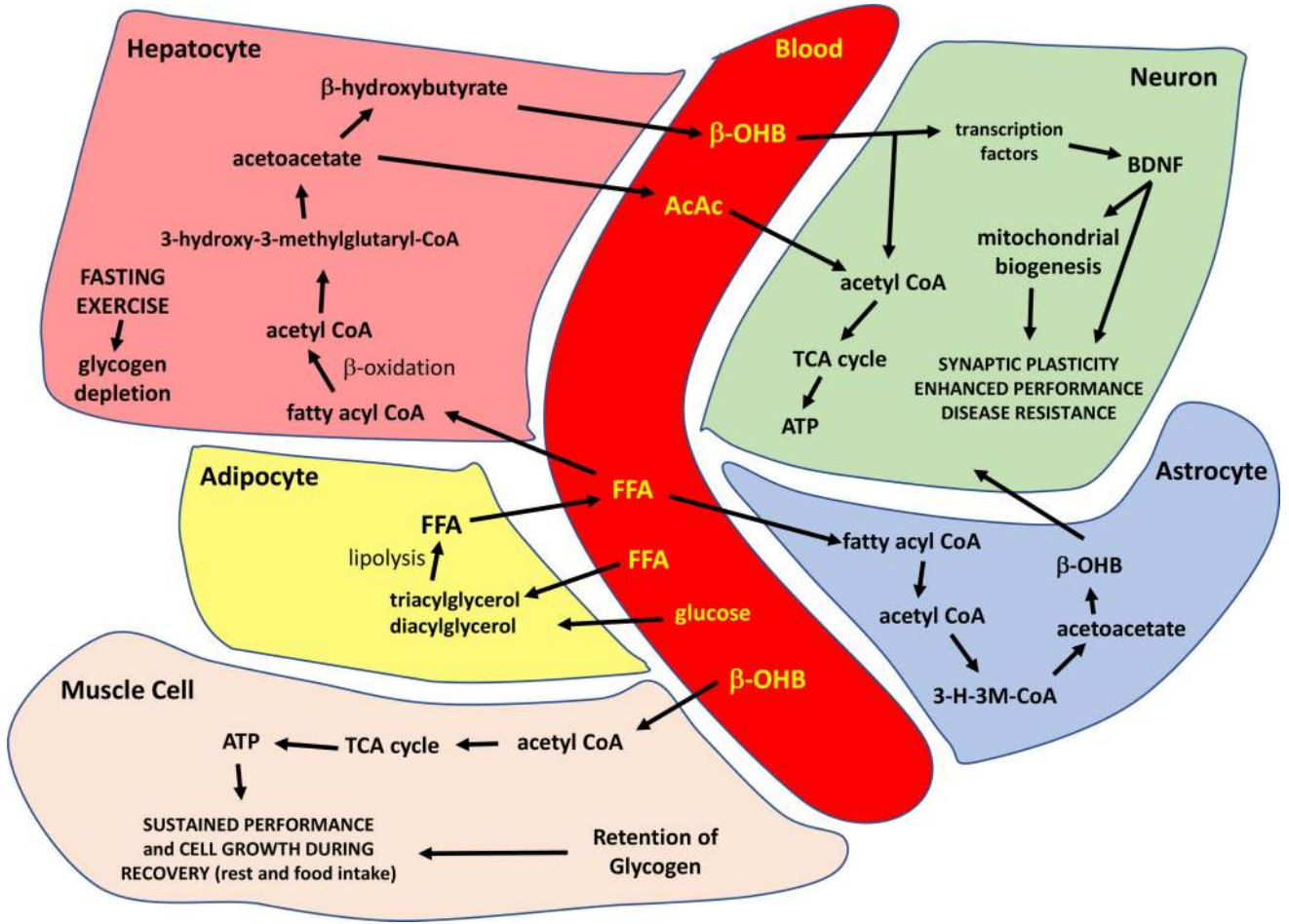


Figure 1. Summary of the major metabolic pathways involved in the metabolic switch and responses of excitable cells to the ketone β-hydroxybutyrate (β-OHB). See text for description. AcAc, acetoacetate; ATP, adenosine triphosphate; FFA, free fatty acids; TCA, tricarboxylic acid.

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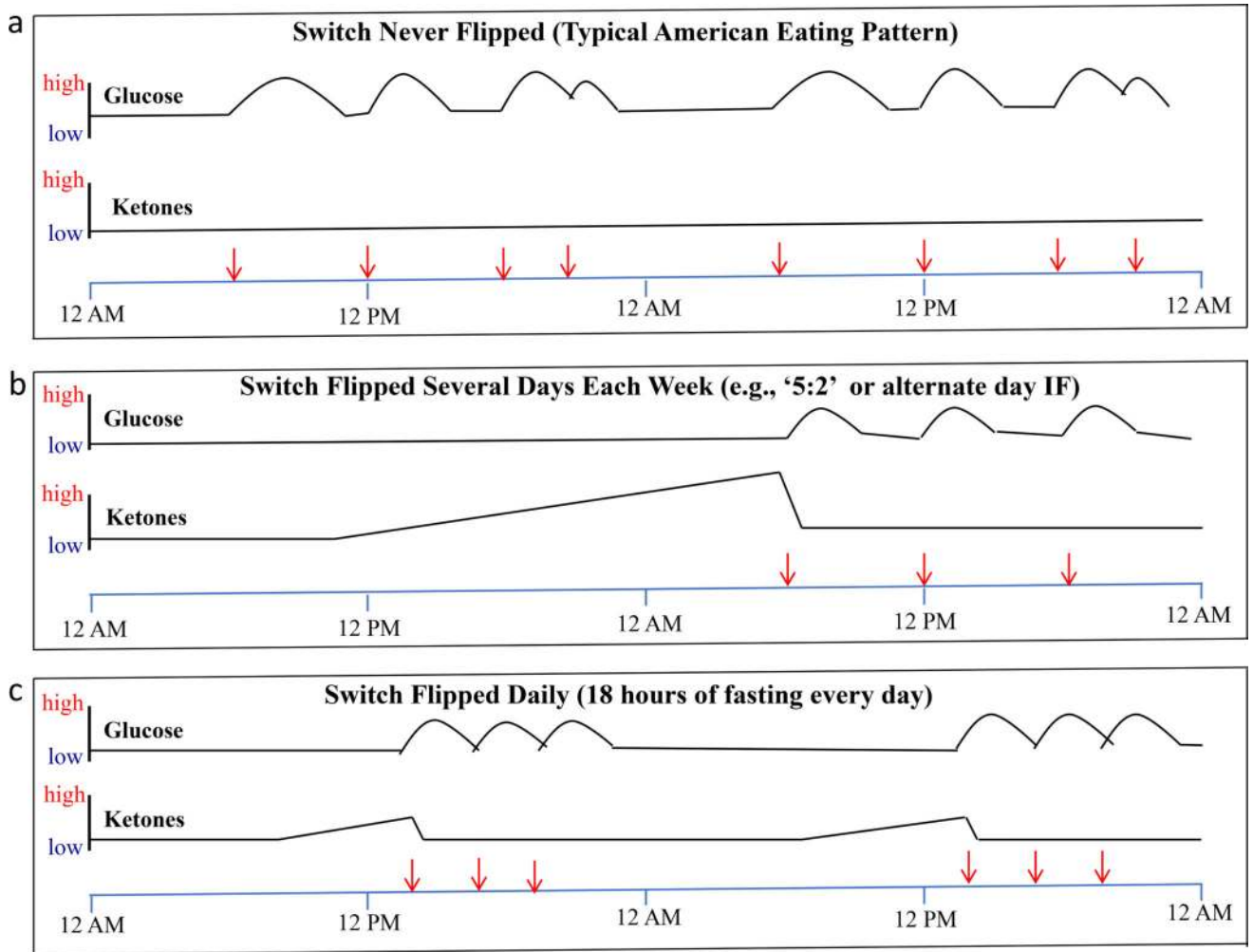


Figure 2.

Profiles of circulating glucose and ketone levels over 48 hours in individuals with a typical American eating pattern or two different IF eating patterns. **(a)** In individuals who consume three meals plus snacks every day the metabolic switch is never 'flipped' and their ketone levels remain very low, and the area under the curve for glucose levels is high compared to individuals on an IF eating pattern. **(b)** In this example, the person fasted completely on the first day and then at three separate meals on the subsequent day. On the fasting day ketones are progressively elevated and glucose levels remain low, whereas on the eating day ketones remain low and glucose levels are elevated during and for several hours following meal consumption. **(c)** In this example the person consumes all of their food within a 6-hour time window every day. Thus, the metabolic switch is flipped on following 12 hours of fasting and remains on for approximately six hours each day, until food is consumed after approximately 18 hours of fasting. Modified from Mattson et al 2016.(9)

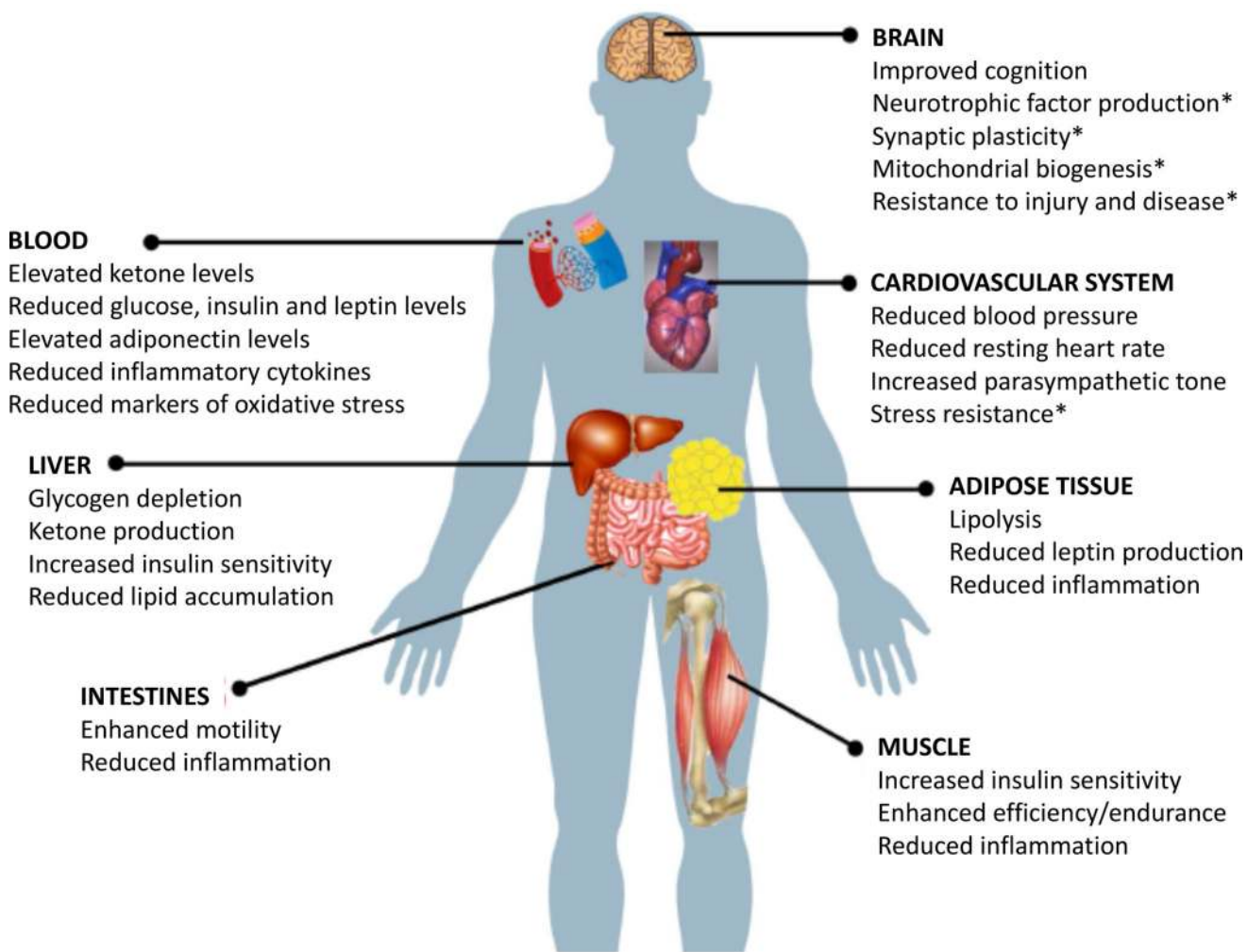


Figure 3.

Examples of functional effects and major cellular and molecular responses of various organ systems to IF. In humans and rodents, IF results in decreased levels of circulating insulin and leptin, elevated ketone levels, and reduced levels of pro-inflammatory cytokines and markers of oxidative stress. Liver cells respond to fasting by generating ketones and by increasing insulin sensitivity and decreasing lipid accumulation. Markers of inflammation in the intestines are reduced by IF. The insulin sensitivity of muscle cells is enhanced and inflammation reduced in muscle cells in response to the metabolic switch triggered by fasting and exercise. Emerging findings further suggest that exercise training in the fasted state may enhance muscle growth and endurance. Robust beneficial effects of IF on the cardiovascular system have been documented including reduced blood pressure, reduced resting heart rate, increased heart rate variability (improved cardiovascular stress adaptation) and resistance of cardiac muscle to damage in animal models of myocardial infarction. Studies of laboratory animals and human subjects have shown that IF can improve cognition (learning and memory); the underlying mechanisms may involve neurotrophic factors, stimulation of mitochondrial biogenesis and autophagy, and the formation of new synapses.

IF also increases the resistance of neurons to stress and suppresses neuroinflammation.

*Demonstrated in animal models, but not yet evaluated in humans.

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Table 1

Definition of terms used to describe different types of eating patterns in this review.

Intermittent Fasting (IF)	This eating pattern involves fasting for varying periods of time, typically for 12 hours or longer.
Calorie Restriction (CR)	This eating pattern involves a continuous reduction in caloric intake without malnutrition.
Time Restricted Feeding (TRF)	This eating pattern involves restricting food intake to specific time periods of the day, typically between an 8 – 12 hours each day
Alternate Day Fasting (ADF)	This eating pattern involves consuming no calories on fasting days and alternating fasting days with a day of unrestricted food intake or “feast” day.
Alternate Day Modified Fasting (ADMF)	This eating pattern involves consuming less than 25% of baseline energy needs on “fasting” days, alternated with a day of unrestricted food intake or “feast” day.
Periodic Fasting (PF)	This eating pattern consists of fasting only 1 or 2 days/week and consuming food ad libitum on 5 to 6 days per week.

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Table 2

Time Restricted Feeding (12<x<24 hrs)

Summary and results from clinical trials on time restricted feeding.

Study	Participants	Duration (Weeks)	BMI (kg/m ²)	Intervention	Methods	Δ Fat mass (kg)	Δ Fat Mass (%)	Δ Lean Mass	Δ Body Weight (kg)	Δ Body Weight (%)
Carlson et al. (2007) (128) Stote et al (2007) (129)	10 women, 5 men (Aged 45.0±0.7)	16	23.4±0.5	Time restricted feeding (TRF).	1 meal per day during 4-hour time period.	↓ 2.1kg ^{***}	↓ 13.0% ^{***}	↑ 1.5kg	↓ 1.4kg ^{**}	↓ 2.1% ^{**}
Klempl et al. (2012) (122)	54 obese women (Aged 35–65)	8	30–39.9	IF and caloric restriction (CR) at 30% total daily caloric needs with either liquids (L) or food (F).	IF CR-L or IF CR-F for 6 days then 1 day fast with only 120kcal of juice powder.	CR-L: ↓ 2.8±1.2kg ^{***} CR-F: ↓ 1.9±0.7kg ^{***}		N/A	CR-L: ↓ 3.9±1.4kg ^{***} CR-F: ↓ 2.5±.6kg ^{***}	CR-L: ↓ 4.1±1.5% ^{***} CR-F: ↓ 2.6± 4% ^{***}
Moro et al. (2016) (125)	34 resistance trained (RT) males (Aged 29.21±3.8)	8	n/a	TRF with a 16 hour fasting period.	100% daily caloric needs in 3 meals within 8 hours (1pm-4pm, 8pm). Fast remaining 16 hours.	↓ 1.62±1.53kg ^{***}	↓ 16.4% ^{***}	↑ 0.64kg	↓ 0.97±1.58kg [*]	↓ 1.2% [*]
Tinsley et al. (2017) (130)	18 RT men (Aged 22.9±4.1)	8		TRF 4 days a week with a 16 hour fasting period.	Unrestricted energy consumption on RT days (3). unrestricted energy consumption in a 4-hour window on other days (4).	↓ 0.6kg	↓ 3.4%	↓ 0.2kg	↓ 1.0kg	↓ 0.6%

Note.

TRF: time restricted feeding; IF: intermittent fasting; CR: calorie restriction; L: liquids; F: food; RT: resistance trained

* p < 0.05

100% d

10% d
**

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Alternate Day Modified Fasting

Table 3

Summary and results from clinical trials on alternate day modified fasting and alternate day fasting.

Study	Participants	Duration (Weeks)	BMI (kg/m ²)	Intervention	Methods	Δ Fat mass (kg)	Δ Fat Mass (%)	Δ Lean Mass	Δ Body Weight (kg)	Δ Body Weight (%)
Bhutani et al. (2013)(131)	64 obese males and females. Aged 42±2 (ADM), 45±5 (combo)	12	35±1	Alternate day modified fast (ADMF)	ADMF: alternated between fasting days (25% baseline calories) and ad libitum on feast days.	ADMF: ↓ 2.0±1.0kg**	ADMF: ↓ 4.7%**	ADMF: ↓ 1.0±1.0kg	ADMF: ↓ 3.0±1.0kg***	ADMF: ↓ 3.2%***
Catenacci et al. (2016) [§] (54)	26 healthy obese subjects (Aged 39, 6±9, 5)	8	ADF: 35.8±4	Alternate day fast (ADF)	ADF: alternated ad libitum feeding and fasting days without food intake	↓ 3.7±0.5kg***	↓ 1.1±0.3%**	↓ 3.2±0.6kg***	↓ 8.2±0.9kg***	↓ 8.8±0.9%***
Eshghinia & Mohammadzadeh (2013)(132)	15 overweight and obese females (Aged 33±6)	6	33.16±5.02	Modified fast consuming 25–30% energy needs.	Consumed 25–30% energy needs diet on 3 weekly fasting days (Sat, Mon and Thursday) and consumed a diet of 1700–1800 kcal/d on feast days.	N/A	↓ 2.8%***		↓ 6.0kg***	↓ 7.1%***
Hoddy et al. (2016)(133)	54 (47 females, 7 male) (Aged 47±3, 46±2, 47±2)	8	34±1	ADMF consuming 25% energy needs.	Alternating 25% baseline energy needs on fast day, ad libitum on feast days. Tertiles based on degree of insulin resistance.	Tertile 1: ↓ 2kg*** Tertile 2: ↓ 2kg*** Tertile 3: ↓ 2kg***	Tertile 1: ↓ 6±1%*** Tertile 2: ↓ 6±1%*** Tertile 3: ↓ 5±1%***	Tertile 1: ↓ 1kg*** Tertile 2: ↓ 2kg*** Tertile 3: ↓ 1kg***	Tertile 1: ↓ 3.7kg*** Tertile 2: ↓ 3.8kg*** Tertile 3: ↓ 3.8kg***	Tertile 1: ↓ 4±1%*** Tertile 2: ↓ 4±1%*** Tertile 3: ↓ 4±1%***
Hoddy et al. (2014)(119)	74 obese (Aged 45±3 lunch (L), 46±2 dinner (D))	8	L: 35±1 D: 34±1	ADMF consuming 500 calories.	ADMF consuming 500 calories at either lunch or dinner and ad libitum on feast days.	L: ↓ 1.8kg*** D: ↓ 2.6kg***	L: ↓ 4.3%*** D: ↓ 6.2%***	L: ↓ 1.3kg*** D: ↓ 1.4kg***	L: ↓ 3.5±0.4kg*** D: ↓ 4.1±0.5kg***	L: ↓ 3.8±0.5%*** D: ↓ 4.2±0.5%***
Klempel et al. (2013)(134)	35 obese (Aged 25–65)	8	30–39.9	ADMF consuming 25% energy needs.	ADMF: High Fat (HF) or Low Fat (LF). Alternating between 25% and	HF: ↓ 5.4±1.5kg*** LF: ↓ 4.2±0.6kg***	HF: ↓ 11.1%*** LF: ↓ 8.8%***	HF: ↑ 1.1±1.3kg LF: ↑ 0.5±0.7kg	HF: ↓ 4.3±1.0kg*** LF: ↓ 3.7±0.7kg***	HF: ↓ 4.8±1.1%*** LF: ↓ 4.2±0.8%***

Study	Participants	Duration (Weeks)	BMI (kg/m ²)	Intervention	Methods	Δ Fat mass (kg)	Δ Fat Mass (%)	Δ Lean Mass	Δ Body Weight (kg)	Δ Body Weight (%)
Trepanowski et al. (2017) (135)	100 overweight and obese subjects	26	35 ± 4	ADMF consuming 25% daily energy needs.	125% energy needs.	↓ 4.2kg [*]	↓ 11.1% [*]	↓ 1.5kg	↓ 6.5kg [*]	↓ 6.8% [*]
	86 females, 14 males (Aged 44±11)	52		ADMF consuming 25% daily energy needs. Additional 6 months maintenance alternating 50% and 150% of caloric needs.		↓ 2.0kg	↓ 5.3%	↓ 0.9kg	↓ 5.7kg [*]	↓ 6.0% [*]
Varady et al. (2013) (12)	32 (Aged 35–65)	12	20–29.9	ADMF consuming 25% daily energy needs.	ADMF: 25% daily caloric intake and ad libitum on feast days.	↓ 3.6±0.7kg ^{***}	↓ 13.8% ^{***}	↓ 1.6 kg	↓ 5.2±0.9kg ^{***}	↓ 6.5±1.0% ^{***}
Varady et al. (2009) (123) Klempel et al. (2010) (145)	16 obese males and females (Aged 46±2)	8	34 ± 1	ADMF consuming 25% daily energy needs.	ADMF: 25% daily energy needs and ad libitum on feast days.	↓ 5.4±0.8kg [*]	↓ 3.0% [*]	↓ 0.1±0.1 kg	↓ 5.6±1.0kg ^{***}	↓ 5.8±1.1% ^{***}
	29 overweight women (Aged: LF: 43.2±2.3 HF: 42.4±3.0)	8	LF: 34.4±8 HF: 34.6±7	ADMF consuming 25% energy needs.	Alternating 25% daily energy needs (1 meal) in either a LF (25% fat) or HF (45% fat) diet and ad libitum on feast days.	LF: ↓ 1.5 kg [*] HF: ↓ 2.9kg [*]	LF: ↓ 4.1% [*] HF: ↓ 8.0% [*]	N/A	LF: ↓ 4.3 kg [*] HF: ↓ 4.7 kg [*]	LF: ↓ 4.9% [*] HF: ↓ 5.3% [*]

Note.

[§] Alternate day fasting which included no food intake;

ADMF: alternate day modified fasting; ADF: alternate day fasting; CR: caloric restriction; L: lunch; D: dinner; HF: high fat; LF: low fat

* p ≤05

** p ≤01

*** p ≤001