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Review Article: Health Benefits of Intermittent Fasting

B. Lakshmi Reddy, PhD[a], **Vamsee S. Reddy, MD**, **Milton H. Saier Jr., PhD**[a]

[a]Department of Molecular Biology, University of California at San Diego 9500 Gilman Dr. La Jolla, CA 92093-0116 USA

Abstract

Summary—We propose that intermittent fasting (time restricted eating), in agreement with the conclusions of other biologists, as revealed in recent publications, promotes the achievement of numerous health benefits including the extension of human and animal life-spans.

Background—There is evidence, obtained both with animal model systems and with humans, that intermittent fasting has health benefits. These benefits include extended longevity, weight loss and counteracting various disease conditions. Such procedures positively influence the benefits of human tissue-specific microbiomes and minimize the consequences of organellar apoptosis.

Key Messages—In this review, we attempt to summarize the predominant evidence, published in the scientific literature, relevant to the conclusions that in general, and in many specific instances, intermittent fasting has long term benefits to animals, including humans, with respect to overall and specific organismal health and longevity.

Keywords

intermittent fasting; cancer; circadian rhythm; metabolism; health

INTRODUCTION

Intermittent fasting (IF), eating by the clock and other time restricted eating (TRE) protocols are gaining popularity as effective long-term strategies toward healthy life-styles. This is because of their many benefits in losing weight, boosting immunity, countering the risks of diabetes, cancer and cardiovascular diseases, and slowing the process of ageing. IF studies in animal models suggest that the process induces longevity, improve metabolic health, and positively influences hormonal changes. IF also seems to influence inflammatory reactions, lipid metabolism and insulin sensitivity. IF is an umbrella term, used for several calorie-restricting fasting regimes: the 5:2 diet where one fasts for two days a week and eats normally during the other days; the 16:8 plan where one eats within an 8-hour window, and fasts for 16 hours; the alternate day fasting protocol in which every other day involves

Corresponding Authors: Milton H. Saier, Jr., PhD[a], msaier@ucsd.edu, B. Lakshmi Reddy, PhD[a], lreddy@ucsd.edu.

Author Contributions

Professor B. Lakshmi Reddy wrote the rough draft of this paper and considered the relevance of the many cited references, Professor Milton Saier reviewed and edited the manuscript, and Dr. Vamsee Reddy provided documentation and recommendations supporting the conclusions of this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

fasting, etc. In a majority of reported cases, these fasting regimes have been shown to be safe: several clinical studies have reported significant metabolic benefits with no or only very mild side effects. Available evidence suggests that fasting is often a safe alternative to pharmaceutical interventions in maintaining health and energy balance with significant public health benefits.

Fasting is not a recently introduced practice as it has deep roots in many religious and spiritual practices. Some Christians believe fasting is a way to draw closer to God. Buddhists often believe that they shouldn't eat after a noon meal, and the intervening time should be spent in meditation. Hindus believe willful detachment from food purifies mind and body, bestowing positive spiritual benefits, and in Islam, fasting is practiced to reinforce faith and piety. The notion that fasting is good for health also has a long history since the publication of the book 'Fasting for the Cure of Disease' in 1908 by Linda B. Hazzard [1], who believed that all functional diseases including infections, headaches, and even sexual dysfunction can be cured by fasting. It was a sad window to the past, because at least nineteen deaths including her own were attributed to Hazzard's fasting cures which clearly involved hazards. In the sections presented below, we provide documentation in the recent scientific literature for the suggestion that IF and TRE can often be beneficial to human health.

THE HISTORY OF FASTING PRACTICES

We have come a long way in understanding cellular metabolism since the famous chemist Antoine Levoisier's experiments in 1782 with frozen guinea pigs that introduced his audience to the relationship between chemistry and physiology. He stuffed guinea pigs into a bucket insulated with ice, collected the melted water, and calculated the energy used by the guinea pigs to melt the ice, believing that the energy came largely from respiration.

Metabolism is a complex chemical process taking place continuously to keep our bodies functioning by converting the food we eat into metabolic intermediates and energy to power our many complex physiological processes. Slow, fast, and average rates of metabolism, regardless of body size, are heavily influenced by endocrine systems, and they vary greatly according to our ages, lifestyles, diets, and levels of inactivity. Metabolism is a dynamic and intricate system, meticulously evolved over hundreds of millions of years from our bacterial ancestors for survival and reproduction. Intermittent fasting (IF) was a normal "feast and famine" type existence for animals and primitive man during our evolutionary histories. It evidently became a way of manipulating metabolism with known benefits of weight loss, increased stress resistance, suppression of inflammation, and numerous physiological changes at the cellular level. It remains an evolutionarily conserved adaptive response for the promotion of health of all animals including *Homo sapiens*.

POTENTIAL MOLECULAR MECHANISMS MEDIATING BENEFITS OF FASTING

Metabolic markers such as organic acids, coenzymes, antioxidants, purines, and pyrimidines have been reported to be upregulated in healthy young volunteers during 58 hours of fasting [2]. These metabolites can activate multiple metabolic pathways, including antioxidative defense, mitochondrial activities, purine and pyrimidine anabolism, and the pentose phosphate pathway [2]. Significant and sustained effects of fasting have been documented on health indicators, including increased insulin sensitivity, decreased blood pressure, reduced body fat, and improved glucose homeostasis and lipid metabolism [3–5].

Fasting can also promote the regeneration and differentiation of multiple tissues and cells and strengthen antitumor immunity [6,7]. Based on research with animal models and human controlled trials, there is no denying that fasting can alter the gut microbiome, autophagy, and mitochondrial functions [8–14].

CURRENT EVIDENCE FOR HEALTH BENEFITS OF FASTING

Hundreds of studies have shown that caloric restriction (CR), reduction of food intake to 30–40% below *ad libitum* intake levels without malnutrition, while retaining essential nutrients, prevents several chronic degenerative inflammatory diseases [15] by activating autophagy [16–18], a degradation process of old proteins and organelles, important for cellular viability and regeneration, and for establishing homeostasis [18,19]. CR may be the best intervention for slowing ageing, extending lifespan, and delaying the onset of age-related diseases in several species, including fruit flies, rodents, and mammals, where these processes have been studied in detail [17,20–27].

IF has been reported to be as effective as CR in randomized controlled trials in promoting weight loss and metabolic improvements [28], not surprisingly in view of their overlapping methods. Fasting programs such as IF and other time restricted eating programs are likely to be effective in part by making people eat less overall, rather than merely offering specific weight-loss benefits. Alternate day fasting, TRE, and other IF strategies are generally found to be effective in producing mild to moderate weight loss and consistent reduction in blood pressure [29]. There is an enormous interest in the public, the media, and the scientific community on the benefits of IF with respect tp metabolic health. Nevertheless, long-term evidence-based human intervention studies are needed to know the differences and negative effects if any of the different IF protocols. This article includes a brief review of the reported benefits of IF on several aspects of metabolic health as well as their molecular causes when available.

Cardiometabolic Health:

Metabolic syndrome, also known as syndrome X, is considered a pathological condition with a combination of cardiovascular risk factors, characterized by insulin resistance, abdominal obesity, atherogenic dyslipidemia, and hypertension [30]. Available studies provide overwhelming evidence that IF is a safe and promising approach to prevent chronic diseases, maintain a healthy weight, and improve metabolic health. IF regimes have been reported to lower fasting insulin concentrations [31–33], and HbA1c (glycated hemoglobin) [34–37] in otherwise healthy individuals with obesity and/or prediabetes.

An overwhelming majority of relevant published studies have reported that fasting regimes result in anywhere between 1.3% to 84% loss of body weight with improvement of metabolic health [32,33,38–42]. Weight loss benefits resulting from a healthier diet after fasting may contribute to the lasting antihypertensive effects of fasting [43]. In addition to weight loss reported due to IF, there is evidence that IF benefits cardiovascular health regardless of changes in body weight [44,45]. IF regimens are also reported to be effective in reducing the systolic and diastolic blood pressure [34,36,38,40,45–47]. The effective reduction in blood pressure due to fasting has prompted some fasting experts to reduce or withdraw antihypertensive medication when initializing fasting therapy to avoid symptomatic hypotension and hyponatremia [15].

Even after the introduction of food, blood pressure can remain below the pre-fasting levels for weeks to a few months, depending on post-fasting nutritional and lifestyle habits [15]. IF lowered LDL cholesterol [34,35,40,47–49] and triglyceride concentrations [35,36,40,41,47–49] with variable results. Circulating inflammatory markers such as TNF-α remained mostly unchanged during IF, with few exceptions [41,47], where reduced inflammatory molecules have been reported. A significant reduction of oxidative stress has been reported in some studies [47].

IF is also known to result in lower risks of coronary artery disease and diabetes [50,51]. Epidemiological studies revealed that routine periodic fasting, as practiced by religious groups, is associated with a lower risk of coronary heart disease in patients undergoing coronary angiography [51]. CR and IF attenuate age-related changes in heart and blood vessels, due to cellular mechanisms directly related to fasting [15]. Alternate day fasting reduces the level of apoptosis in the peri-infarct area in experimental ischemia [52] and enhances ischemic preconditioning [53]. A recent review of randomized clinical trials involving human subjects concluded that IF is beneficial in lowering cardiovascular risk factors by improving lipid profiles, metabolic syndrome indicators, and insulin sensitivities while reducing body weight and inflammatory biomarkers [54].

In preparing this review, we found published evidence that IF reduces cardiovascular risks. We opted not to discuss non-peer-reviewed reports of IF causing harm to cardiovascular health. In most of the latter studies, there is no information regarding the dietary quality, length of eating windows, and lifestyle factors such as alcohol use as well as physical activities of the subjects. Most published studies are of short duration on healthy adults or with some obese and pre-diabetic subjects. There is a lack of long-term studies of individuals with cardiovascular disease. We need more controlled randomized long-term clinical studies with larger sample size, specifying pre-existing conditions, dietary quality, lifestyle, and incorporating different IF regimes to understand the effect of IF on cardiovascular disease.

Cancer:

Over a century ago, Moreschi reported that tumors in mice grafted with a sarcoma grew less frequently and more slowly in animals on low-calorie diets [55]. Then Rous [56] confirmed that transplanted tumors grew slowly in underfed mice compared with controls. In cancer patients, fasting can decrease the growth of induced tumors and their associated side effects while enhancing chemotherapeutic efficacy [57,58]. IF has also been reported to inhibit the growth of cancer cells by interfering with their energy metabolism, thus making cancer cells more susceptible to cancer therapies [59–61].

IF can suppress tumor growth and increase survival rates of patients with glioblastoma [62,63]. Periodic fasting has been reported to be effective in reducing pre-neoplastic lesions [64]. Fasting promotes tissue and cell regeneration and differentiation while strengthening antitumor immunity [6]. Fasting can also promote the regeneration and differentiation of multiple tissues and cells; it strengthens antitumor immunity [6,7].

Circadian Rhythms:

The endogenous circadian clock of a living organism is a product of evolution, essential for the optimization of several physiological processes in a wide range of organisms. The time of the day plays an important role in the integration of metabolism, energetics, physical coordination, hormonal secretion and sleep in animals [65]. Desynchronization between the suprachiasmatic nuclei (SCN) in the hypothalamus and similar sensors in peripheral tissues such as the liver, disrupt energy balance [66], leading to increased risk of chronic diseases [67]. Some research has suggested that fasting-related benefits are achieved in part by regulating the peripheral circadian clocks, including those in the liver, muscle, adipose tissue and intestine. Moreover, the clock is known to influence bacterial populations and activities of the gut microbiome (see below) [68–71].

In addition to *what* we eat, *when* we eat is likely to be important for the optimal benefits of fasting. The duration and timing of fasting rather than or in addition to the number of calories or nutrient composition may play a major role in achieving health benefits [72,73]. The timing of feeding-fasting cycles regulates the expression of several tissue-specific transcription factors, which in combination with clock proteins can drive rhythmic gene expression [74,75]. Eating early, within an eight-hour period, and then not eating after 3 pm (compared to eating over a 12-hour period), has been reported to reduce appetite, lower blood pressure, and delay the onset of diabetes [76].

The timing of eating may influence the metabolism of carbohydrates and lipids since circadian rhythms control and regulate metabolic pathways differently during the day and evening. Therefore, depending on the daily eating time, the same foods may lead to different metabolic outcomes. While the total expenditure of energy may be the same, individuals eating late nights oxidized more carbohydrates, while their lipid oxidation is lower compared to those who skipped late night snacking but ate breakfast [77]. Circadian misalignment, resulting in negative metabolic effects and lowered glucose tolerance in shift workers, increased their risk of type 2 diabetes, cardiovascular disease, and cancer [78–82]. Firefighters and other shift workers may benefit by eating within the same 10-hour eating frame daily from 7 am to 9 pm, to counter the disruption of circadian rhythms with health consequences such as increased risk of diabetes and cardiometabolic disorders [83]. Other possible clock-dependent metabolic consequences of fasting such as on glycogenolysis and gluconeogenesis in the liver, nutrient absorption in the gastrointestinal tract, and noninsulin-mediated glucose uptake have not been studied.

The Gut Microbiome:

Fasting and feeding rhythms significantly alter the gut microbiota [84,85]. IF is believed to influence metabolic regulation via the gut microbiome as well as essential lifestyle behaviors such as sleep [86]. Mice on an every-other day fasting regimen selectively activate beige fat thermogenesis and alleviate obesity related metabolic diseases, likely via the microbiota-beige-fat axis [10]. Fecal transplants from IF-treated mice to naïve recipients enhanced antioxidative microbial metabolic pathways [87]. The 8-week IF treatment significantly reduced fat mass and oxidative stress while modifying inflammatory cytokines and improving vasodilatory parameters, while a 2-day IF treatment improved adipokines, preventing lipid peroxidation, and improving vascular endothelial function in people with MS. These effects were associated with alterations in the composition of the gut microbiota, microbial related metabolites, and metabolic pathways in the intestinal microbiome [88]. Obesity related changes in the gut microbiota can alter gut permeability and bacterial translocation, promoting systemic inflammation [89]. Based on studies in animal models and human controlled trials, there is no denying that fasting can alter the gut microbiome, autophagy, and mitochondrial functions [8–14].

Anti-inflammatory and neuroprotective benefits of IF and CR have been reported in animal models of stroke [90] and systemic infections as well as in humans with inflammatory systemic conditions [41]. Protection against autoimmunity in Multiple Sclerosis (MS) patients by altering the gut microbiome [87] is another reported benefit. IF is known to reduce inflammation, demyelination, and axonal damage in murine experimental autoimmune encephalomyelitis [87,91,92]. Significant inter-individual differences of the effects of IF were likely caused, at least in part, by changes in the gut microbiota [93].

Aging:

Progressive decline in the efficiency of physiological processes with age is due, in part, to accumulation of reactive oxidative metabolites [94–97]. We have known for over seventy-five years that caloric restriction extends the maximal lifespan. Brain, heart and skeletal muscle accumulate high levels of oxidative damage, and these organs are therefore targets for several age-related disorders that are attenuated by CR [97,98]. For healthy people, fasting improves systemic metabolic indices and enhances the functions of multiple organs, thereby creating a beneficial cycle, especially in young adults [99–101]. In older adults with mild cognitive impairment, a 36-month IF regimen may reduce the level of oxidative stress by increasing superoxide dismutase activities [102,103].

Fasting has also been shown to delay cognitive impairment, improve hippocampus-dependent memory, and slow the progression of Alzheimer's disease (AD), although the underlying mechanisms are not well understood [13,104–106]. Mitochondrial dysfunction and oxidative stress are characteristic features of both senescence and aging; moreover, they have been implicated in several diseases, such as ischemia–reperfusion (IR) injury [107,108]. Fasting may significantly protect against acute liver and kidney injury as well as renal fibrosis as shown in animal models of IR [107,109–111]. Fasting may also reduce DNA damage which is related to the upregulation of key DNA repair proteins such as apurinic/apyrimidinic endonuclease-1 [58]. Interestingly, it has been suggested that fasting can increase telomere length by suppressing mTOR signaling in planarian stem cells [112].

Ketogenesis:

Fasting can attenuate disturbances of glucose and lipid metabolism, promote the regeneration of stem cells and organs, and inhibit disease progression in obese individuals and patients with metabolic syndromes [113,114]. When stored glucose levels are depleted, cells switch to various adaptive metabolic processes such as reducing the basal metabolic rate, lipolysis and ketogenesis. They also modulate hormone levels and decrease oxidative stress and inflammation [68,86,115,116]. When blood glucose levels are depleted, ketone bodies and lactic acid are the main fuels in the brain as they can cross the blood brain barrier via endothelial cells and astrocytes [117]. The protective molecular mechanisms in cells to survive periods of deprivation of energy resources delay ageing and promote organismal fitness.

During fasting, ketone bodies contribute to around 60% of the energy in the brain, replacing glucose as the primary energy source [118]. In cases of AD, Parkinson’s disease (PD), Amyotrophic lateral sclerosis (ALS), Frontotemporal dementia (FTD), and Huntington’s disease (HD), disease severity is in part due to glucose hypometabolism in affected areas [119–122]. Ketone bodies produced during fasting can have neuroprotective effects, decreasing neurodegeneration [123]. β-Hydroxybutyrate (BHB), the most abundant ketone body, inhibits inflammation in myeloid cells, reducing age-related inflammation. Ketone bodies are produced in the liver but are not degraded there, and preserving them for extrahepatic tissue use such as the brain, heart and skeletal muscle has definite health benefits. BHB produced by small intestinal stem cells maintains their “stemness” within crypts [124].

Ketones are reported to regulate memory responses in CD8 T cells and restrain macrophage activation during acute pancreatitis [125]. BHB produced in renal epithelial cells mediates protective effects of nicotinamide [126], and a failing heart is known to increase the consumption of ketone bodies [127]. BHB also acts as a histone deacetylase inhibitor, thereby influencing gene expression [128]. Based on the broad spectrum of actions of BHB, ketone bodies are believed to be important regulatory factors in chronic inflammation during aging [129,130], indicating that fasting is intricately linked to immune system function.

FASTING THERAPIES:

Fasting therapies have long traditional roots worldwide with fasting clinics, hospitals, retreats, and departments focused on benefits observed for integrative medicine. Fasting cures have been popular in Europe since their introduction over one hundred years ago by physicians like Buchinger [131], Krauss [132], and Mayr [133]. Beneficial effects of fasting have been reported when treating several chronic diseases such as metabolic diseases [134–136], pain syndromes [137–139], hypertension [140–142], chronic inflammatory diseases [43,143], atopic diseases [144,145], and psychosomatic conditions [146–148], with substantial evidence for rheumatic diseases [149–153]. Fasting is also considered as a favorable treatment option for other diseases such as irritable bowel syndrome (IBS), food allergies, skin diseases and recurrent infections, as well as asthma, inflammatory bowel disease, multiple sclerosis and other types of allergies [15]. Short term fasting may lead to clarity of mind and help in the development of a positive attitude to life. At least some of these effects may be due to neuroendocrine activation, depending on the individual's metabolic and endocrine status [137].

Conclusion

There is ample evidence for beneficial outcomes of fasting. Even though we do not clearly understand many of the specific mechanisms, animal studies have shown lifelong benefits of IF. Unfortunately, however, reported human studies have been of short duration, and the baseline parameters of the study populations are highly variable [154–157]. In human trials, adherence to the diet patterns is self-reported, which may include biases. A majority of clinical studies are focused on overweight individuals. More studies are needed to generalize the benefits of IF to younger more healthy individuals, and the safety of these procedures must be thoroughly established. Widely reported IF studies may also provide an opportunity to develop targeted therapeutic and pharmacological interventions to treat chronic diseases. It is important to note that no single pharmaceutical medication can provide such a wide spectrum of benefits on metabolic health as IF. Along with IF, a combination of strategies such as regular exercise; avoiding alcohol, processed foods and energy rich high calorie diets are essential to adapt to an active lifestyle. Low calorie vegetable diets with adequate protein content are likely to be widely beneficial, and the treatment of chronic diseases such as obesity is very likely to enhance one's quality of life and increase the life spans of humans generally.

Many individuals may not be able to adhere to fasting regimes over long periods, and in some individuals, fasting may reinforce eating disorders. People may also experience a yo-yo effect and gain weight after weight reduction during fasting. Fasting individuals should also be under supervision to ensure adequate fluid intake and electrolyte balance. Proper supervision is also vital in clinical settings where patients may experience tiredness, nausea, and altered sleep patterns. Thus, although clear health benefits have been repeatedly attributed to fasting protocols, much more research will be required to quantitate these benefits as applied to large numbers of individuals examined with respect to each of the many human disease states considered to have benefited from IF. It will also be necessary to document the variations in responses of different individuals within the human and animal populations.

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