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INTERMITTENT FASTING: IS IT BENEFICIAL FOR HEALTH?

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Summary: During evolution, animals, including humans, developed in conditions of relative food scarcity. Adapting to such life circumstances, they developed adaptive metabolic changes that allowed them to function well even during periods when food was not available. Intermittent fasting (IF) encompasses eating patterns in which individuals refrain from consuming nutrients for extended periods or consume them in small quantities with alternating periods of normal food intake. IF has become an increasingly popular dietary practice, and its application can be found in various cultural, spiritual, religious, and health traditions throughout human civilization. New evidence has shown that the health benefits of IF extend beyond caloric restriction and weight loss. These benefits include metabolic changes in energy production and overall improvement in physiological markers of metabolic health. It is believed that IF reduces systemic inflammation and plays a role in the prevention and treatment of chronic diseases. In this paper, we aim to review available discussions on the physiological significance and impact of intermittent fasting on health.

Key words: intermittent fasting, therapeutic method, fasting in history, fasting and health, metabolic changes, ketone bodies, autophagy, gluconeogenesis, regeneration and stress, caloric restriction, lipolysis, sirtuins, cardiometabolic effects, atherosclerosis

INTRODUCTION

Intermittent fasting or fasting as a therapeutic method has been used at least since the 5th century BC. At that time, Hippocrates recommended abstinence from food or drink for patients exhibiting certain disease symptoms. Some doctors later recognized the instinct of fasting (in patients who, in certain diseased states, naturally experience a loss of appetite) and believed that providing food during such conditions was unnecessary and possibly even harmful, believing that fasting was an important natural part of the recovery process. The understanding of the physiological effects of fasting began to develop in the second half of the 19th century when some of the first organized fasting studies were conducted on animals and humans. In the 20th century, as knowledge of nutrition and the nutritional needs of the human body grew, fasting methods became more sophisticated, and a wide range of ways to apply this form of eating emerged.

The term fasting for Orthodox Christians refers to the abstention from certain types of food, primarily meat, dairy products, and eggs, and in some fasting periods, even fish, oil, and alcoholic beverages are avoided. In this paper, fasting will refer to the occasional interruption of the intake of any type of food (or the consumption of food and caloric drinks in minimal quantities) during periods typically ranging from 12-36 hours. Intermittent fasting (IF) can be practiced daily, alternating every other day, twice a week, or once a week. Fasting can be practiced for religious reasons as well as for health purposes. Members of certain religious communities traditionally fast on specific days of the week or calendar year. In many healthcare institutions, patients under medical supervision follow a fasting regimen or calorie restriction to control body weight, prevent, or treat diseases.

Fasting differs from caloric restriction (CR), where daily caloric intake is chronically reduced by 20-40%, but meal frequency is maintained. Unlike fasting and CR, starvation is chronic nutritional insufficiency often used as a substitute for the word fasting, but it is also used to define extreme forms of fasting (e.g., starvation), which can lead to degeneration and death. Research on animal models, as well as studies on humans, shows that fasting leads to ketogenesis, promotes strong changes in metabolic pathways and cellular processes such as stress resistance, lipolysis, and autophagy, and can have medical applications [1].

Intermittent fasting is technically not just a diet plan but a way of eating that focuses on timing rather than the type of food. Studies on animals and humans have shown that many health benefits of intermittent fasting are not solely a result of reduced free radical production or weight loss. Instead, intermittent fasting triggers evolutionarily preserved, adaptive cellular responses that improve glucose regulation, increase stress resistance, and suppress inflammation. During fasting, cells activate pathways that enhance defense against oxidative and metabolic stress and those that remove or repair damaged molecules [2]. The remarkable effects of typical CR (20-40%) on aging and diseases in mice and rats are often seen as mammalian responses during evolution to adapt to periods of limited food availability. However, the cellular and molecular mechanisms responsible for the protective effects of CR likely evolved billions of years earlier in prokaryotes attempting to survive in environments that were largely or completely devoid of energy sources [3]. For example, the bacterium E. coli, transferred from a nutrient-rich medium to a calorie-free medium, survives four times longer, an effect reversed by adding various nutrients, but not acetate, a carbon source associated with starvation conditions [4]. The shortening of the bacterium's lifespan in a rich medium, but not acetate, suggests that a ketone-body-like carbon source such as acetate could be part of an "alternative metabolic program" that evolved over billions of years in microorganisms, now allowing mammals to survive periods of food scarcity by obtaining most of their energy through fatty acid and ketone body catabolism, including acetoacetate and β-hydroxybutyrate [5]. In Saccharomyces cerevisiae (brewer's yeast), transferring cells from a standard growth medium to water also causes consistent double chronological lifespan extension, as well as a significant increase in resistance to multiple stressors [6]. Another organism model where fasting extends lifespan is the nematode Caenorhabditis elegans. Food deprivation conditions achieved by feeding the worms with little or no bacteria lead to significant lifespan extension [1]. In the fruit fly, most studies suggest that intermittent food deprivation does not affect lifespan. However, it has consistently been shown that reducing or diluting food extends the longevity of Drosophila, suggesting that flies may benefit from dietary restriction but may be sensitive even to short periods of starvation. Taken together, these results indicate that food deprivation can lead to lifespan-extending effects across a wide range of organisms but also emphasize that different organisms have different responses to fasting [1]..

Metabolic Changes During Fasting

In most mammals, the liver serves as the main reservoir for glucose, which is stored in the form of glycogen. In humans, depending on the level of physical activity, after 12 to 24 hours of fasting, the glucose levels in the serum drop by 20% or more. The glycogen reserves in the liver become depleted. The body shifts to a metabolic state in which the liver and kidneys produce glucose from non-carbohydrate sources, such as glycogenic amino acids from muscles (isoleucine, phenylalanine, tyrosine, tryptophan), glycerol from fats, and lactic acid, followed by lipolysis in adipose tissue, releasing free fatty acids and glycerol, which the body uses as energy. While most tissues can use fatty acids for energy, during extended fasting periods, the brain, in addition to glucose, relies on ketone bodies β-hydroxybutyrate and acetoacetate for energy consumption. Ketone bodies are produced in hepatocytes from acetyl-CoA formed through β-oxidation of fatty acids released into the bloodstream by adipocytes, and also through the conversion of ketogenic amino acids (leucine and lysine). After 3-5 days of fasting, the liver produces ketone bodies (beta-hydroxybutyrate and acetoacetate) from fatty acids through ketogenesis, which become the main energy source for the brain and muscles. At the same time, the use of protein as an energy source decreases. After 5 days without food, the brain almost completely switches to ketone bodies as an energy source, thus protecting muscle mass. Minimal gluconeogenesis still occurs, approximately 80 grams daily, with glucose being produced only in amounts necessary for cells that cannot use ketone bodies (e.g., erythrocytes and some parts of the brain) [7]. Depending on body weight and composition, ketone bodies, free fatty acids, and gluconeogenesis allow most people to survive for 30 or more days in conditions of food scarcity, and allow certain species, such as royal penguins, to survive without food for more than 5 months [8].

Metabolic Adaptations to Intermittent Fasting

In humans, the three most studied intermittent fasting regimens are alternate-day fasting (one day without food, the next day food ad libitum), 5:2 intermittent fasting (fasting for 2 days each week), and daily time-restricted feeding. Diets that significantly reduce caloric intake for 1 day or more each week (e.g., reducing to 500–700 calories per day) lead to increased levels of ketone bodies on those days [9, 10].

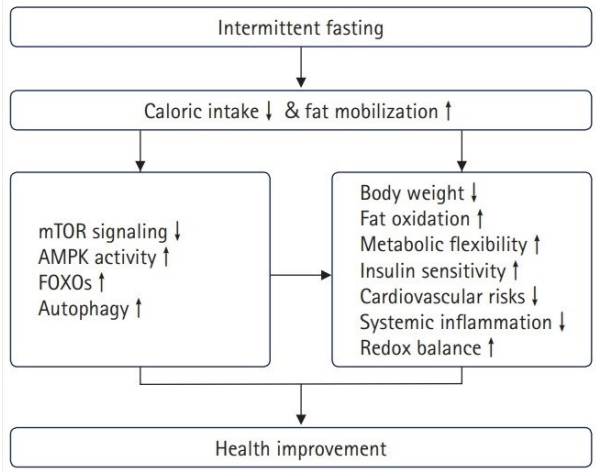
The metabolic shift from using glucose as a fuel source to using fatty acids and ketone bodies ("metabolic switch") results in a decreased respiratory quotient (the ratio of carbon dioxide produced to oxygen consumed), indicating greater metabolic flexibility and efficiency in energy production from fatty acids and ketone bodies [11].

Ketone bodies are not only fuels used during fasting periods; they are powerful signaling molecules with significant effects on cellular and organ functions. Ketone bodies act as metabolic signals that regulate epigenetics through beta-hydroxybutyrate (BHB), which inhibits histone deacetylase (HDAC). This inhibition then results in an antioxidant response and lifespan extension. They increase the activity of sirtuins (especially SIRT1 and SIRT3), which reduces oxidative stress. Ketones also modulate inflammatory and antioxidant pathways by promoting the activation of Nrf2 (Nuclear factor erythroid 2-related factor 2), the primary regulator of the antioxidant response, and by reducing the activity of NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), a key factor in inflammatory processes. Additionally, ketones increase stress resistance and promote autophagy through AMPK (AMP-activated protein kinase), which stimulates autophagy and mitochondrial biogenesis, contributing to cellular health and stress resilience. Ketone bodies indirectly inhibit mTORC1 activity (the mechanistic/mammalian target of rapamycin complex), the major regulator of cellular growth and protein synthesis. Mechanistically, mTOR is a key regulator of autophagy and cellular metabolism in mammals. Reduced mTOR activity shifts cellular resources from non-essential anabolic reactions toward catabolic processes, including activation of complexes important for autophagy. Reduced mTOR activity is linked to extended lifespan and protection from age-related diseases [12].

By affecting these key cellular pathways, ketone bodies produced during fasting have profound effects on systemic metabolism. Furthermore, ketone bodies stimulate the expression of genes for brain-derived neurotrophic factor, with implications for brain health and psychiatric and neurodegenerative disorders [13]. Many studies have shown that some of the benefits of intermittent fasting are separate from its effects on weight loss. These benefits include: improvements in glucose regulation, regulation of blood pressure, reduction in heart rate, increased endurance training efficiency, and loss of abdominal fat [14].].

Picture 1. POSSIBLE MECHANISMS OF INTERMITTENT FASTING ON HEALTH IMPROVEMENT

Source (25.02.2025): *Song DK, Kim YW. Beneficial effects of intermittent fasting: a narrative review. J Yeungnam Med Sci. 2023 Jan;40(1):4-11. https://pmc.ncbi.nlm.nih.gov/articles/PMC9946909/*



The Effects of Intermittent Fasting on Health and Aging

After nearly a century of research on caloric restriction in animal models, the general conclusion was that reduced food intake significantly extends the lifespan of the animals studied. In one of the earliest studies on intermittent fasting, Goodrick and colleagues showed that the average lifespan of rats was extended by up to 80% when maintained on an alternate day feeding regimen, starting when they were young adults. However, the magnitude of the effects of caloric restriction on healthspan and lifespan varies and can be influenced by gender, diet, age, and genetic factors [2]. A meta-analysis of data available from 1934 to 2012 showed that caloric restriction in rats extended the average lifespan by 14 to 45%, but only by 4 to 27% in mice [15].

Conflicting results from two significant studies on monkeys raised doubts about the relationship between improved health status and extended lifespan through caloric restriction. One study on rhesus monkeys showed a positive effect of caloric restriction on both health and survival [16], while another study, also on rhesus monkeys, did not show a significant reduction in mortality with caloric restriction, despite clear improvements in overall health [17]. A subsequent study showed that differences in daily caloric intake, the timing of the intervention, food composition, feeding protocols, gender, and genetic background could explain the varying effects of caloric restriction on lifespan in the two previous studies [18].

Intermittent fasting in humans alleviates obesity, insulin resistance, dyslipidemia, hypertension, and inflammation. It seems that intermittent fasting provides more health benefits than can be attributed solely to a reduction in caloric intake. In one study, 16 healthy participants who underwent an alternate-day fasting regimen for 22 days lost 2.5% of their initial body weight and 4% of body fat, along with a 57% reduction in fasting insulin levels [19]. In two other studies, approximately 100 overweight women in each study were divided into two groups: one following a 5:2 intermittent fasting regimen, and the other reducing their daily caloric intake by 25%. Participants in both groups lost the same amount of weight during the 6-month period, but those in the 5:2 intermittent fasting group had a greater increase in insulin sensitivity and a larger reduction in waist circumference [20].

Benefits of Intermittent Fasting for the Aged and Diseased Vasculature

Vascular aging involves arterial stiffness and the formation of fibrolipid lesions in the arterial wall, leading to atherosclerosis. The main clinical manifestations of atherosclerosis include coronary artery disease, ischemic stroke, and peripheral artery disease, which are caused by hyperlipoproteinemia (low-density lipoprotein LDL cholesterol), inflammation, vascular remodeling, and plaque formation [21]. Intermittent fasting (IF) is associated with a reduction in LDL cholesterol levels [22]. In rats, both in the absence and presence of various stressors (e.g., swimming), intermittent fasting reduces resting blood pressure and heart rate. The reduction in blood pressure may be partially due to enhanced endothelial cell-dependent vasodilation [23,24].

Furthermore, intermittent fasting activates the parasympathetic nervous system by stimulating brain cells. During fasting, neurotrophic factors are released, and acetylcholine is secreted, which, via the vagus nerve, leads to a decrease in heart rate and blood pressure [25].

Risks of Intermittent Fasting for the Aged and Diseased Heart and Vasculature

Despite the numerous health benefits of intermittent fasting (IF), some risks have been reported in various models of cardiovascular diseases. For example, rats subjected to alternate-day fasting for 6 months showed reduced diastolic compliance of the left ventricle and diminished cardiac reserve [26].

The efficacy of activating autophagy in senescent cells remains a subject of ongoing debate, as autophagy has also been reported to promote cellular aging by facilitating the synthesis of aging-associated proteins. Furthermore, excessive stimulation of autophagy can lead to several pathological outcomes, including inhibition of angiogenesis [27]. Therefore, reduced regenerative capacity of the endothelium and the accumulation of senescent cells in older individuals may

potentially limit the beneficial effects of intermittent fasting on vascular health.

In older adults, particularly those with hypertension or other cardiovascular diseases, potential fluctuations in blood pressure during intermittent fasting periods may raise concerns regarding cardiovascular risks, orthostasis, and fall-related injuries [28]. Another risk associated with intermittent fasting arises from metabolic changes, such as electrolyte imbalances or activation of the sympathetic nervous system, which can predispose older individuals to dehydration and cardiac arrhythmias, especially in the presence of pre-existing heart conditions.

In summary, due to the lack of data, the implementation of intermittent fasting in older individuals or patients with cardiovascular diseases requires careful consideration due to potential risks, which depend on the specific fasting regimen, cardiac condition, comorbidities, gender, and age [29].

Effect of Intermittent Fasting on Cardiometabolic Health

The weight loss induced by intermittent fasting is primarily attributed to a reduction in fat mass. Studies have documented reductions in subcutaneous and visceral fat, with the latter being particularly beneficial due to its association with metabolic dysregulation and increased cardiovascular risk [30].

Waist circumference, a key anthropometric marker of cardiovascular risk used to assess abdominal adiposity, is strongly associated with all-cause mortality and cardiovascular mortality. It has been shown that waist circumference significantly decreases in individuals practicing intermittent fasting. This reduction in waist circumference is directly correlated with a lower risk of coronary artery disease and other cardiovascular pathologies [31].

Moreover, intermittent fasting improves several cardiovascular risk factors, including blood pressure, lipid profile, resting pulse, glucose and insulin levels, and insulin resistance. Furthermore, intermittent fasting can alleviate chronic inflammation associated with aging by reducing systemic inflammatory markers and oxidative stress linked to atherosclerosis in humans [29].

Aging is a critical factor in the pathogenesis and progression of heart failure (HF), increasing the incidence and severity of HF. Several studies have suggested that intermittent fasting may improve risk factors associated with the development of HF in both healthy individuals and those with obesity and ischemic heart disease [32].

For instance, in one study, participants who reported routinely practicing intermittent fasting at least once a month for a minimum of 5 years experienced a 71% reduction in the risk of heart failure compared to those who did not fast [33]. Another prospective observational study found that later periods of the first and last meals were associated with a greater risk of cardiovascular events, consistent with randomized studies reporting that late evening meals may exacerbate cardiovascular risk factors [34]. These inconsistent findings require further research into the relationship between intermittent fasting and heart failure through large randomized controlled trials investigating the effect of fasting at different times of the day.

The effect of intermittent fasting on muscle health is a topic of debate as it remains unclear whether intermittent fasting preserves lean muscle mass during weight loss or exacerbates the breakdown of muscle proteins and net catabolism. While some earlier studies suggested a reduction in lean mass with dieting, the general consensus is that intermittent fasting does not have a detrimental effect on lean mass, even with weight loss in otherwise healthy individuals, as well as in insulin-treated diabetic patients [35].

Physical and Cognitive Effects of Intermittent Fasting

In both animals and humans, physical function improves with intermittent fasting. For example, despite having similar body weights, mice maintained on an intermittent fasting regimen exhibit better running endurance than mice with unlimited access to food [2]. Balance and coordination are also improved in animals following time-restricted daily feeding or alternate-day fasting regimens [36]. Juveniles who fast for 16 hours daily lose fat while maintaining muscle mass over 2 months of intense training [37]. Animal studies show that intermittent fasting improves cognition across various domains, including spatial memory, associative memory, and working memory [38]. Alternate-day fasting and daily caloric restriction counteract the harmful effects of obesity, diabetes, and neuroinflammation on

spatial learning and memory. In a clinical trial, older adults on a short-term caloric restriction regimen experienced improved verbal memory. In a study involving overweight adults with mild cognitive impairment, 12 months of caloric restriction led to improvements in verbal memory, executive function, and global cognition [39, 40]. A large, multicenter, randomized clinical trial demonstrated that 2 years of daily caloric restriction resulted in significant improvements in working memory [41]. Further research is needed to explore the relationship between intermittent fasting and cognition in older adults, especially considering the absence of pharmacological therapies affecting brain aging and the progression of neurodegenerative diseases.

DISCUSSION

An increasing body of evidence supports intermittent fasting (IF) in all its variations as a potentially safe and feasible dietary intervention for improving human health. IF can improve physiological and molecular markers of aging and provide benefits for cardiovascular and metabolic health in patients with obesity, type 2 diabetes, metabolic syndrome, and heart failure [29]. Significant weight loss and other health benefits have been associated with two types of intermittent fasting: modified alternate-day fasting (alternating between a day of normal food intake and a day consuming up to 600 calories) and the "5:2 diet" (2 days of no caloric intake per week) [42].

While clinical evidence is mostly of a research nature, these studies provide a solid rationale for investigating the efficacy of IF in improving cardiovascular health, particularly in the elderly population at risk for or already experiencing cardiovascular diseases. Future randomized trials with larger sample sizes and longer durations will be necessary to assess the long-term outcomes, adherence, and safety of IF, especially in older participants.

Despite the health benefits of intermittent fasting and its applicability to many diseases, there are barriers to widespread adoption of these dietary patterns in the community and by patients. First, the traditional three-meal-a-day pattern with snacks is so ingrained in our culture that patients or physicians rarely consider changing this eating pattern. The abundance of food and extensive marketing in developed countries also pose significant barriers that must be overcome. Second, when transitioning to an intermittent fasting regimen, many people experience hunger, irritability, and reduced concentration during periods of food restriction. However, these initial side effects usually subside within a month, and patients should be informed of this [2].

Given the limitations and risks outlined above, patients should be cautioned that eating patterns involving extended periods without food could pose risks for people with diabetes who are on insulin or otherwise prone to hypoglycemia [42]. Physician education is also recommended for patients with a range of chronic conditions or at risk of such conditions, particularly those associated with overeating and a sedentary lifestyle, on how to implement intermittent fasting for prevention or as part of early treatment for these conditions.

Another important aspect to consider is that intermittent fasting alters the gastrointestinal microbiome [43]. Fasting regimens appear to have a positive impact on gut microbiota. Future studies characterizing the health effects of fasting regimens on the human microbiome have the potential to make an important contribution to this field. Therefore, it will also be crucial to investigate changes in metabolites produced by gut bacteria, focusing on the molecular mechanisms underlying the effects of intermittent fasting on cellular aging.

CONCLUSION

Intermittent fasting relies on the concept of a "metabolic switch," which involves a shift from glucose-dependent metabolism during a typical diet to ketones derived from fat cells during fasting. This "metabolic switch" may improve glucose regulation and reduce inflammation. The stress of fasting also increases autophagy, which removes damaged molecules. Given these physiological changes, intermittent fasting can offer significant long-term health benefits. Animal models of intermittent fasting show that this dietary pattern improves the health of the animals throughout their lifespan. Clinical studies in human models have also demonstrated significant health benefits, although these studies have mostly involved relatively short-term interventions lasting several months. Preclinical studies and clinical trials have shown

that intermittent fasting offers a broad range of advantages for many health conditions, such as obesity, diabetes, cardiovascular diseases, certain cancers, and neurological disorders. Numerous studies suggest that intermittent fasting regimens may be a promising approach for weight loss and improving metabolic health in people who can tolerate periods without food or consume very little at certain times of the day or on specific days of the week. For healthy, normal-weight, or obese adults, there is little evidence that intermittent fasting regimens are harmful physically or mentally. Future studies should determine whether the benefits observed in animal models can be sustained over long-term intermittent fasting in humans of various ages and health statuses. Further understanding of the processes linking intermittent fasting to many health benefits may allow us to develop targeted pharmacological therapies, including interventions on the gut microbiome, that mimic the effects of intermittent fasting without requiring fundamental changes to eating habits.

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