REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Effects of Intermittent Fasting on Health, Aging, and Disease

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According to Weindruch and Sohal in a 1997 article in the *Journal*, reducing food availability over a lifetime (caloric restriction) has remarkable effects on aging and the life span in animals.[1] The authors proposed that the health benefits of caloric restriction result from a passive reduction in the production of damaging oxygen free radicals. At the time, it was not generally recognized that because rodents on caloric restriction typically consume their entire daily food allotment within a few hours after its provision, they have a daily fasting period of up to 20 hours, during which ketogenesis occurs. Since then, hundreds of studies in animals and scores of clinical studies of controlled intermittent fasting regimens have been conducted in which metabolic switching from liver-derived glucose to adipose cell–derived ketones occurs daily or several days each week. Although the magnitude of the effect of intermittent fasting on life-span extension is variable (influenced by sex, diet, and genetic factors), studies in mice and nonhuman primates show consistent effects of caloric restriction on the health span (see the studies listed in Section S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Studies in animals and humans have shown that many of the health benefits of intermittent fasting are not simply the result of reduced free-radical production or weight loss.[2-5] Instead, intermittent fasting elicits evolutionarily conserved, adaptive cellular responses that are integrated between and within organs in a manner that improves glucose regulation, increases stress resistance, and suppresses inflammation. During fasting, cells activate pathways that enhance intrinsic defenses against oxidative and metabolic stress and those that remove or repair damaged molecules (Fig. 1).[5] During the feeding period, cells engage in tissue-specific processes of growth and plasticity. However, most people consume three meals a day plus snacks, so intermittent fasting does not occur.[2,6]

Preclinical studies consistently show the robust disease-modifying efficacy of intermittent fasting in animal models on a wide range of chronic disorders, including obesity, diabetes, cardiovascular disease, cancers, and neurodegenerative brain diseases.[3,7-10] Periodic flipping of the metabolic switch not only provides the ketones that are necessary to fuel cells during the fasting period but also elicits highly orchestrated systemic and cellular responses that carry over into the fed state to bolster mental and physical performance, as well as disease resistance.[11,12]

Here, we review studies in animals and humans that have shown how intermittent fasting affects general health indicators and slows or reverses aging and disease processes. First, we describe the most commonly studied intermittent-fasting regimens and the metabolic and cellular responses to intermittent fasting. We then present and discuss findings from preclinical studies and more recent clinical studies that tested intermittent-fasting regimens in healthy persons and in patients with metabolic disorders (obesity, insulin resistance, hypertension, or a

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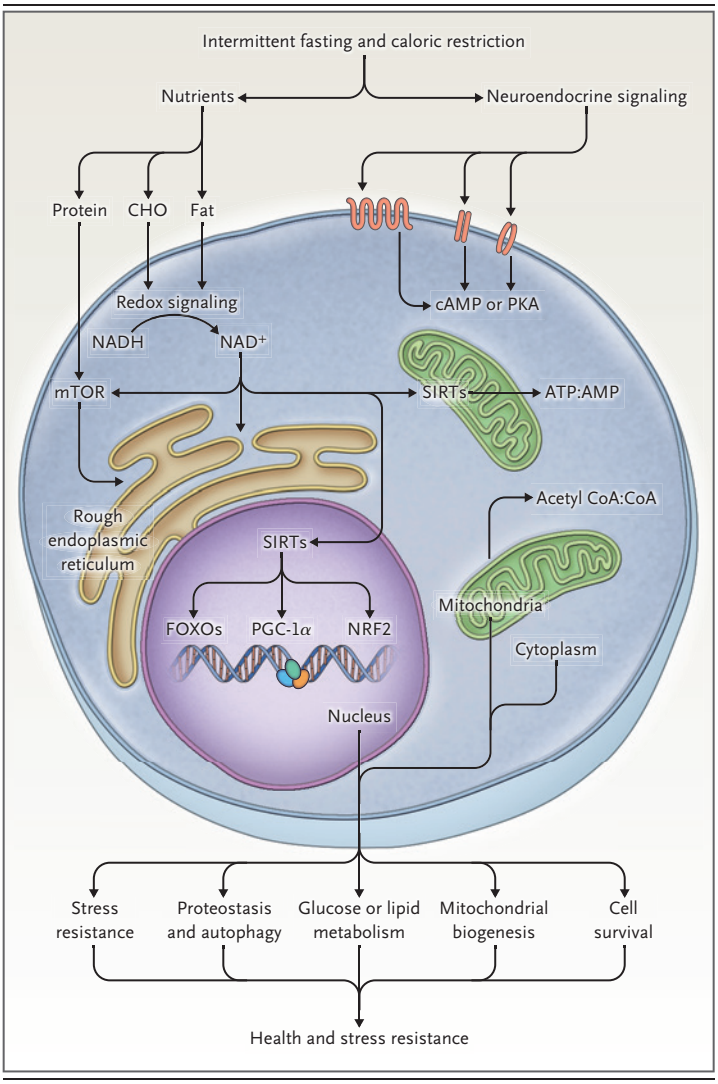

Figure 1. Cellular Responses to Energy Restriction That Integrate Cycles of Feeding and Fasting with Metabolism.

Total energy intake, diet composition, and length of fasting between meals contribute to oscillations in the ratios of the levels of the bioenergetic sensors nicotinamide adenine dinucleotide (NAD^+) to NADH, ATP to AMP, and acetyl CoA to CoA. These intermediate energy carriers activate downstream proteins that regulate cell function and stress resistance, including transcription factors such as forkhead box Os (FOXOs), peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α), and nuclear factor erythroid 2–related factor 2 (NRF2); kinases such as AMP kinase (AMPK); and deacetylases such as sirtuins (SIRTs). Intermittent fasting triggers neuroendocrine responses and adaptations characterized by low levels of amino acids, glucose, and insulin. Down-regulation of the insulin–insulin-like growth factor 1 (IGF-1) signaling pathway and reduction of circulating amino acids repress the activity of mammalian target of rapamycin (mTOR), resulting in inhibition of protein synthesis and stimulation of autophagy. During fasting, the ratio of AMP to ATP is increased and AMPK is activated, triggering repair and inhibition of anabolic processes. Acetyl coenzyme A (CoA) and NAD^+ serve as cofactors for epigenetic modifiers such as SIRTs. SIRTs deacetylate FOXOs and PGC-1α, resulting in the expression of genes involved in stress resistance and mitochondrial biogenesis. Collectively, the organism responds to intermittent fasting by minimizing anabolic processes (synthesis, growth, and reproduction), favoring maintenance and repair systems, enhancing stress resistance, recycling damaged molecules, stimulating mitochondrial biogenesis, and promoting cell survival, all of which support improvements in health and disease resistance. The abbreviation cAMP denotes cyclic AMP, CHO carbohydrate, PKA protein kinase A, and redox reduction–oxidation.

combination of these disorders). Finally, we provide practical information on how intermittent-fasting regimens can be prescribed and implemented. The practice of long-term fasting (from many days to weeks) is not discussed here, and we refer interested readers to the European clinical experience with such fasting protocols.[13]

INTERMITTENT FASTING AND METABOLIC SWITCHING

Glucose and fatty acids are the main sources of energy for cells. After meals, glucose is used for energy, and fat is stored in adipose tissue as triglycerides. During periods of fasting, triglycerides are broken down to fatty acids and glycerol, which are used for energy. The liver converts fatty acids to ketone bodies, which provide a major source of energy for many tissues, especially the brain, during fasting (Fig. 2). In the fed state, blood levels of ketone bodies are low, and in humans, they rise within 8 to 12 hours after the onset of fasting, reaching levels of 0.2 to 0.5 mM, which are maintained through 24 hours, with a subsequent increase to 1 to 2 mM by 48 hours.[14,15] In rodents, an elevation of plasma ketone levels occurs within 4 to 8 hours after the onset of fasting, reaching millimolar levels within 24 hours.[16] The timing of this response gives some indication of the appropriate periods for fasting in intermittent-fasting regimens.[2,3]

In humans, the three most widely studied intermittent-fasting regimens are alternate-day

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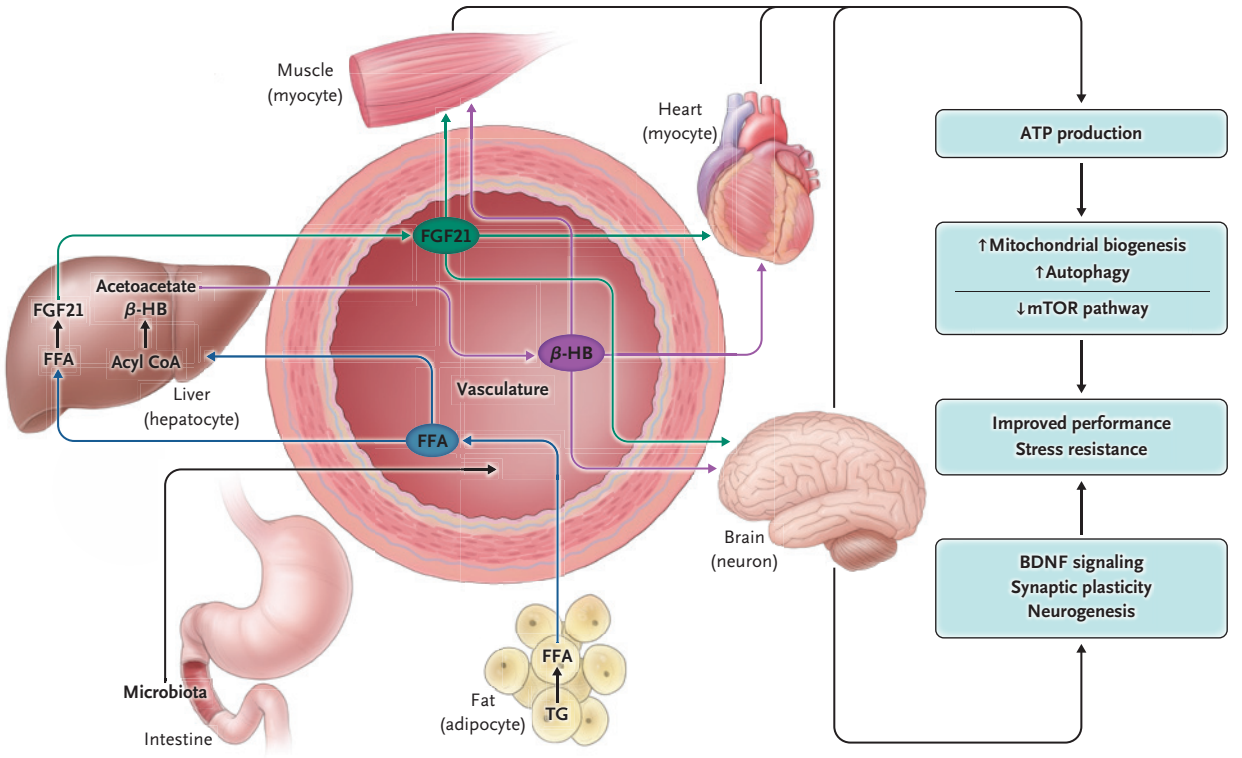

Figure 2. Metabolic Adaptations to Intermittent Fasting.

Energy restriction for 10 to 14 hours or more results in depletion of liver glycogen stores and hydrolysis of triglycerides (TGs) to free fatty acids (FFAs) in adipocytes. FFAs released into the circulation are transported into hepatocytes, where they produce the ketone bodies acetoacetate and β-hydroxybutyrate (β-HB). FFAs also activate the transcription factors peroxisome proliferator–activated receptor α (PPAR-α) and activating transcription factor 4 (ATF4), resulting in the production and release of fibroblast growth factor 21 (FGF21), a protein with widespread effects on cells throughout the body and brain. β-HB and acetoacetate are actively transported into cells where they can be metabolized to acetyl CoA, which enters the tricarboxylic acid (TCA) cycle and generates ATP. β-HB also has signaling functions, including the activation of transcription factors such as cyclic AMP response element–binding protein (CREB) and nuclear factor κB (NF-κB) and the expression of brain-derived neurotrophic factor (BDNF) in neurons. Reduced levels of glucose and amino acids during fasting result in reduced activity of the mTOR pathway and up-regulation of autophagy. In addition, energy restriction stimulates mitochondrial biogenesis and mitochondrial uncoupling.

fasting, 5:2 intermittent fasting (fasting 2 days each week), and daily time-restricted feeding.[11] Diets that markedly reduce caloric intake on 1 day or more each week (e.g., a reduction to 500 to 700 calories per day) result in elevated levels of ketone bodies on those days.[17-20] The metabolic switch from the use of glucose as a fuel source to the use of fatty acids and ketone bodies results in a reduced respiratory-exchange ratio (the ratio of carbon dioxide produced to oxygen consumed), indicating the greater metabolic flexibility and efficiency of energy production from fatty acids and ketone bodies.[3]

Ketone bodies are not just fuel used during periods of fasting; they are potent signaling molecules with major effects on cell and organ functions.[21] Ketone bodies regulate the expression and activity of many proteins and molecules that are known to influence health and aging. These include peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α), fibroblast growth factor 21,[22,23] nicotinamide adenine dinucleotide (NAD^+), sirtuins,[24] poly(adenosine diphosphate [ADP]–ribose) polymerase 1 (PARP1), and ADP ribosyl cyclase (CD38).[25] By influencing these major cellular pathways, ketone bodies produced

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during fasting have profound effects on systemic metabolism. Moreover, ketone bodies stimulate expression of the gene for brain-derived neurotrophic factor (Fig. 2), with implications for brain health and psychiatric and neurodegenerative disorders.[5]

How much of the benefit of intermittent fasting is due to metabolic switching and how much is due to weight loss? Many studies have indicated that several of the benefits of intermittent fasting are dissociated from its effects on weight loss. These benefits include improvements in glucose regulation, blood pressure, and heart rate; the efficacy of endurance training[26,27]; and abdominal fat loss[27] (see Supplementary Section S1).

INTERMITTENT FASTING AND STRESS RESISTANCE

In contrast to people today, our human ancestors did not consume three regularly spaced, large meals, plus snacks, every day, nor did they live a sedentary life. Instead, they were occupied with acquiring food in ecologic niches in which food sources were sparsely distributed. Over time, *Homo sapiens* underwent evolutionary changes that supported adaptation to such environments, including brain changes that allowed creativity, imagination, and language and physical changes that enabled species members to cover large distances on their own muscle power to stalk prey.[6]

The research reviewed here, and discussed in more detail elsewhere,[11,12] shows that most if not all organ systems respond to intermittent fasting in ways that enable the organism to tolerate or overcome the challenge and then restore homeostasis. Repeated exposure to fasting periods results in lasting adaptive responses that confer resistance to subsequent challenges. Cells respond to intermittent fasting by engaging in a coordinated adaptive stress response that leads to increased expression of antioxidant defenses, DNA repair, protein quality control, mitochondrial biogenesis and autophagy, and down-regulation of inflammation (Fig. 3). These adaptive responses to fasting and feeding are conserved across taxa.[10] Cells throughout the bodies and brains of animals maintained on intermittent-fasting regimens show improved function and robust resistance to a broad range of potentially damaging insults, including those involving metabolic, oxidative, ionic, traumatic, and proteotoxic stress.[12] Intermittent fasting stimulates autophagy and mitophagy while inhibiting the mTOR (mammalian target of rapamycin) protein-synthesis pathway. These responses enable cells to remove oxidatively damaged proteins and mitochondria and recycle undamaged molecular constituents while temporarily reducing global protein synthesis to conserve energy and molecular resources (Fig. 3). These pathways are untapped or suppressed in persons who overeat and are sedentary.[12]

EFFECTS OF INTERMITTENT FASTING ON HEALTH AND AGING

Until recently, studies of caloric restriction and intermittent fasting focused on aging and the life span. After nearly a century of research on caloric restriction in animals, the overall conclusion was that reduced food intake robustly increases the life span.

In one of the earliest studies of intermittent fasting, Goodrick and colleagues reported that the average life span of rats is increased by up to 80% when they are maintained on a regimen of alternate-day feeding, started when they are young adults. However, the magnitude of the effects of caloric restriction on the health span and life span varies and can be influenced by sex, diet, age, and genetic factors.[7] A meta-analysis of data available from 1934 to 2012 showed that caloric restriction increases the median life span by 14 to 45% in rats but by only 4 to 27% in mice.[28] A study of 41 recombinant inbred strains of mice showed wide variation, ranging from a substantially extended life span to a shortened life span, depending on the strain and sex.[29,30] However, the study used only one caloric-restriction regimen (40% restriction) and did not evaluate health indicators, causes of death, or underlying mechanisms. There was an inverse relationship between adiposity reduction and life span[29] suggesting that animals with a shortened life span had a greater reduction in adiposity and transitioned more rapidly to starvation when subjected to such severe caloric restriction, whereas animals with an extended life span had the least reduction in fat.

The discrepant results of two landmark studies in monkeys challenged the link between health-span extension and life-span extension

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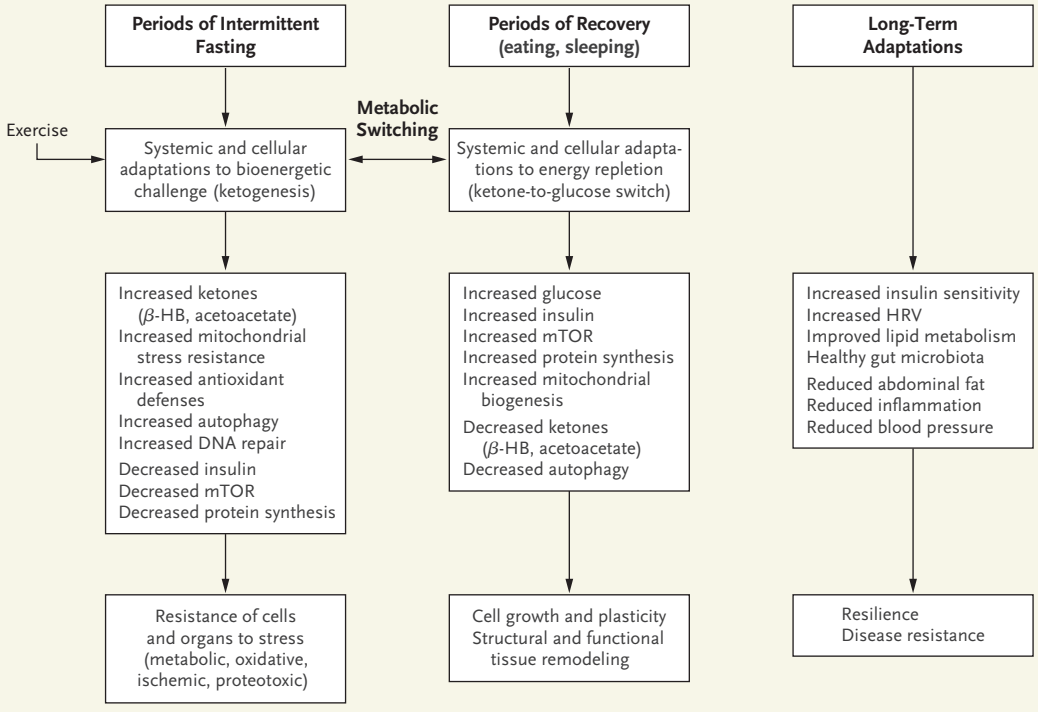

Figure 3. Cellular and Molecular Mechanisms Underlying Improved Organ Function and Resistance to Stress and Disease with Intermittent Metabolic Switching.

Periods of dietary energy restriction sufficient to cause depletion of liver glycogen stores trigger a metabolic switch toward use of fatty acids and ketones. Cells and organ systems adapt to this bioenergetic challenge by activating signaling pathways that bolster mitochondrial function, stress resistance, and antioxidant defenses while up-regulating autophagy to remove damaged molecules and recycle their components. During the period of energy restriction, cells adopt a stress-resistance mode through reduction in insulin signaling and overall protein synthesis. Exercise enhances these effects of fasting. On recovery from fasting (eating and sleeping), glucose levels increase, ketone levels plummet, and cells increase protein synthesis, undergoing growth and repair. Maintenance of an intermittent-fasting regimen, particularly when combined with regular exercise, results in many long-term adaptations that improve mental and physical performance and increase disease resistance. HRV denotes heart-rate variability.

with caloric restriction. One of the studies, at the University of Wisconsin, showed a positive effect of caloric restriction on both health and survival,[31] whereas the other study, at the National Institute on Aging, showed no significant reduction in mortality, despite clear improvements in overall health.[32] Differences in the daily caloric intake, onset of the intervention, diet composition, feeding protocols, sex, and genetic background may explain the differential effects of caloric restriction on life span in the two studies.[7]

In humans, intermittent-fasting interventions ameliorate obesity, insulin resistance, dyslipidemia, hypertension, and inflammation.[33] Intermittent fasting seems to confer health benefits to a greater extent than can be attributed just to a reduction in caloric intake. In one trial, 16 healthy participants assigned to a regimen of alternate-day fasting for 22 days lost 2.5% of their initial weight and 4% of fat mass, with a 57% decrease in fasting insulin levels.[34] In two other trials, overweight women (approximately 100 women in each trial) were assigned to either a 5:2 intermittent-fasting regimen or a 25% reduction in daily caloric intake. The women in the two groups lost the same amount of weight during the 6-month period, but those in the group assigned to 5:2 intermittent fasting had a greater increase in insulin sensitivity and a larger reduction in waist circumference.[20,27]

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PHYSICAL AND COGNITIVE EFFECTS OF INTERMITTENT FASTING

In animals and humans, physical function is improved with intermittent fasting. For example, despite having similar body weight, mice maintained on alternate-day fasting have better running endurance than mice that have unlimited access to food. Balance and coordination are also improved in animals on daily time-restricted feeding or alternate-day fasting regimens.[35] Young men who fast daily for 16 hours lose fat while maintaining muscle mass during 2 months of resistance training.[36]

Studies in animals show that intermittent fasting enhances cognition in multiple domains, including spatial memory, associative memory, and working memory[37]; alternate-day fasting and daily caloric restriction reverse the adverse effects of obesity, diabetes, and neuroinflammation on spatial learning and memory (see Section S4).

In a clinical trial, older adults on a short-term regimen of caloric restriction had improved verbal memory.[38] 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] More recently, a large, multicenter, randomized clinical trial showed that 2 years of daily caloric restriction led to a significant improvement in working memory.[40] There is certainly a need to undertake further studies of intermittent fasting and cognition in older people, particularly given the absence of any pharmacologic therapies that influence brain aging and progression of neurodegenerative diseases.[12]

CLINICAL APPLICATIONS

In this section, we briefly review examples of findings from studies of intermittent fasting in preclinical animal models of disease and in patients with various diseases. Additional published studies are listed in Section S5.

OBESITY AND DIABETES MELLITUS

In animal models, intermittent feeding improves insulin sensitivity, prevents obesity caused by a high-fat diet, and ameliorates diabetic retinopathy.[41] On the island of Okinawa, the traditional population typically maintains a regimen of intermittent fasting and has low rates of obesity and diabetes mellitus, as well as extreme longevity.[42] Okinawans typically consume a low-calorie diet from energy-poor but nutrient-rich sources, particularly Okinawan sweet potatoes, other vegetables, and legumes.[42] Likewise, members of the Calorie Restriction Society, who follow the CRON (Calorie Restriction with Optimal Nutrition) diet,[43-45] have low rates of diabetes mellitus, with low levels of insulin-like growth factor 1, growth hormone, and markers of inflammation and oxidative stress.[4,20,33,43]

A multicenter study showed that daily caloric restriction improves many cardiometabolic risk factors in nonobese humans.[46-50] Furthermore, six short-term studies involving overweight or obese adults have shown that intermittent fasting is as effective for weight loss as standard diets.[51] Two recent studies showed that daily caloric restriction or 4:3 intermittent fasting (24-hour fasting three times a week) reversed insulin resistance in patients with prediabetes or type 2 diabetes.[52,53] However, in a 12-month study comparing alternate-day fasting, daily caloric restriction, and a control diet, participants in both intervention groups lost weight but did not have any improvements in insulin sensitivity, lipid levels, or blood pressure, as compared with participants in the control group.[54]

CARDIOVASCULAR DISEASE

Intermittent fasting improves multiple indicators of cardiovascular health in animals and humans, including blood pressure; resting heart rate; levels of high-density and low-density lipoprotein (HDL and LDL) cholesterol, triglycerides, glucose, and insulin; and insulin resistance.[41,43,47,55] In addition, intermittent fasting reduces markers of systemic inflammation and oxidative stress that are associated with atherosclerosis.[17,27,36,56] Analyses of electrocardiographic recordings show that intermittent fasting increases heart-rate variability by enhancing parasympathetic tone in rats[57] and humans.[58] The CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy) study showed that a 12% reduction in daily calorie intake for a period of 2 years improves many cardiovascular risk factors in nonobese persons.[46-50] Varady et al. reported that alternate-day fasting was effective for weight loss and cardioprotection in normal-weight and

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overweight adults.[59] Improvements in cardiovascular health indicators typically become evident within 2 to 4 weeks after the start of alternate-day fasting and then dissipate over a period of several weeks after resumption of a normal diet.[57]

CANCER

More than a century ago, Moreschi and Rous described the beneficial effect of fasting and caloric restriction on tumors in animals. Since then, numerous studies in animals have shown that daily caloric restriction or alternate-day fasting reduces the occurrence of spontaneous tumors during normal aging in rodents and suppresses the growth of many types of induced tumors while increasing their sensitivity to chemotherapy and irradiation.[7-9,60] Similarly, intermittent fasting is thought to impair energy metabolism in cancer cells, inhibiting their growth and rendering them susceptible to clinical treatments.[61-63] The underlying mechanisms involve a reduction of signaling through the insulin and growth hormone receptors and an enhancement of the forkhead box O (FOXO) and nuclear factor erythroid 2–related factor 2 (NRF2) transcription factors. Genetic deletion of NRF2 or FOXO1 obliterates the protective effects of intermittent fasting against induced carcinogenesis while preserving extension of the life span,[64,65] and deletion of FOXO3 preserves the anticancer protection but diminishes the longevity effect.[66] Activation of these transcription factors and downstream targets by means of intermittent fasting may provide protection against cancer while bolstering the stress resistance of normal cells (Fig. 1).

Clinical trials of intermittent fasting in patients with cancer have been completed or are in progress. Most of the initial trials have focused on compliance, side effects, and characterization of biomarkers. For example, a trial of daily caloric restriction in men with prostate cancer showed excellent adherence (95%) and no adverse events.[67] Several case studies involving patients with glioblastoma suggest that intermittent fasting can suppress tumor growth and extend survival.[9,68] Ongoing trials listed on ClinicalTrials.gov focus on intermittent fasting in patients with breast, ovarian, prostate, endometrial, and colorectal cancers and glioblastoma (see Supplementary Table S1). Specific intermittent-fasting regimens vary among studies, but all involve imposition of intermittent fasting during chemotherapy. No studies have yet determined whether intermittent fasting affects cancer recurrence in humans.[9]

NEURODEGENERATIVE DISORDERS

Epidemiologic data suggest that excessive energy intake, particularly in midlife, increases the risks of stroke, Alzheimer's disease, and Parkinson's disease.[69] There is strong preclinical evidence that alternate-day fasting can delay the onset and progression of the disease processes in animal models of Alzheimer's disease and Parkinson's disease.[5,12] Intermittent fasting increases neuronal stress resistance through multiple mechanisms, including bolstering mitochondrial function and stimulating autophagy, neurotrophic-factor production, antioxidant defenses, and DNA repair.[12,70] Moreover, intermittent fasting enhances GABAergic inhibitory neurotransmission (i.e., γ-aminobutyric acid–related inhibitory neurotransmission), which can prevent seizures and excitotoxicity.[71] Data from controlled trials of intermittent fasting in persons at risk for or affected by a neurodegenerative disorder are lacking. Ideally, an intervention would be initiated early in the disease process and continued long enough to detect a disease-modifying effect of the intervention (e.g., a 1-year study).

ASTHMA, MULTIPLE SCLEROSIS, AND ARTHRITIS

Weight loss reduces the symptoms of asthma in obese patients.[72] In one study, patients who adhered to the alternate-day fasting regimen had an elevated serum level of ketone bodies on energy-restriction days and lost weight over a 2-month period, during which asthma symptoms and airway resistance were mitigated.[17] A reduction in symptoms was associated with significant reductions in serum levels of markers of inflammation and oxidative stress.[17] Multiple sclerosis is an autoimmune disorder characterized by axon demyelination and neuronal degeneration in the central nervous system. Alternate-day fasting and periodic cycles of 3 consecutive days of energy restriction reduce autoimmune demyelination and improve the functional outcome in a mouse model of multiple sclerosis (experimentally induced autoimmune encephalomyelitis).[73,74] Two recent pilot studies showed that patients with multiple sclerosis who adhere to intermittent-

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fasting regimens have reduced symptoms in as short a period as 2 months.[73,75] Because it reduces inflammation,[17] intermittent fasting would also be expected to be beneficial in rheumatoid arthritis, and indeed, there is evidence supporting its use in patients with arthritis.[76]

SURGICAL AND ISCHEMIC TISSUE INJURY

Intermittent-fasting regimens reduce tissue damage and improve functional outcomes of traumatic and ischemic tissue injury in animal models. Preoperative fasting reduces tissue damage and inflammation and improves the outcomes of surgical procedures.[77] In animal models of vascular surgical injury, 3 days of fasting reduced ischemia–reperfusion injury in the liver and kidneys and, before the injury, resulted in a reduction in trauma-induced carotid-artery intimal hyperplasia.[78] A randomized, multicenter study showed that 2 weeks of preoperative daily energy restriction improves outcomes in patients undergoing gastric-bypass surgery.[79] Such findings suggest that preoperative intermittent fasting can be a safe and effective method of improving surgical outcomes.

Several studies have shown beneficial effects of intermittent fasting in animal models of traumatic head or spinal cord injury. Intermittent fasting after injury was also effective in ameliorating cognitive deficits in a mouse model of traumatic brain injury.[80] When initiated either before or after cervical or thoracic spinal cord injury, intermittent fasting reduces tissue damage and improves functional outcomes in rats. Emerging evidence suggests that intermittent fasting may enhance athletic performance and may prove to be a practical approach for reducing the morbidity and mortality associated with traumatic brain and spinal cord injuries in athletes. (See the section above on the physical effects of intermittent fasting.) Studies in animals have shown that intermittent fasting can protect the brain, heart, liver, and kidneys against ischemic injury. However, the potential therapeutic benefits of intermittent fasting in patients with stroke or myocardial infarction remain to be tested.

PRACTICAL CONSIDERATIONS

Despite the evidence for the health benefits of intermittent fasting and its applicability to many diseases, there are impediments to the widespread adoption of these eating patterns in the community and by patients. First, a diet of three meals with snacks every day is so ingrained in our culture that a change in this eating pattern will rarely be contemplated by patients or doctors. The abundance of food and extensive marketing in developed nations are also major hurdles to be overcome.

Second, on switching to an intermittent-fasting regimen, many people will experience hunger, irritability, and a reduced ability to concentrate during periods of food restriction. However, these initial side effects usually disappear within 1 month, and patients should be advised of this fact.[17,20,27]

Third, most physicians are not trained to prescribe specific intermittent-fasting interventions. Physicians can advise patients to gradually, over a period of several months, reduce the time window during which they consume food each day, with the goal of fasting for 16 to 18 hours a day (Fig. 4). Alternatively, physicians can recommend the 5:2 intermittent-fasting diet, with 900 to 1000 calories consumed 1 day per week for the first month and then 2 days per week for the second month, followed by further reductions to 750 calories 2 days per week for the third month and, ultimately, 500 calories 2 days per week for the fourth month. A dietitian or nutritionist should be consulted to ensure that the nutritional needs of the patient are being met and to provide continued counseling and education. As with all lifestyle interventions, it is important that physicians provide adequate information, ongoing communication and support, and regular positive reinforcement.

CONCLUSIONS

Preclinical studies and clinical trials have shown that intermittent fasting has broad-spectrum benefits for many health conditions, such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders. Animal models show that intermittent fasting improves health throughout the life span, whereas clinical studies have mainly involved relatively short-term interventions, over a period of months. It remains to be determined whether people can

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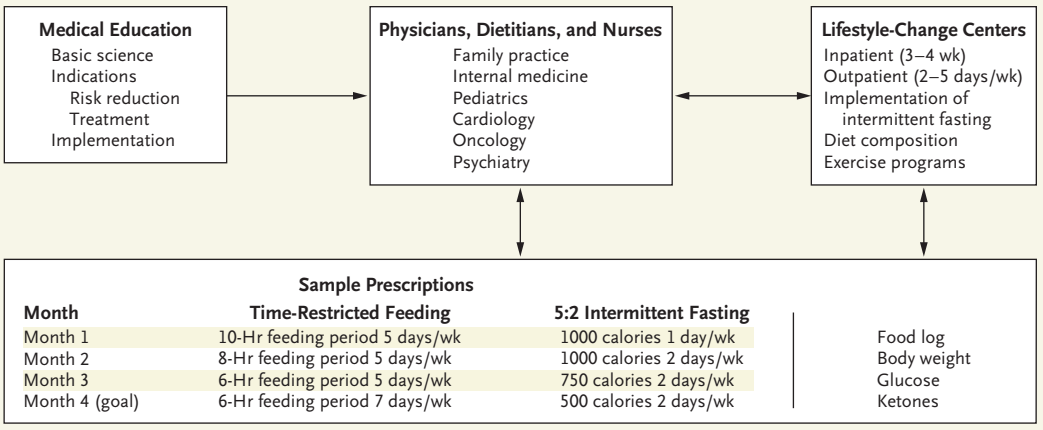

Figure 4. Incorporation of Intermittent-Fasting Patterns into Health Care Practice and Lifestyles.

As a component of medical school training in disease prevention, students could learn the basics of how intermittent fasting affects metabolism and how cells and organs respond adaptively to intermittent fasting, the major indications for intermittent fasting (obesity, diabetes, cardiovascular disease, and cancers), and how to implement intermittent-fasting prescriptions to maximize long-term benefits. Physicians can incorporate intermittent-fasting prescriptions for early intervention in patients with a range of chronic conditions or at risk for such conditions, particularly those conditions associated with overeating and a sedentary lifestyle. One can envision inpatient and outpatient facilities staffed by experts in diet, nutrition, exercise, and psychology that will help patients make the transition to sustainable intermittent-fasting and exercise regimens (covered by basic health insurance policies). As an example of a specific prescription, the patient could choose either a daily time-restricted feeding regimen (an 18-hour fasting period and a 6-hour eating period) or the 5:2 intermittent-fasting regimen (fasting [i.e., an intake of 500 calories] 2 days per week), with a 4-month transition period to accomplish the goal. To facilitate adherence to the prescription, the physician's staff should be in frequent contact with the patient during the 4-month period and should closely monitor the patient's body weight and glucose and ketone levels.

maintain intermittent fasting for years and potentially accrue the benefits seen in animal models. Furthermore, clinical studies have focused mainly on overweight young and middle-age adults, and we cannot generalize to other age groups the benefits and safety of intermittent fasting that have been observed in these studies.

Although we do not fully understand the specific mechanisms, the beneficial effects of intermittent fasting involve metabolic switching and cellular stress resistance. However, some people are unable or unwilling to adhere to an intermittent-fasting regimen. By further understanding the processes that link intermittent fasting with broad health benefits, we may be able to develop targeted pharmacologic therapies that mimic the effects of intermittent fasting without the need to substantially alter feeding habits.

Studies of the mechanisms of caloric restriction and intermittent fasting in animal models have led to the development and testing of pharmacologic interventions that mimic the health and disease-modifying benefits of intermittent fasting. Examples include agents that impose a mild metabolic challenge (2-deoxyglucose, metformin, and mitochondrial-uncoupling agents), bolster mitochondrial bioenergetics (ketone ester or nicotinamide riboside), or inhibit the mTOR pathway (sirolimus).[12] However, the available data from animal models suggest that the safety and efficacy of such pharmacologic approaches are likely to be inferior to those of intermittent fasting.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Weindruch R, Sohal RS. Caloric intake and aging. N Engl J Med 1997;337:986-94.
2. Panda S. Circadian physiology of metabolism. Science 2016;354:1008-15.
3. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science 2018;362:770-5.
4. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab 2014;19:181-92.
5. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci 2018;19:63-80.
6. Mattson MP. An evolutionary perspective on why food overconsumption impairs cognition. Trends Cogn Sci 2019;23:200-12.
7. Mattison JA, Colman RJ, Beasley TM, et al. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun 2017;8:14063.
8. Meynet O, Ricci JE. Caloric restriction and cancer: molecular mechanisms and clinical implications. Trends Mol Med 2014;20:419-27.
9. Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer 2018;18:707-19.
10. Speakman JR, Mitchell SE. Caloric restriction. Mol Aspects Med 2011;32:159-221.
11. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. Obesity (Silver Spring) 2018;26:254-68.
12. Mattson MP, Arumugam TV. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab 2018;27:1176-99.
13. Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A. Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PLoS One 2019;14(1):e0209353.
14. Cahill GF Jr. Starvation in man. N Engl J Med 1970;282:668-75.
15. Browning JD, Baxter J, Satapati S, Burgess SC. The effect of short-term fasting on liver and skeletal muscle lipid, glucose, and energy metabolism in healthy women and men. J Lipid Res 2012;53:577-86.
16. Foster DW. Studies in the ketosis of fasting. J Clin Invest 1967;46:1283-96.
17. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med 2007;42:665-74.
18. Knopp RH, Magee MS, Raisys V, Benedetti T, Bonet B. Hypocaloric diets and ketogenesis in the management of obese gestational diabetic women. J Am Coll Nutr 1991;10:649-67.
19. Skrha J, Kunesová M, Hilgertová J, Weiserová H, Krízová J, Kotrlíková E. Short-term very low calorie diet reduces oxidative stress in obese type 2 diabetic patients. Physiol Res 2005;54:33-9.
20. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes (Lond) 2011;35:714-27.
21. Newman JC, Verdin E. β-Hydroxybutyrate: a signaling metabolite. Annu Rev Nutr 2017;37:51-76.
22. Fisher FM, Maratos-Flier E. Understanding the physiology of FGF21. Annu Rev Physiol 2016;78:223-41.
23. Gälman C, Lundåsen T, Kharitonenkov A, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARalpha activation in man. Cell Metab 2008;8:169-74.
24. Imai SI, Guarente L. It takes two to tango: NAD+ and sirtuins in aging/longevity control. NPJ Aging Mech Dis 2016;2:16017.
25. Lee HC. Physiological functions of cyclic ADP-ribose and NAADP as calcium messengers. Annu Rev Pharmacol Toxicol 2001;41:317-45.
26. Anson RM, Guo Z, de Cabo R, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci U S A 2003;100:6216-20.
27. Harvie M, Wright C, Pegington M, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. Br J Nutr 2013;110:1534-47.
28. Swindell WR. Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan. Ageing Res Rev 2012;11:254-70.
29. Liao CY, Rikke BA, Johnson TE, Gelfond JA, Diaz V, Nelson JF. Fat maintenance is a predictor of the murine lifespan response to dietary restriction. Aging Cell 2011;10:629-39.
30. Liao CY, Rikke BA, Johnson TE, Diaz V, Nelson JF. Genetic variation in the murine lifespan response to dietary restriction: from life extension to life shortening. Aging Cell 2010;9:92-5.
31. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009;325:201-4.
32. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature 2012;489:318-21.
33. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. Cell Metab 2018;27(4):805.e4-815.e4.
34. Heilbronn LK, Smith SR, Martin CK, Anton SD, Ravussin E. Alternate-day fasting in nonobese subjects: effects on body weight, body composition, and energy metabolism. Am J Clin Nutr 2005;81:69-73.
35. Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metab 2014;20:991-1005.
36. Moro T, Tinsley G, Bianco A, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. J Transl Med 2016;14:290.
37. Wahl D, Coogan SC, Solon-Biet SM, et al. Cognitive and behavioral evaluation of nutritional interventions in rodent models of brain aging and dementia. Clin Interv Aging 2017;12:1419-28.
38. Witte AV, Fobker M, Gellner R, Knecht S, Flöel A. Caloric restriction improves memory in elderly humans. Proc Natl Acad Sci U S A 2009;106:1255-60.
39. Horie NC, Serrao VT, Simon SS, et al. Cognitive effects of intentional weight loss in elderly obese individuals with mild cognitive impairment. J Clin Endocrinol Metab 2016;101:1104-12.
40. Leclerc E, Trevizol AP, Grigolon RB, et al. The effect of caloric restriction on working memory in healthy non-obese adults. CNS Spectr 2019 April 10 (Epub ahead of print).
41. Wan R, Camandola S, Mattson MP. Intermittent food deprivation improves cardiovascular and neuroendocrine responses to stress in rats. J Nutr 2003;133:1921-9.
42. Willcox DC, Willcox BJ, Todoriki H, Curb JD, Suzuki M. Caloric restriction and human longevity: what can we learn from the Okinawans? Biogerontology 2006;7:173-7.
43. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A 2004;101:6659-63.
44. Fontana L, Villareal DT, Das SK, et al. Effects of 2-year calorie restriction on circulating levels of IGF-1, IGF-binding proteins and cortisol in nonobese men and women: a randomized clinical trial. Aging Cell 2016;15:22-7.
45. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. Ageing Res Rev 2017;39:36-45.
46. Rochon J, Bales CW, Ravussin E, et al. Design and conduct of the CALERIE study: comprehensive assessment of the long-

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term effects of reducing intake of energy. J Gerontol A Biol Sci Med Sci 2011;66:97-108.
47. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. Am J Physiol Endocrinol Metab 2018;314:E396-E405.
48. Martin CK, Bhapkar M, Pittas AG, et al. Effect of calorie restriction on mood, quality of life, sleep, and sexual function in healthy nonobese adults: the CALERIE 2 randomized clinical trial. JAMA Intern Med 2016;176:743-52.
49. Heilbronn LK, de Jonge L, Frisard MI, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA 2006;295:1539-48.
50. Ravussin E, Redman LM, Rochon J, et al. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. J Gerontol A Biol Sci Med Sci 2015;70:1097-104.
51. Harvie M, Howell A. Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight and normal weight subjects — a narrative review of human and animal evidence. Behav Sci (Basel) 2017;7(1):E4.
52. Furmli S, Elmasry R, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. BMJ Case Rep 2018; 2018:bcr-2017-221854.
53. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell Metab 2018;27(6):1212-1221.e3.
54. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. JAMA Intern Med 2017;177: 930-8.
55. Lefevre M, Redman LM, Heilbronn LK, et al. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. Atherosclerosis 2009;203:206-13.
56. Kroeger CM, Klempel MC, Bhutani S, Trepanowski JF, Tangney CC, Varady KA. Improvement in coronary heart disease risk factors during an intermittent fasting/calorie restriction regimen: relationship to adipokine modulations. Nutr Metab (Lond) 2012;9:98.
57. Mager DE, Wan R, Brown M, et al. Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. FASEB J 2006;20:631-7.
58. Stein PK, Soare A, Meyer TE, Cangemi R, Holloszy JO, Fontana L. Caloric restriction may reverse age-related autonomic decline in humans. Aging Cell 2012;11: 644-50.
59. Varady KA, Bhutani S, Klempel MC, et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. Nutr J 2013;12:146.
60. O'Flanagan CH, Smith LA, McDonell SB, Hursting SD. When less may be more: calorie restriction and response to cancer therapy. BMC Med 2017;15:106.
61. Harvie M, Howell A. Energy restriction and the prevention of breast cancer. Proc Nutr Soc 2012;71:263-75.
62. Klement RJ, Champ CE. Calories, carbohydrates, and cancer therapy with radiation: exploiting the five R's through dietary manipulation. Cancer Metastasis Rev 2014;33:217-29.
63. Martinez-Outschoorn UE, Peiris-Pagés M, Pestell RG, Sotgia F, Lisanti MP. Cancer metabolism: a therapeutic perspective. Nat Rev Clin Oncol 2017;14:11-31.
64. Pearson KJ, Lewis KN, Price NL, et al. Nrf2 mediates cancer protection but not prolongevity induced by caloric restriction. Proc Natl Acad Sci U S A 2008;105: 2325-30.
65. Yamaza H, Komatsu T, Wakita S, et al. FoxO1 is involved in the antineoplastic effect of calorie restriction. Aging Cell 2010;9:372-82.
66. Shimokawa I, Komatsu T, Hayashi N, et al. The life-extending effect of dietary restriction requires Foxo3 in mice. Aging Cell 2015;14:707-9.
67. Demark-Wahnefried W, Nix JW, Hunter GR, et al. Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer. BMC Cancer 2016;16:61.
68. Elsakka AMA, Bary MA, Abdelzaher E, et al. Management of glioblastoma multiforme in a patient treated with ketogenic metabolic therapy and modified standard of care: a 24-month follow-up. Front Nutr 2018;5:20.
69. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol 2018;14:168-81.
70. Menzies FM, Fleming A, Caricasole A, et al. Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities. Neuron 2017;93:1015-34.
71. Liu Y, Cheng A, Li YJ, et al. SIRT3 mediates hippocampal synaptic adaptations to intermittent fasting and ameliorates deficits in APP mutant mice. Nat Commun 2019;10:1886.
72. Jensen ME, Gibson PG, Collins CE, Hilton JM, Wood LG. Diet-induced weight loss in obese children with asthma: a randomized controlled trial. Clin Exp Allergy 2013;43:775-84.
73. Choi IY, Piccio L, Childress P, et al. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell Rep 2016;15:2136-46.
74. Cignarella F, Cantoni C, Ghezzi L, et al. Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metab 2018;27(6):1222.e6-1235.e6.
75. Fitzgerald KC, Vizthum D, Henry-Barron B, et al. Effect of intermittent vs. daily calorie restriction on changes in weight and patient-reported outcomes in people with multiple sclerosis. Mult Scler Relat Disord 2018;23:33-9.
76. Müller H, de Toledo FW, Resch KL. Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. Scand J Rheumatol 2001; 30:1-10.
77. Mitchell JR, Beckman JA, Nguyen LL, Ozaki CK. Reducing elective vascular surgery perioperative risk with brief preoperative dietary restriction. Surgery 2013; 153:594-8.
78. Mauro CR, Tao M, Yu P, et al. Preoperative dietary restriction reduces intimal hyperplasia and protects from ischemia-reperfusion injury. J Vasc Surg 2016;63(2): 500.e1-509.e1.
79. Van Nieuwenhove Y, Dambrauskas Z, Campillo-Soto A, et al. Preoperative very low-calorie diet and operative outcome after laparoscopic gastric bypass: a randomized multicenter study. Arch Surg 2011;146:1300-5.
80. Liu Y, Wang R, Zhao Z, et al. Short-term caloric restriction exerts neuroprotective effects following mild traumatic brain injury by promoting autophagy and inhibiting astrocyte activation. Behav Brain Res 2017;331:135-42.

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