doi: 10.31674/mjmr.2018.v02i04.007

MJMR

FASTING AS THERAPY – A REVIEW

Dr. Madhumita Sen
Senior Lecturer, MAHSA University, Selangor, Malaysia.
Corresponding author's email: duttamonasen@gmail.com

ABSTRACT

Intermittent fasting is a dietary intervention that will cycle between brief periods of fasting, with either no food or significant dietary calorie restriction, and periods of unrestricted eating. Calorie restriction has been shown in animals to increase lifespan and improve tolerance to various metabolic stresses in the body. Therefore, a review of available studies regarding intermittent fasting on animal and human health was performed. The objective of this review is to summarise the various effects of intermittent fasting regimens, and discuss physiological processes by which intermittent fasting could lead to improved health outcomes. A search was performed on PubMed with the terms "intermittent fasting," "benefits of fasting," "fasting" and "autophagy". Modified fasting regimens appear to promote weight loss and may improve metabolic health and may offer simple, non-pharmacological approaches to improving health.

Keywords: Fasting, Obesity, Metabolic syndrome, Caloric restriction, Insulin resistance

INTRODUCTION

Intermittent fasting (IF) is an eating regimen that incorporates brief periods of fasting, when a person has either no food or significant calorie reduction, between periods of normal or unrestricted eating. Previous studies have shown that calorie restriction in animals can increase lifespan and improve tolerance to various metabolic stresses in the body.

Therefore, a review of available studies on intermittent fasting on animal and human health was performed. Fasting had earlier been in the domain of alternative medicine and was frowned upon or dismissed in modern medical literature. Yoshinori Ohsumi, the 2016 Nobel Prize winner in Medicine for research into autophagy has brought the field of fasting as therapy into the scientific limelight, from the obscurity of alternative therapies.

The objective of this review is to provide a fresh look into intermittent fasting regimens, and discuss the physiological mechanisms by which intermittent fasting might lead to improved health outcomes. Different types of fasting regimens appear to promote weight loss and may improve metabolic health. Evidence also supports the hypothesis that eating patterns that reduce or eliminate nighttime eating and prolong nightly fasting intervals may result in sustained improvements in human health. If proven to be efficacious, these eating regimens offer promising non-pharmacological approaches to improving health in the population, with multiple public health benefits.

Objectives

Question being addressed: Studies addressing fasting as therapy and their effect on various health parameters.

RESEARCH METHODOLOGY

A search was performed using PubMed/Medscape, and the terms "intermittent fasting," "fasting," "fasting therapy," "time-restricted feeding," "diabetes and fasting," "metabolic syndrome and fasting," and "food timing" were used.

Fasting as Therapy

The evolution of the human genotype is believed to have slowly occurred from 600,000 BC to 25,000 BC, when humans were hunter-gatherers. During this period, major energy oscillations appear to have selected genes that regulate metabolism for efficient nutrient usage and increased fat storage, which represents an evolutionary benefit consistent with the thrifty genotype theory proposed by James V. Neel.

When the environment changed drastically in the 19th, 20th and more so, the 21st centuries, with urbanization and easy availability of food, the genotype remained unaltered. This imbalance has resulted in an epidemic of conditions characterized by metabolic disturbances, such as obesity, metabolic syndrome and diabetes mellitus type 2 (Neel, 1962).These metabolic disturbances have led to an increase in the prevalence

of cardiovascular, neurological and other degenerative diseases. Many recent experimental studies have clarified some of the metabolic mechanisms involved with fasting. Animal models undergoing cyclical fasts have shown positive changes in glucose (lower plasma glucose and insulin levels) and in lipid metabolism (reduced visceral fat tissue and increased plasma adiponectin level), and an increased resistance to stress (Azevedo, Ikeoka & Caramelli, 2013).

In humans, fasting is achieved by ingesting no or minimal amounts of food and caloric beverages for periods that typically range from 12 hours to three weeks. Many religious groups have incorporated periods of fasting into their routine, including Muslims, Christians, Jews, Buddhists and Hindus who traditionally fast on designated days of the week or calendar year. Over time, science has debunked these beliefs and observances. However, the benefits of fasting are being discovered more and more today. An appreciation of the physiology of fasting is essential to the understanding of therapeutic effect of food deprivation in various diseases. The physiological adaptive mechanisms that come into play during this type of food deprivation are similar to starvation (Kerndt *et al*., 1982).

Physiology of Fasting

The physiology of fasting has been extensively studied, and three phases of fasting have been identified (Secor & Carey, 2016).

Phase one: can be called the Gastrointestinal phase, and starts immediately following the last meal, lasting approximately for following six hours. During this phase the body still uses glucose, amino acids and fats, as they are absorbed from the intestinal tract following digestion. Insulin plays the major role in this phase and causes the liver and muscle to take the blood glucose into the cells and store it as glycogen.

Phase Two: This phase, variable in duration and generally the longest,are all the steps of substrate utilization and metabolic provisioning to maintain homeostasis in the face of fasting. It encompasses the body's ability to withstand the lack of food until the next meal.This is the glycogenolysis phase, during which time the liver and muscle, under the influence of decreased insulin and increased glucagon, break down their glycogen to glucose. Characteristic of this phase is an increase in production of lipid-derived ketone bodies that serve as a glucose substitute for tissues (e.g., neural and cardiac) that normally have a high preference for glucose. Phase II ends with the resumption of feeding.One key mechanism responsible for many of the beneficial effects of fasting that occurs during this phase is the “flipping” of the metabolic switch. The “metabolic switch” is the body's preferential shift from utilization of glucose from glycogenolysis, to fatty acids and fatty acid-derived ketones. There is now a growing body of research to indicate ketones are the preferred fuel for both the brain and body during periods of fasting and extended exercise (Puchalska & Crawford, 2017).

The metabolic switch typically occurs between 12 to 36 hours after the cessation of food consumption depending on the liver glycogen content at the beginning of the fast, and on the amount of the individual's energy expenditure/exercise during the fast. The lipids in adipocytes are then metabolized to FFAs (free fatty acids), which are released into the blood. Simultaneously, other cell types like the astrocytes in the brain may also start generating ketones. FFAs are transported into hepatocytes where they are metabolized by β-oxidation to produce the ketones β-hydroxy butarate and acetoacetate, which may in turn induce mitochondrial biogenesis, thus increasing the number of active mitochondria in the cells.

Phase Three:The Gluconeogenesis phase. If feeding is not resumed prior to reaching a threshold level of lack of lipid storage, fasting physiology transitions to Phase III. This phase is characterized by a switch from lipid to amino acid catabolism. Because proteins possess one-eighth the energy per unit mass than fat, the rate of body mass loss is accelerated during Phase III. If feeding does not resume, the continued depletion of proteins and tissues (i.e., cachexia) will eventually lead to organ failure, loss of homeostasis, and mortality (i.e., death from starvation (Longo & Mattson, 2014).

LITERATURE REVIEW: The aim of fasting therapy is therefore to reach stage II but not stage III of fasting,

to achieve the benefits of the intervention.

Pathology of adipose tissue and the role of fasting

Adipose tissue is now known to function as an endocrine organ involved in regulating metabolism, rather than just a passive reservoir for energy storage. Adipocytes produce important pro-inflammatory adipokines, such as leptin, tumour necrosis factor alpha (TNF-), resistin, angiotensinogen, interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1), as well as non-esterified fatty acids and C-reactive protein (CRP), which are atherogenic. Adipocytes, mesenchymal cells, and infiltrating macrophages together produce cytokines and adipokines that have an important regulatory effect on inflammation, insulin sensitivity, coagulation, vascular homeostasis, appetite, energy expenditure, etc. When this production is deregulated, e.g., by excessive adipose tissue, the organism appears to develop low-grade chronic inflammation, leading to insulin resistance and cardiovascular disease.Certain adipokines also have cardio-protective action, such as adiponectin, which is found abundantly in human circulation.

In most mammals, the liver serves as the main reservoir of glucose, which is stored in the form of glycogen. In humans, depending upon their level of physical activity, 12 to 24 hours of fasting typically results in a 20% or greater decrease in serum glucose and depletion of the hepatic glycogen, accompanied by a switch to a metabolic mode in which non-hepatic glucose, fat-derived ketone bodies and free fatty acids are used as energy sources. Whereas most tissues can utilize fatty acids for energy, during prolonged periods of fasting, the brain relies on the ketone bodies β-hydroxy-butyric acid and acetoacetic acid in addition to glucose for energy consumption. Ketone bodies are produced in hepatocytes from the acetyl-CoA generated from β oxidation of fatty acids released into the bloodstream by adipocytes.

Depending on body weight and composition, the ketone bodies, free fatty acids and gluconeogenesis allow the majority of human beings to survive 30 or more days in the absence of any food.A major model organism in which fasting extends lifespan is the nematode *Caenorhabditiselegans (C. elegans; J. Li et al)*. Food deprivation conditions achieved by feeding wormswith very little bacteriaor no food at all, lead to a major increase in lifespan. The mechanisms of food deprivation-dependent lifespan extension involve the down-regulation of the amino acid pathways and enzymes which requires stress resistance transcription factors (Li *et al*., 2015)

Studies show that hunger is also an adaptive response to food deprivation that involves sensory, cognitive and neuroendocrine changes which motivate food seeking behaviours. It has been proposed that hunger by itself, as well as its related neuronal networks, neuropeptides and hormones play major roles in the beneficial effects of energy restriction on aging and disease susceptibility. When mice in which the hypothalamic 'hunger peptide' NPY is selectively ablated undergo Calorie restriction (CR), the ability of CR to suppress tumour growth is abolished. The latter study further showed that the ability of CR to elevate circulating adiponectin levels was also compromised in NPY-deficient mice. Thus, hunger may be a critical factor involved in widespread central and peripheral adaptive responses to food deprivation for extended time periods and disease susceptibility. The hunger response may also improve immune function during aging as ghrelin-deficient mice show accelerated thymic involution during aging, and treatment of middle aged mice with ghrelin increases thymocyte numbers and improves the functional diversity of T-cells (Peng *et al.,* 2012).

In mammals, severe CR/food deprivation results in a decrease in the size of most organs except the brain, and the testicles in male mice. From an evolutionary point of view, this implies that maintenance of a high level of cognitive function under conditions of food scarcity is of pre-eminent importance. A highly conserved behavioural trait of all mammals is to be active when hungry and sedentary when satiated.Inrodents, alternating days of normal feeding and fasting (intermittent fasting – IF) can enhance brain function asindicated by improvements in performance on behavioural tests of sensory and motor function as well as learning and memory.Further studies have demonstrated that when nutrients are depleted from the environment, mammalian as well as yeast cells begin to degrade their own cytosol and

organelles. This bulk protein degradation leads to autophagy, the process in which cytoplasmic components are delivered to the lysosome resulting eventually in degradation of cytoplasmic materials and cell death.This appears especially true for rapidly dividing cells, and cells with the most mutations (Noda & Ohsumi, 1998).

Effects of Fasting on body mechanisms

Fasting and aging

The remarkable effects of the typical 20–40% CR on aging and diseases in mice and rats are often viewed as responses evolved in mammals to adapt to periods of limited availability of food.In the yeast *S. cerevisiae*, switching cells from standard growth medium to water also causes a consistent 2-fold chronological lifespan extension as well as a major increase in the resistance to multiple stresses(Arun *et al*., 2009).Intermittent Fasting every other day extended the lifespan of rats more than fasting every 3rd or 4th day. Fasting for 24 hours twice weekly throughout adult life resulted in a significant increase in lifespan of black-hooded rats. Emerging findings suggest that exercise and IF retard aging and some age-related diseases by improved cellular stress adaptation. When IF was started at 1.5 months in two different mice strains, it either increased longevity or had no effect. However, intermittent fasting reduced lifespan when initiated at 10 months of age (older mice). These results in rodents point to the fact that fasting can increase lifespan, but to maximize its longevity effects, it must be started at a younger age. The mechanisms responsible for the detrimental effects that may be counterbalancing its anti-aging effects are still largely unknown. One possibility is that fasting may be protective in young and middle aged laboratory mice that are either gaining or maintaining a body weight, but may be detrimental in older animals that, similar to humans, begin to lose weight prior to their death (Stranahan & Mattson, 2012).

Fasting and cancer

Fasting can have positive effects in cancer prevention and treatment. In mice, alternate day fasting caused a major reduction in the incidence of lymphomas and fasting for 1 day per week delayed spontaneous tumorigenesis. Among the major effects of fasting relevant to aging and diseases are changes in the levels of IGF-1, IGFBP1, glucose, and insulin. Fasting for 3 or more days causes a 30% or more decrease in circulating insulin and glucose, as well as rapid decline in the levels of insulin like growth factor 1 (IGF-1). These hormones are associated with accelerated aging and cancer. However, the major decrease in glucose, insulin and IGF-1 caused by fasting, which is accompanied by cell death and/or atrophy in a wide range of tissues and organs including the liver and kidneys, is followed by a period of abnormally high cellular proliferation in these tissues on refeeding, during the replenishment of growth factors . When combined with carcinogens during refeeding, this increased proliferative activity can actually increase carcinogenesis and/or pre-cancerous lesions in tissues including liver and colon (Tessitore *et al*., 1996).These studies underline the need for an in depth understanding of the mechanisms of action of fasting in cellular proliferation.However, multiple cycles of periodic fasting can be as effective as toxic chemotherapy in the treatment of some cancers in mice (Lee *et al*., 2012).

In the treatment of cancer, fasting has been shown to have more consistent and positive effects. Fasting for 2–3 days was shown to protect mice during a variety of chemotherapy, an effect called differential stress resistance (DSR). This reflects the inability of cancer cells to become protected against chemotherapeutic drugs in response to fasting conditions. Also, during fasting, cancer cells are unable to adapt, a phenomenon called differential stress sensitization (DSS), which means that most mutations are harmful to the cell and that the many mutations accumulated in cancer cells promote growth under standard conditions but tend to make them die out more easily in extreme environments. In mouse models of metastatic tumours, combinations of fasting and chemotherapy that cause DSR and DSS, result in 20 to 60% cancer-free survival compared to the same levels of chemotherapy or fasting alone.

Fasting and neuro-degeneration

Compared to control rats, who were allowed to eat ad-libitum, rats maintained on an IF diet showed less neuronal dysfunction and degeneration, and lower levels of clinical symptoms in models of Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).

The cellular mechanisms that cause thebeneficial effects of fasting on the nervous system include reduced accumulation of oxidatively damaged molecules, improved cellular bioenergetics, enhanced neurotrophic factor signalling, and reduced inflammation. Fasting may also promote restoration of damaged nerve cell circuits by stimulating synapse formation and the production of new neurons from neural stem cells (neurogenesis).Interestingly however, there is evidence that fasting can hasten neurodegeneration in some models of inherited amyotrophic lateral sclerosis, perhaps because the motor neurons affected in these models do not adapt so well to the moderate stress imposed by fasting (Mattson, Cutler & Camandola, 2007).

In human studies, after 3–4 months, CR improved cognitive function (verbal memory) in overweight women. Similarly, when subjects with mild cognitive impairment were maintained for 1 month on a low glycaemic diet, they exhibited improved delayed visual memory as well (Bayer-Carter *et al*., 2011).

Fasting and Neuroprotection

During evolution, those individuals who were able to survive through long periods of fasting and whose brains were able to adapt to the stress, lived longer and passed on their ability to the next generations. Repeating cycles of a metabolic challenge that induces ketosis (fasting and/or exercise) followed by a recovery period (eating, resting and sleeping), may optimize the neuronal circuits involved in cognition and mood throughout the lifespan. Mattson, *et al* (2018) found that the'metabolic switching'of brain cell utilisation from glucose to ketones promotes neuroplasticity and resistance of the brain to injury and disease (Mattson *et al*., 2018).One of the interesting adaptive responses of the brain to limited food availability during human evolution is the production of brain-derived neurotrophic factor (BDNF). Brain-derived neurotrophic factor (BDNF) is produced as an adaptive response of the brain to limited food availability. The genes encoding BDNF and its receptor TrkB appeared in genomes relatively recently along the evolutionary pathway, as they are present in vertebrates, but absent from the invertebrates (Wan *et al*., 2010).IF has also been seen to be associated with increased synaptic plasticity and increased production of new neurons from neural stem cells (Rothman *et al*., 2012).

Fasting may increase the production of BDNF, resulting in improved neuronal network activity, enhanced synaptic plasticity and improved stress tolerance in brain regions involved in cognition. BDNF signalling in the brain may also mediate behavioural and metabolic responses to fasting and exercise, including regulation of appetite, activity levels, peripheral glucose metabolism and autonomic control of the cardiovascular and gastrointestinal systems. The receptors for both BDNF and insulin are coupled in metabolic pathways. Studies on rats and mice have shown that running wheel exercise along with IF increases BDNF expression in several regions of the brain, inducing synaptic plasticity, neurogenesis and neuronal resistance to injury and disease. BDNF signalling in the brain may also mediate behavioural and metabolic responses to fasting and exercise, including regulation of appetite, activity levels, peripheral glucose metabolism and autonomic control of the cardiovascular and gastrointestinal systems (Wan *et al*., 2010).

Studies evaluating the potential of IF in recovery from spinal cord injury have also shown interesting results.Plunet, et al. assessed the effect of alternate day fasting in a group of male Sprague–Dawley rats after cervical spinal cord injury. The intervention proved to be neuroprotective, with a 50% reduction in degeneration of nerve cells and increased sprouting of corticospinal axons. The intervention also improved behavioural recovery, evident by improved gait-pattern and forelimb function during horizontal ladder-crossing and better vertical exploration (Plunet *et al*., 2008).Animals on an IF diet also fare better than ad libitum-fed controls after acute neuronal injury including severe epileptic seizures, stroke, and traumatic brain and spinal cord injuries (Arumugam *et al*., 2010).

Fasting, inflammation and hypertension

In humans, one of the best demonstrations of the beneficial effects of long-term fasting lasting one to 3 weeks is in the treatment of rheumatoid arthritis (RA). In agreement with the results in rodents, there is little doubt that during the period of fasting both inflammation and pain are reduced in RA patients. However, after the normal diet is resumed, inflammation returns unless the fasting period is followed by a vegetarian diet, a combination therapy that has beneficial effects lasting for two years or longer (Müller *et al*., 2001).Alternate day IF also resulted in significant reductions in markers of

inflammation associated oxidative stress in asthma patients during a 2 month period (Johnson *et al*., 2007). Thus, for many patients able and willing to endure long-term fasting and to permanently modify their diet, fasting cycles would have the potential to augment existing medical treatments. Water only and some other forms of long-term fasting have also shown to have potent effects on ameliorating hypertension. An average of 13 days of water only fast resulted in lowering the systolic blood pressure (BP) below 120 in 82% of subjects with borderline hypertension with a mean 20 mm Hg reduction in BP.BP remained significantly lower compared to baseline even after subjects resumed their normal diet for an average of 6 days (Goldhamer *et al*., 2002).Preliminary studies are promising but there is a definite need for larger controlled and randomized clinical studies that focus on periodic fasting strategies that are feasible for the general population.

Fasting and the metabolic syndrome

Metabolic syndrome, defined as abdominal adiposity, combined with insulin resistance, elevated triglycerides and/or hypertension, greatly increases the risk of cardiovascular disease, diabetes, and stroke. Fasting can prevent and reverse all aspects of the metabolic syndrome in rodents: abdominal fat, inflammation and blood pressure are reduced, insulin sensitivity is increased, and the functional capacities of the nervous, neuromuscular and cardiovascular systems are improved (Ahmet *et al*., 2005). Periodic fasting can reverse multiple features of the metabolic syndrome in humans as well. It enhances insulin sensitivity, stimulates lipolysis and reduces blood pressure. Body fat and blood pressure were reduced and glucose metabolism improved in obese subjects in response to an alternate day modified fast (Klempel *et al*., 2013).

Overweight subjects maintained for 6 months on a twice weekly fasting diet in which they consumed only 500–600 calories on the fasting days, lost abdominal fat, displayed improved insulin sensitivity and reduced blood pressure. Three weeks of alternate day fasting resulted in reductions in body fat and insulin levels in normal weight men and women. Ramadan fasting (2 meals/day separated by approximately 12 hours) in subjects with metabolic syndrome resulted in decreased plasma glucose levels and increased insulin sensitivity (Shariatpanahi *et al*., 2007). Antimetabolic syndrome effects of IF were also observed in healthy young men (BMI of 25) after 15 days of alternate day fasting: their whole-body glucose uptake rates increased significantly (increased insulin sensitivity), levels of plasma ketone bodies and adiponectin were elevated, all of which occurred without a significant decrease in body weight (Longo & Mattson, 2014).

In a study by Zauner et al, resting energy expenditure increased significantly from day 1 to day 3 of a fast. The increase in resting energy expenditure was associated with an increase in the norepinephrine concentration. Serum glucose decreased significantly, whereas insulin did not change.They concluded that resting energy expenditure increases during fasting, accompanied by an increase in plasma norepinephrine. This increase in norepinephrine may be the initial signal for metabolic changes in early starvation. Fasting also increased the thermogenic effect of the adrenaline (Webber et al., 1995 & Zauner *et al*., 2000).

Insulin sensitivity

Several major physiological responses to fasting are similar to those caused by regular aerobic exercise including increased insulin sensitivity and cellular stress resistance, reduced resting blood pressure and heart rate, and increased heart rate variability as a result of increased parasympathetic tone (Wan *et al*., 2010). In a human based study, 137 Australian adults with type 2 diabetes (77 women and 60 men) were randomly assigned to diet groups. Of these 137 participants, 67 were randomized to the continuous energy restriction group and 70 were randomized to the intermittent energy restriction group. Ninety-seven participants (70.8%) completed the study, and the dropout rates were similar in both groups (21participants in the continuous energy restriction group and 19 participants in the intermittent energy restriction group; P = .71).Baseline characteristics were comparable between groups. From baseline to 12 months, the mean HbA1c level reduced significantly, with no difference between treatment groups; (–0.5% [0.2%] in the continuous energy restriction group vs–0.3%[0.1%] in the intermittent energy restriction group; P = .65), and the results did not differ using completers analysis. The

results demonstrated that a 2-day intermittent energy restriction diet is comparable to a continuous energy restriction diet for improvements in glycaemic control (Carter, Clifton & Keogh, 2018).

β cell Regeneration in the Pancreas

During mouse development, at embryonic day E8.5, pancreatic progenitor cells are converted into bipotent epithelial cells that generate endocrine precursor cells expressing the factor Neurogenin3 (Ngn3). Ngn3+ endocrine precursors differentiate into all the islet endocrine cells including glucagon producing α cells and insulinproducing β cells.Mice on the FMD (fasting mimicking diet) were fed 50% of the standard daily calorie intake on day 1 and 10% of normal daily calorie intake on days 2 to 4.All mice were supplied with fresh food during the morning hours (8am–10am). FMD mice generally consumed the supplied food within the first few hours of the light cycle. Control-fed animals usually consumed the supplied food during the dark hours. Post-FMD refeeding: after the end of the day 2–4 diet, mice were fed ad libitum regular chow for up to 10 days to regain body weight before the next FMD cycle. FMD altered the gene expression profile that normally suppresses the generation of β cells. These results suggest that glucagon and insulin expression are transiently suppressed in α and β cells during the FMD, followed by lineage reprograming in committed cells. Another possibility is that the FMD may cause cell death and then stimulate progenitor or other cells to regenerate β cells (Cheng *et al*., 2017).

Fasting and cardio-protection

Wan, *et al* looked at male Wistar rats undergoing intermittent fastingand then evaluated the response to cardiovascular stress in by using a telemetric transistor. They found that the rats in the fasting group showed rapid return to basal values of blood pressure and heart rate after induced cardiovascular stress, and presented no alterations in the plasma levels of stress biomarkers, such as adrenocorticotropic hormone and corticosterone, during stress.Adiponectin levels also increased significantly in the fasting group; and the data suggests that adiponect in is responsible for the beneficial effects of fasting on the cardiovascular system (Wan *et al*., 2010).

Another study maintained 30 Sprague-Dawley rats under intermittent fasting for three months and a control group with normal feeding. Thereafter, all animals were submitted to coronary artery ligation to induce myocardial infarction (MI) or to sham surgery. The intermittent fasting group showed lower left ventricular (LV) mass, lower LV wall thickness, and significantly less ventricular remodelling than the control group. Also, 23 hours after surgery, a significantly reduced degree of apoptosis and neutrophil infiltration was noted in the intermittent fasting group with MI. The authors proposed that intermittent fasting induces an ischemic preconditioning in the cardiac muscle that protects myocardial cells from ischemic damage (Ahmet *et al*., 2005 & Azevedo, Ikeoka & Caramelli, 2013).

Fasting and Auto – Immune Disease

Recent studies indicate that both the type and levels of nutrients can influence the generation, survival and function of lymphocytes and therefore can affect several autoimmune diseases. Fasting mimicking diets and IFcan affect autoimmunity and immune-senescence (Choi, Lee & Longo, 2017).To protect the host from infections and malignancies, immune cells need to respond promptly to antigens and danger signals, including massive expansion of T cells and B cells, migration of cells to relevant tissue sites, and synthesis of cytokines and effector molecules. As a result, immune stimulation imposes considerable demands for energy and biosynthetic precursors. Lymphocytes fulfil these demands through swift metabolic changes and rapidly generate energy and building blocks. Disease-relevant T cells depend on long-lasting energy supply. Chronic autoimmune diseases, which depend on long-lived and highly-differentiated lymphocytes, are a high energy-consuming state and therefore susceptible to metabolic manipulations. Energy deprivation can redirect glucose utilization and affect the cells' redox status with ROS depletion, causing apoptosis (Yang *et al*., 2015).

Fasting and Mood

Major depressive disorder is the most commonly diagnosed neuropsychiatric condition with characteristics of low mood, reduced responsiveness to

pleasurable stimuli, lack of appetite, insomnia and even suicidal intentions.The monoamine hypothesis suggests that depression results from an aberrant neurotransmission of serotonin and noradrenalinein the hippocampus as well as subsequent hypothalamic pituitary adrenal (HPA) axis activation. At present, calorie restriction has attracted increasing attention due to its evident effects on the neuroendocrine system and mood condition. Short term and mild calorie restriction, as well as moderate exercise have exhibited antidepressant effects, through activating neuroendocrine hormones to compensate for energy deficiency. Possible Mechanisms Underlying Antidepressant Efficacy of Calorie Restriction may involve Orexin Signalling Activation and Ghrelin regulation. Ketones also play a crucial role in improving mood, ameliorating pain, and protecting neurons against hypoglycaemia. The antidepressant effects of calorie restriction might be dependent on the increased production of ketone. Zhang, et al, in their studies on rodent models showed that fasting can enhance the availability of brain tryptophan and serotonin (Zhang *et al*., 2015).However, most prolonged calorie restriction or severe dietary restriction, including fasting, often caused damage to neurons and can exaggerate depressive behaviours.

DISCUSSION

Modern humans evolved to survive periods of food shortage (feast and famine) and have voluntarily fasted for at least 2000 years. Fasting is broadly defined as the voluntary abstinence of some or all caloric foods and/or beverages for therapeutic, spiritual, or political reasons. In the past decades, research on animals and humans has uncovered several potentially health-promoting physiologic responses to fasting including ketogenesis, hormone modulation, reduced inflammation, and increased stress resistance, lipolysis, and autophagy. Clinical research also indicates that fasting reduces cancer, neurodegeneration, Type 2 Diabetes Mellitus, and improves hypertension, rheumatoid arthritis, cardiovascular disease, metabolic syndrome, mood, and quality of life.

Health Careproviders have repeatedly noted that conventional weight-loss diets with daily energy restriction are difficult to adhere to in the long term. However, intermittent energy restriction, in which short periods of calorie restriction followed by longer periods of habitual eating,offers a reduced burden of dietary restriction and maytherefore, be more acceptable to most people.In animal studies, intermittent energy restriction appears to be equally effective as continuous energy restriction for the reduction of disease risk factors.Studies in the healthy overweight and obese human population have also shown that intermittent energy restriction is an effectivemethod for achieving weight loss comparable to that achieved by continuous energy restriction. Intermittent Fasting (IF) can be achieved in with a minimal decrease in overall calorie intake if the refeeding period in which subjects eat normally is considered.

Adverse effects of fasting

Although continuous calorie restriction during old age may continue to protect from age-related diseases, they could have detrimental effects on the immune system and the ability to respond to certain infectious diseases, wounds and other challenges. However, intermittent fasting designed to avoid weight loss and maximize nourishment have the potential to have beneficial effects even in the very old. Overall, the majority of adverse events experienced during medically supervised fasting are mild to moderate in nature and are known reactions to fasting.

In one study, 652 patients were instructed to eat a diet of fresh raw fruits and vegetables and steamed starchy vegetables for at least 2 days before fasting. During the fast, patients remained on site, drank a minimum of 40 ounces of distilled water per day, and minimized physical activity. Fasting duration was stratified by water-only fast length: 2–7 (short), 8–14 (medium), 15–21 (long), or 22+ (extended) days. These categories were chosen to represent lengths of typical fasts. Water-only fasts were discontinued when symptoms stabilized, the patient requested termination of the fast, or the clinician deemed it necessary for medical reasons.

Data on adverse events were collected from clinical chart notes of self-reported symptoms, clinical and diagnostic findings, and medical management of symptoms. Adverse events that were commonly experienced during visits, including nausea, headache, insomnia, back pain, dyspepsia, and fatigue, were predominately mild. There were two (0.002% of visits) serious adverse events that required hospitalization. One was a grade 3 dehydration event that occurred on fasting day 3 in a 73-year-old, male.The other was

grade 4 hyponatremia that occurred on fasting day 9 in a 70-year-old, male patient (Finnell *et al*., 2018).

RECOMMENDATION

The first thing to let your patients know is that this is not a diet. This is a treatment for their disease.

Various studies on animals have demonstrated replicable effects of fasting on health parameters including improved insulin sensitivity, and reduced levels of blood pressure, body fat, IGF-I, insulin, glucose, and inflammation. One mechanism of action of fasting is that it increases the ability of cells to respond to stress states, which result in an improved ability to cope with more severe stress and oppose disease processes. Also, by protecting cells suppressing growth of damaged and mutated cells and enhancing their apoptosis, fasting could slow down or prevent the formation and growth of cancers. Intermittent fasting (IF) is a term used to describe an eating patterns in which no or few calories are consumed for varying time periods that can range from 12 hours to several days, on a recurring basis (*see Table*).

Table : Types of fasting used as therapy

Intermittent Fasting (IF)	This eating pattern involves fasting for varying periods of time, typically for 12 - 16 hours or longer with normal eating pattern for the rest of the day.
Calorie Restriction (CR)	This eating pattern involves a continuous reduction in caloric intake without malnutrition.
Time Restricted Feeding (TRF)	This eating pattern involves restricting food intake to specific time periods of the day, typically between an 8 – 12 hours each day. Used in animal studies only.
Alternate Day Fasting (ADF)	This eating pattern involves consuming no calories on fasting days and alternating fasting days with a day of unrestricted food intake or "feast" day.
Alternate Day Modified Fasting (ADMF)	This eating pattern involves consuming less than 25% of baseline energy needs on "fasting" days, alternated with a day of unrestricted food intake or "feast" day.
Periodic Fasting (PF)	This eating pattern consists of fasting only 2 or 3 days/week and consuming food ad libitum on 5 to 6 days per week. (called the 4:3 or 5:2 pattern)
Fasting Mimicking Diet (FMD)	A plant-based diet that provides between 34% and 54% of the normal caloric intake for 5 days a month.

(*Anton et al., 2018; Longo & Mattson, 2014*).

As mentioned earlier, to achieve the beneficial effects of fasting, the 'metabolic switch' that occurs during the later part of the second phase of fasting is essential. It represents a shift from lipid synthesis and fat storage to mobilization of fat in the form of free fatty acids (FFAs) and fatty-acid derived ketones. For this reason, fasting regimes have the potential tomanage obesity and related metabolic conditions, including metabolic syndrome and type 2 diabetes (Varady & Hellerstein, 2008).Today's typical Western eating pattern of three or more meals per day creates a situation where we never flip the metabolic switch and thus our ketone levels remain continuously low. Additionally, as our insulin resistance increases with excess weight and diabetes, the time it takes to flip the switch is prolonged. Three intermittent fasting protocols that have been most thoroughly studied in laboratory mice and rats are ADF, TRF (8 – 12 hour feeding window each day) and a very low calorie diet three consecutive days/week (4:3 IF). In addition, IF studies were done on rats or mice where they were made to fast for at least 18 hours/day. The observed reduction in body fat and increase of ketone levels in these mice indicates the metabolic switch occurs in rodents on about 30–40% of calorie

restriction.

As more and more animal and human RCTs demonstrate the health benefits of IF in different disease conditions, it is important to understand the reasons that may prevent health professionals from using fasting therapy more widely in the management of these lifestyle related diseases. We can surmise that more clinical trials on intermittent fasting, with end points that focus on disease outcomes should be pursued. The feasibility of such approaches should also be carefully evaluated as some previous trials have reported high levels of hunger and potential discomfort on fasting days (Anton *et al*., 2018).We know that advocating lifestyle change is easy, but not commonly adhered to by the patients. Hence my recommendation is to use IF as a treatment method, and not a lifestyle change. However, not many studies have been done on fasting regimens in children, the very old and underweight individuals, and it is possible that IF and fasting mimicking diets would be harmful to these cohorts. Fasting periods lasting longer than 24 hours and particularly those lasting 3 or more days should be done under the supervision of a physician and preferably in a hospital setting under direct observation.

Finally, physicians should ask their patients to choose a fasting-based intervention that they believe they could comply with easily based on their present lifestyle. Examples include the '5:2' or '4:3' IF diet or the alternate day modified fasting diet. Fasting regimens could also be tailored for specific diseases as adjunct therapies. Results of initial trials of IF (fasting 2 days per week or every other day) in humans suggest that there is a critical transition period of 3 – 6 weeks during which time the brain and body adapt to the new food restriction regime. It is possible that it takes this time for the brain to overcome the "addiction" to eating food 3-4 times a day. One should also note that the quality of the food eaten on non-fasting days remains important to prevent disease. The mostly plant-based Mediterranean or Okinawa low protein diets are the best meal plans to follow for long term health benefits.

Abbreviations:
CR = Calorie restriction
IF = Intermittent fasting
RCTs = randomised controlled trials

Conflict of Interest: None

CONCLUSION

Caloric restriction is to increase lifespan and to improve tolerance to various stresses in body. Various effects of intermittent fasting regimens and physiological process lead to improved health outcomes. We can conclude by saying that more clinical trials on intermittent fasting with end points that focus on disease outcomes should be pursued.

REFERENCES

Ahmet, I., Wan, R., Mattson, M., Lakatta, E. & Talan, M. (2005). Cardioprotection by Intermittent Fasting in Rats. *Circulation*, 112(20), pp 3115-3121.

Anton, S., Moehl, K., Donahoo, W., Marosi, K., Lee, S., Mainous, A., Leeuwenburgh, C. & Mattson, M. (2018). Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. *Obesity*, 26(2), pp 254-268.

Arum, O., Bonkowski, M., Rocha, J. & Bartke, A. (2009). The growth hormone receptor gene-disrupted mouse fails to respond to an intermittent fasting diet. *Aging Cell*, 8(6), pp 756-760.

Arumugam, T., Phillips, T., Cheng, A., Morrell, C., Mattson, M. & Wan, R. (2010). Age and energy intake interact to modify cell stress pathways and stroke outcome. *Annals of Neurology*, 67(1), pp 41-52.

Azevedo, F., Ikeoka, D. & Caramelli, B. (2013). Effects of intermittent fasting on metabolism in men. *Revista da Associação Médica Brasileira*, 59(2), pp 167-173.

Bayer-Carter, J., Green, P., Montine, T., VanFossen, B., Baker, L., Watson, G., Bonner, L., Callaghan, M., Leverenz, J., Walter, B., Tsai, E., Plymate, S., Postupna, N., Wilkinson, C., Zhang, J., Lampe, J., Kahn, S. & Craft, S. (2011). Diet Intervention and Cerebrospinal Fluid Biomarkers in Amnestic Mild Cognitive Impairment. *Archives of Neurology*, 68(6), pp 743–752.

Carter, S., Clifton, P. & Keogh, J. (2018). Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 Diabetes. *JAMA Network Open*, 1(3), p. e180756.

Cheng, C., Villani, V., Buono, R., Wei, M., Kumar, S.,

Yilmaz, O., Cohen, P., Sneddon, J., Perin, L. & Longo, V. (2017). Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes. *Cell*, 168(5), pp 775-788.

Choi, I., Lee, C. & Longo, V. (2017). Nutrition and fasting mimicking diets in the prevention and treatment of autoimmune diseases and immunosenescence. *Molecular and Cellular Endocrinology*, 455, pp 4-12.

Finnell, J., Saul, B., Goldhamer, A. & Myers, T. (2018). Is fasting safe? A chart review of adverse events during medically supervised, water-only fasting. *BMC Complementary and Alternative Medicine*, 18(1).

Goldhamer, A., Lisle, D., Sultana, P., Anderson, S., Parpia, B., Hughes, B. & Campbell, T. (2002). Medically Supervised Water-Only Fasting in the Treatment of Borderline Hypertension. *The Journal of Alternative and Complementary Medicine*, 8(5), pp 643-650.

H. Müller, F. & Wilhelmi de Toledo, K (2001). Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. *Scandinavian Journal of Rheumatology*, 30(1), pp1-10.

Johnson, J., Summer, W., Cutler, R., Martin, B., Hyun, D., Dixit, V., Pearson, M., Nassar, M., Tellejohan, R., Maudsley, S., Carlson, O., John, S., Laub, D. & Mattson, M. (2007). Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radical Biology and Medicine*, 42(5), pp 665-674.

Kerndt, P., Naughton, J., Driscoll, C. & Loxterkamp, D. (1982). Fasting: The History, Pathophysiology and Complications. *Western Journal of Medicine*, 137(5), pp 379 - 399.

Klempel, M., Kroeger, C. & Varady, K. (2013). Alternate day fasting (ADF) with a high-fat diet produces similar weight loss and cardio-protection as ADF with a low-fat diet. *Metabolism*, 62(1), pp 137-143.

Lee, C., Raffaghello, L., Brandhorst, S., Safdie, F., Bianchi, G., Martin-Montalvo, A., Pistoia, V., Wei, M., Hwang, S., Merlino, A., Emionite, L., de Cabo, R. & Longo, V. (2012). Fasting Cycles Retard Growth of Tumors and Sensitize a Range of Cancer Cell Types to Chemotherapy. *Science Translational Medicine*, 4(124), pp 124ra27-124ra27.

Li, J., Cui, X., Wang, Z. & Li, Y. (2015). rBTI extends Caenorhabditis elegans lifespan by mimicking calorie restriction. *Experimental Gerontology*, 67, pp 62-71.

Longo, V. & Mattson, M. (2014). Fasting: Molecular Mechanisms and Clinical Applications. *Cell Metabolism*, 19(2), pp 181-192.

Mattson, M., Cutler, R. & Camandola, S. (2007). Energy Intake and Amyotrophic Lateral Sclerosis. *NeuroMolecular Medicine*, 9(1), pp 17-20.

Mattson, M., Moehl, K., Ghena, N., Schmaedick, M. & Cheng, A. (2018). Intermittent metabolic switching, neuroplasticity and brain health. *Nature Reviews Neuroscience*, 19(2), pp 63-80.

Müller, H., de Toledo, F. & Resch, K. (2001). Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. *Scandanavian Journal of Rheumatology,* 30(1), pp 1–10.

Neel, J. (1962). Diabetes Mellitus: A "Thrifty" Genotype Rendered Detrimental by "Progress"?. *American Journal of Human Genetics*, 14(4), pp 353 - 362.

Noda, T. and Ohsumi, Y. (1998). Tor, a Phosphatidylinositol Kinase Homologue, Controls Autophagy in Yeast. *Journal of Biological Chemistry*, 273(7), pp 3963-3966.

Peng, W., Robertson, L., Gallinetti, J., Mejia, P., Vose, S., Charlip, A., Chu, T. & Mitchell, J. (2012). Surgical Stress Resistance Induced by Single Amino Acid Deprivation Requires Gcn2 in Mice. *Science Translational Medicine*, 4(118), pp 118ra11-118ra11.

Plunet, W., Streijger, F., Lam, C., Lee, J., Liu, J. & Tetzlaff, W. (2008). Dietary restriction started after spinal cord injury improves functional recovery. *Experimental Neurology*, 213(1), pp 28-35.

Puchalska, P. & Crawford, P. (2017). Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell Metabolism*, 25(2), pp 262-284.

Rothman, S., Griffioen, K., Wan, R. & Mattson, M. (2012). Brain-derived neurotrophic factor as a regulator of systemic and brain energy metabolism and cardiovascular health. *Annals of the New York Academy of Sciences*, 1264(1), pp 49-63.

Secor, S. and Carey, H. (2016). Integrative Physiology of Fasting. *Comprehensive Physiology*, 6(2), pp 773-825.

Shariatpanahi, Z., Shariatpanahi, M., Shahbazi, S., Hossaini, A. and Abadi, A. (2007). Effect of Ramadan fasting on some indices of insulin resistance and components of the metabolic syndrome in healthy male adults. *British Journal of Nutrition*, 100(1).

Stranahan, A. and Mattson, M. (2012). Recruiting adaptive cellular stress responses for successful brain ageing. *Nature Reviews Neuroscience*, 13(3), pp 209-216.

Tessitore, L., Tomasi, C., Greco, M., Sesca, E., Laconi, E., Maccioni, O., Ramo, R. & Pani, P. (1996). A subnecrogenic dose of diethylnitrosamine is able to initiate hepatocarcinogenesis in the rat when coupled with fasting/refeeding. *Carcinogenesis.*, 17(2), pp 289-292.

Varady, K. & Hellerstein, M. (2008). Do calorie restriction or alternate-day fasting regimens modulate adipose tissue physiology in a way that reduces chronic disease risk?. *Nutrition Reviews*, 66(6), pp 333-342.

Wan, R., Ahmet, I., Brown, M., Cheng, A., Kamimura, N., Talan, M. & Mattson, M. (2010). Cardioprotective effect of intermittent fasting is associated with an elevation of adiponectin levels in rats. *The Journal of Nutritional Biochemistry*, 21(5), pp 413-417.

Webber, J., Taylor, J., Greathead, H., Dawson, J., Buttery, P. & MacDonald, I. (1995). The effects of fasting on the thermogenic, metabolic and cardiovascular responses to infused adrenaline. *British Journal of Nutrition*, 74(04), pp 477-490.

Yang, Z., Matteson, E., Goronzy, J. & Weyand, C. (2015). T-cell metabolism in autoimmune disease. *Arthritis Research & Therapy*, 17(1).

Zauner, C., Schneeweiss, B., Kranz, A., Madl, C., Ratheiser, K., Kramer, L., Roth, E., Schneider, B. & Lenz, K. (2000). Resting energy expenditure in short-term starvation is increased as a result of an increase in serum norepinephrine. *The American Journal of Clinical Nutrition*, 71(6), pp 1511-1515.

Zhang, Y., Liu, C., Zhao, Y., Zhang, X., Li, B. & Cui, R. (2015). The Effects of Calorie Restriction in Depression and Potential Mechanisms. *Current Neuropharmacology*, 13(4), pp 536-542.