FASTING AND ITS EFFECTS ON HEALTH AND DISEASE

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ABSTRACT

Obesity remains a critical health issue in the United States, with prevalence increasing and significant impacts on morbidity, mortality, and economic productivity. Current management strategies include lifestyle interventions, medications, and surgical approaches, each with limitations and complications. Recently, intermittent fasting (IF) has gained popularity as a weight loss technique due to its ease of implementation and potential metabolic benefits. Evidence from various studies indicates that IF can lead to significant reductions in body weight, fat mass, and improvements in metabolic health markers such as insulin sensitivity and lipid profiles. Additionally, IF appears to beneficially alter gut microbiota composition and reduce inflammatory markers, potentially mitigating risks associated with obesity-related diseases. However, more human interventional trials are necessary to fully understand IF's long-term effects and establish it as a viable strategy for obesity management. This paper examines the physiological effects of IF on the body through a systems-based approach.

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Introduction

Obesity remains an ongoing and critical issue in the United States. According to the NIH, the prevalence of obesity among adults has increased from 30% to 42%, greatly impacting health and overall morbidity and mortality of the population (*Overweight & Obesity Statistics - NIDDK*, n.d.). The prejudice and stigmatized views obesity has in society increase its treatment complications further exacerbating the diseases chronic relapsing state. Obesity should not be blamed on the individual since there are multifactorial causes to the disease and addressing them all together should be done without bias.

When taken at the population level, we can see the economic impacts of obesity. Debilitating complications from the disease leads to over a several billion dollar loss of economic activity for the nation (Hammond & Levine, 2010). Research by Global Data has shown that in Michigan alone, obesity has resulted in a reduction in the states labor force of approximately 100,000 people leading to a loss economic activity in the state by over a billion dollars. In terms of the individual, obesity is associated with the development of type 2 diabetes mellitus, cardiovascular diseases, types of cancer, non-alcoholic fatty liver, neurologic conditions, and other adverse pathological conditions (González-Muniesa *et al*., 2017).

Current management of obesity include lifestyle interventions and healthy nutrition and physical activity approaches to weight loss are usually the first line recommendations. In certain cases, with either no improvement or not meeting weight goals, medication and surgical approaches can be used. Although both the mentioned management methods work to help weight loss, they aren't without its complications and issues. In recent years GLP-1 receptor agonists have become widely commercialized for use to treat obesity and type 2 diabetes. Although these drugs have shown great effect, it's popular profile has brought cases of misuse (Wiener *et al*., 2024).

Medications such as Qsymia (phentermine-topiramate) and Contrave (naltrexone-bupropion) can be used to treat obesity but their effectiveness is hindered by patient compliance as well as a consistent diet and exercise (Gadde *et al*., 2011; Greenway *et al.*, 2010).

In addition to medication, surgical interventions another treatment for severe cases of obesity. There are three main types of bariatric surgeries involved in obesity treatment, all of them decrease volume of the stomach pouch by resection or by direct bypass. These invasive interventions can have lifelong changes to the patient, from nutritional deficiencies to lifelong therapy and monitoring (González-Muniesa *et al.*, 2017). Even with this invasive approach to treatment, relapsing might still occur.

Intermittent fasting (IF) has become increasingly popular as a nutritional weight loss technique in recent years. IF refers to eating plans that alternate between a state on no caloric intake for a minimum of 12 hours and a phase of eating (Anton *et al*., 2018). The goal of IF is to temporally calorie restrict the body long enough to trigger fat burning to occur. During fasting periods, the only things consumed are water and a few electrolytes if needed. During feasting periods one can restrict their feeding to a particular diet, such as a low-carb diet, if they need or they can eat what they want during that meal. IF results in a calorie restriction by restricting the time. The decreased eating window allows for less meals therefore having a reduction in total caloric intake. The ease of this type of technique and the flexible protocol, although not for everyone, make this a more amiable form of diet.

There three main types IF techniques: alternative day fasting (ADF), 5:2 fasting, and Time-restricted eating (TRE) (Varady *et al*., 2022). All three of these techniques share one similarity a temporal restriction in your eating time. ADF involves fasting for an entire day, ‘fast day’ and alternating with a ‘feast day’. The 5:2 diet is when there is 2 fast days per week that occur consecutively or non-consecutively with 5 feast days for the week. TRE is a form of IF that is limiting the daily eating window each day to a small amount such as 18:6 or 20:4. During this type of IF, you only eat for small feast window duration.

Since IF is so easier to implement into everyday life, needing no extra equipment or dietary restriction, individuals will have less drop out. The total calorie reduction from cutting down the number of meals is a technique anyone can do, which will lead to a progressive weight loss. This paper will go through the effects of IF on the body in a systems-based approach to better understand the physiological effects on our body.

Body Composition, Metabolic, and Gut Microbiota

<u>Body Weight and Lean Mass</u>

A meta-analysis of IF studies by (Varady, 2011) show the effects of IF on body weight concluded that over 3-12 weeks there is reductions in body weight of 4-8% from baseline. These protocols did not control for diet and the participants ate as desired. They compared this to calorie restricted and diet-controlled studies of similar 4-12 week duration and found similar degrees of weight loss between the two.

Harris *et al.* showed that in a long term (12 month) intervention between a IF protocol compared to a calorie restriction protocol, both protocols resulted in a sustainable reduction in body weight but that there was significant decrease on the waist circumference and body fat in the IF group compared to the calorie restrictive group. This is an optimistic result since waist circumference is a simple measure to predict visceral fat, high BMI, and central fat distribution, markers of metabolic syndrome (Fang *et al*., 2018).

Even though a reduction in body weight in the goal for any weight loss diet, knowing what percentage of the weight loss is fat compared to lean mass is critically important. During calorie restriction diets, the weight lost is approximately 75% from fast mass and 25% lost is from lean mass (Heymsfield *et al.*, 2014), and since lean mass is related to resting metabolic rate (K. O. Johnson et al., 2021), the need to preserve as much lean mass during a nutritional diet is paramount. Varady *et al*, showed that there is a much lower portion (10%) of lean mass lost during an IF type protocol over the course of 4-12 weeks than for calorie restrictive diets who primarily lose about 25% lean mass during over the course of the same duration. It is important to not however that the ways the lean mass percentages were calculated differed from the two studies. For the calorie restrictive study, a dual-energy x-ray absorptiometry (DXA) scan was used to obtain the data for lean mass while in the IF study bioelectrical impedance analysis (BIA) was used. A DXA scan would give a more accurate and direct reading on your body composition versus a BIA which will give you an indirect reading.

Metabolic Effects

In 1963, Randle *et al*. proposed a theory of energy metabolism during feeding and fasting called the "glucose fatty-acid cycle". This theory proposes that glucose and fatty acid compete for oxidation. Since then, more information about the underlying mechanisms about this cycle have been found. There are 4 stages of the fed-fast cycle. The stages in series are fed-state, the post absorptive (early fasting state), the fasting state, and the starvation (long-term fast) state. In all these stages, most of the tissues use glucose as their primary energy source throughout the day. Postprandial, insulin secretes to facilitate uptake of glucose for cellular metabolism while also upregulating fat synthesis and suppressing its breakdown. This makes it easier for fat to accumulate with excess glucose. During prolonged fasting, adipose tissues use their triglycerides as a source for energy by breaking it down into fatty acids and glycerol. After, the liver changes the fatty acids into ketone bodies. Various tissues such as the brain use ketone bodies as a main source of energy during fasting. Normal eating routines only involve the fed and post-absorptive states. During intermittent fasting, an individual goes between 3 out of the 4 stages: the fed, post absorptive and fasting stages. During the feeding state, insulin is the main hormone that helps get fuel from glucose. Compared to the fasting state, the main hormone is glucagon, which helps the body use liver glycogen stores for energy. The metabolic switch occurs when liver glycogen stores are depleted, and the body starts metabolizing fatty acids. This metabolic switching from occurs typically beyond the 12 hour mark of the fast (Anton *et al*., 2018). After this point Lipids in adipocytes are metabolized to free fatty acids, which are subsequently released into blood. Along with this ketone generation begin to occur thorough the β-oxidation of free fatty acids in the liver. This metabolic switching, from the fed to fast state, results in a preservation of lean mass and a reduction of fat storage resulting in improved metabolism (Anton *et al*., 2018).

Gut Microbiota

The human intestinal system carries a large number of bacteria that have a significant impact of the overall health of the individual (Hughes & Holscher, 2021). The diversity and composition of this microbiota is influenced by the host genetic background and thus unique to each individual (Martin-Gallausiaux *et al*., 2021). These organisms have diverse functions within our systems and are associated with many beneficial physiological effects for its host. Over the last decade studies into how alterations in the normal microbiota of an individual from disease states have affected pathological states in the host (Lepage *et al*., 2013). These alterations in the gut flora can lead to both positive and negative effects on the host. Diets and exercise have been shown to immensely alter gut microbiota composition in individuals (Hughes & Holscher, 2021). Hughes & Holscher go on to discuss how if the microbiota of an individual is at a negatively impacting state, you can adjust lifestyle and nutritional changes to bring back the gut microbiota composition back to a homeostatic level with the individual's body. The *Bacteroides* and *Firmicutes* species has been known to promote a beneficial host relationship and disruptions in the species composition specifically for *Bacteroides* has been associated with an increase in metabolic or inflammatory disease such as obesity, atherosclerosis, diabetes, and neurological disorders (Zeb *et al*., 2023). Along with disease profiles increase in *Bacteroides* and *Prevotellaceae* species variation has been associated with positive lipid profiles, leading to decreases in low-density lipoprotein (LDL), and triglyceride levels.

In recent years with the popular emergence of IF diets, studies have been done to show how IF can alter an individual's gut microbiota (Popa *et al*., 2023)(Zeb *et al*., 2023). It is believed that the pattern of fasting-feasting cycles of IF cause periodic changes in the gut microbiome that may lead to reversing dysbiosis and host metabolic disorders (Popa *et al.*, 2023). Popa et al. discussed how IF groups, varying from a fasting protocol of 12 hours plus, had significant shifts in microbial composition toward a positive direction, increasing in genera of *Bacteroides, Prevotellaceae, and Lactobacillus.* These shifts were also seen with lowered inflammatory markers tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8). There was one study which showed no significant changes in the abundance of microbiota, but that study only had a fasting time of 8 hours which may not confer the full benefit of the fasting cycle.

Cardiovascular System

Cardiovascular Disease

Obesity has been well linked to the development of cardiovascular disease in individuals (Powell-Wiley *et al.*, 2021). Cardiac health biomarkers are substances or molecules that can be measured in the blood and indicate the presence or severity of cardiovascular diseases or conditions. These biomarkers can help in the diagnosis, prognosis, and monitoring of heart-related issues. Some common cardiac health biomarkers include troponin, B-type natriuretic peptide (BNP), C-reactive protein (CRP), and lipid profile components such as LDL cholesterol and HDL cholesterol (Dhingra & Vasan, 2017). Tracking these biomarkers can provide valuable information to healthcare providers to assess an individual's cardiac health status. The influence of IF on cardiovascular disease risk has been looked at by various articles. Keenan *et al*. 2022 conducted a secondary analysis on a 12-week intervention investigating the effects of 5:2 fast compared to calorie restrictive group under similar conditions. They collected samples from each group to track cardiometabolic blood markers. They found that even though both energy restrictive diets significantly reduced total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels over the 12-week intervention, the IF group had a significantly greater reduction when compared to the calorie restricted group. It is to be noted that sex hormonal characteristics might have an influence on the results in the study, with the women in the calorie restrictive group showing a lack of change from baseline for TC and LDL-C at the end of the study.

Several studies using mice have been completed, which show that IF can reduce atherosclerotic plaques in obese mice (Al Zein *et al*., 2023). Atherosclerosis is a condition characterized by the buildup of plaque in the arteries. The plaque is made up of the following substances: fats, cholesterol, calcium and other substances in blood. With time, the plaque gets tough and narrows the arteries, which in the end can restrict blood flow to vital organs. Atherosclerosis is a progressive condition that can lead to serious complications, such as heart attack, stroke, or peripheral artery disease, depending on which arteries are affected. Adipose tissue dysfunction plays an important role in the development of atherosclerosis by upregulating proinflammatory adipokines and downregulating anti-inflammatory adipokines. Intermittent fasting has proven to lessen oxidative stress and inflammation especially in the cardiovascular system, which ultimately decreases atherosclerosis risk. Zein *et al*. discusses how a TRF diet in mice has shown to decrease diet-induced obesity and inflammation, while also improving atherogenic indices.

Autophagy and Myocardial Infarction Effects

Autophagy related to IF may have an effect on helping rats with myocardial infarction (El Agaty *et al*., 2022). Autophagy is a natural process within the body that involves the degradation and recycling of damaged or unnecessary cellular components. During autophagy, cells break down dysfunctional proteins, lipids, and organelles through a series of complex mechanisms. This process helps maintain cellular homeostasis by removing waste and promoting cell survival and renewal. The regulation of mitochondrial autophagy has an important role in cardiac homeostasis. Activation of autophagy during ischemic injury or ischemic/perfusion injury is thought to be cardioprotective as well as reduce the oxidative stress burden on cardiomyocytes (Ryter *et al.*, 2019). Agaty *et al*, showed that IF induced autophagy in an aged population of rats helps alleviate age-associated cardiac changes to decrease the susceptibility of an acute myocardial infarction. They saw that there was significant upregulation of Atg-5 a known autophagy marker in the IF group compared to the non-IF. Then they found that in the old aged IF group, cardiac markers of inflammation and oxidative stress were lower including, troponin-I, CK-MB, and TNF-α. These changes mean that there is an increase in tolerance of aged myocardium to an acute cardiac event in rats treated with IF as compared to those that aren't.

Even though there is positive research in animal models for the effectiveness of IF diets in reducing atherosclerosis and resulting cardiovascular disease risk, more human interventional trials should be done to have a better grasp to its effects.

The Biliary System

Hepatic Effects

The metabolic switch that occurs during fasting was discussed earlier in this paper. This switch encourages the breakdown of stored fat into fatty acids and glycerol, which are then transported to the liver and converted into ketones for energy. As glycogen stores become depleted, insulin sensitivity improves and the body increasingly relies on fat reserves, potentially enhancing fat loss (Anton *et al*., 2018). Additionally, intermittent fasting may increase the production of norepinephrine, a hormone that boosts fat mobilization and oxidation. Over time, these effects can lead to improved metabolic health, including reduced body fat and better regulation of blood sugar levels (Stockman *et al*., 2018). Since the biliary system plays such a pivotal role in fat metabolism and IF has altering effects on fat metabolism in the liver and body, the effect of IF on the biliary system should be investigated.

Fasting-mimicking diet (FMD) have been shown to have hepatic and blood marker changes (Brandhorst *et al*., 2024), revealing its potential to reduce biological age and decrease disease risk. One hundred participants followed an FMD, characterized by low-calorie, low-protein, and plant-based nutrition. After 3-month period participants showed significant reductions in total body fat and hepatic fat fraction confirmed with MRI. Brandhorst *et al.* 2024 also combined biomarkers from multiple systems (albumin, alkaline phosphatase, serum creatinine, C-reactive protein, Hba1c, systolic blood pressure, and total cholesterol) and used the data to form one variable meant to simulate the rate of organismal aging and found a reduction in biological age by 2.7 years compared with the chronological age. In a post-hoc analysis, participants with higher baseline levels of body mass index (BMI), blood pressure, fasting glucose, insulin-like growth factor -1 (IGF-1), triglycerides, total cholesterol, LDL cholesterol, and C-reactive protein experienced more substantial reductions in these measures compared to those with lower baseline levels. These results indicate that FMD may mimic traditional fasting's benefits, enhancing metabolic health, lowering age-related disease risks, and potentially extending health span. This study builds on their previous study of mice which found that mice on a FMD showed significant improvements in reduced liver enzymes (ALT and AST) indicating better liver function.

ADF effects on body weight and dyslipidemia in patients with non-alcoholic fatty liver disease (NAFLD) have also been investigated (Cai *et al*., 2019). Non-alcoholic fatty liver disease (NAFLD) is a disease in which there is an overt amount of fat deposition in hepatocytes in individuals who have little to no consumption of alcohol. It ranges in severity from simple fatty liver (steatosis), where there is fat build-up without inflammation or liver damage, to non-alcoholic steatohepatitis (NASH), which involves inflammation and damage to liver cells, potentially leading to fibrosis (scarring) and cirrhosis (severe liver damage) (Pouwels *et al*., 2022). The randomized controlled trial by Cai *et al*, participants were assigned to either an ADF regimen or a control group with no dietary restrictions. The study aimed to determine if ADF could lead to weight loss and improvements in lipid profiles, which are critical factors in managing NAFLD. Findings revealed that participants in the ADF group experienced significant reductions in body weight and decreased fat mass. The ADF group also had improved lipid levels (total cholesterol and triglycerides) compared to the control group, suggesting that ADF may be a beneficial intervention for managing NAFLD.

Gallbladder Effects

Regular eating stimulates the gallbladder to release bile into the small intestine. Intermittent fasting cycles disrupt this regular bile release rhythm. The gallbladder might contract less frequently, potentially leading to increased bile stasis. Highly concentrated bile may increase the risk of gallstone formation in some individuals. Gallstones are solid particles that form from bile cholesterol or bilirubin. Intermittent fasting, especially if it results in rapid weight loss, can increase the risk of cholesterol gallstones. When fasting, the decrease in gallbladder contractions can lead to bile stagnation, which, combined with concentrated bile, fosters an environment conducive to gallstone formation (Van Erpecum *et al*., 1992). Past data from Bloch *et al.* suggested that fasting for periods of 12-16 resulted in an increased percentage of cholesterol and gallbladder volume but also suggested that for longer fasts of 20+ hours actually reduced gallbladder volume by unknown mechanisms. Since these studies were done quite long ago, new studies should be done to again look at how fasting effects gallbladder health for us to get a better picture of the safety issues regarding this new weight loss method.

Neuronal changes

The current research and understanding of IF effect on brain and cognition is based primarily on animal studies. Since fasting increases ketone levels in the body, a potential impact of ketones on Alzheimer's disease is a growing area of interest in research. Ketones, supplied as an alternative energy source for the brain, hold promise for addressing the energy deficits seen in Alzheimer's patients who struggle with glucose metabolism (Hersant & Grossberg, 2022). Moreover, ketones exhibit neuroprotective qualities and may protect against β-amyloid and its toxins. Buildup of β-amyloid and tau proteins have been implicated in the pathogenesis of various types of dementia. Ketones may enhance cognitive function and memory by stimulating the production of neurotrophic factors and enhancing synaptic function. Additionally, ketones might influence the accumulation of amyloid plaques, a characteristic feature of Alzheimer's disease, by potentially reducing amyloid burden (Hersant & Grossberg, 2022).

Studies have examined the intricate connection between intermittent fasting (IF) and cognitive function, particularly focusing on Alzheimer's disease (AD) (Elias *et al*., 2023). IF can impact metabolism, cellular mechanisms, and neuroprotection, potentially influencing Alzheimer's disease pathology by modulating processes like autophagy and neuroinflammation. Elias *et al*. discusses how signaling pathways affected by IF, such as insulin sensitivity and AMPK activation, highlighting the need for further clinical studies to confirm IF's efficacy in enhancing cognitive health and addressing Alzheimer's disease progression. Overall, they suggest that intermittent fasting shows promise in positively impacting cognitive health and potentially mitigating risks associated with Alzheimer's disease.

Motor coordination and balance has been test in mice on a FMD protocol (Brandhorst et al., 2015). Brandhorst *et al* 2015 tested this by measuring their performance on accelerating rotarod. The FMD mice consistently were better at accelerating rotarod, however when correcting for weight, there was no definite difference between the control and FMD group. Short term memory between groups was assessed by novel object recognition test and long-term memory was assessed by maze exploration time. Both these tests resulted in improvements by the FMD group suggesting there is improvement in motor learning and hippocampus dependent short- and long-term cognition when compared to the control group.

Immunologic Changes

Fasting has shown to play a major role in adaptive cellular responses that overall reduce oxidative damage and subsequent inflammation. In ovariectomized rats who show signs of neuroinflammation (elevated levels of IL-1β, IL-6, and TNF-α) and an antioxidative/oxidative imbalance (Albrahim *et al*., 2023). Albrahim *et al* showed IF had a significant impact on reducing the proinflammatory markers mentioned as well as increasing the mRNA expression of superoxide dismutase (SOD1/2) and glutathione peroxidase (GPx1), two mechanisms by which the human body decreases oxidative damage.

Fasting has the potential to decrease the risk of acquiring cancer as well as reducing in treatment length once diagnosed (Longo & Mattson, 2014). Fasting reduces IGF-1, insulin and glucose levels and increases IGF-1 binding protein (IGFBP1) as well as ketone bodies. Elevated IGF - 1 is associated with increased risk of developing cancers when compared to individuals who have growth hormone receptor deficiency that results in severe IGF-1 deficiency. IF induced reduction in IGf-1, insulin, and glucose helps provide environment that decreases DNA damage and carcinogenesis.

Fasting in general has shown to decrease inflammation. Patients with rheumatoid arthritis (RA), an autoimmune disease-causing inflammation of the joints, were shown to have decreased inflammation and pain with fasting (H. Müller, 2001). However, once the normal diet resumed the inflammation returned. This suggests IF can be used adjunct to treatment for RA patients. ADF showed reduced levels of TNF-α in patients with asthma (J. B. Johnson et al., 2007). The study showed decreased oxidative stress markers. For people with such inflammatory disease, intermittent fasting could be an augment to their current medical therapy or even replace it.

Reductions in periodontal inflammation is seen with IF (Lira-Junior *et al*., n.d.). Twenty-one patients were put on a 6 month 5:2 IF protocol which looked at periodontal parameters, bleeding on probing (BOP), probing pocket depth (PPD), visible plaque index (VPI), and subgingival microbiota. After 6 months significant improvement of BOP and PPD were seen while VIP had little change from baseline. Subgingival microbiota had no significant change.

As mentioned earlier, the current research of fasting and its impacts on the nervous system is from animal studies. Longo & Mattson discussed how IF diet rats, including those expressing mutant dominant human genes that cause dementia (Huntington disease, Alzheimer's, Parkinson's), were found to show less neuron degeneration and dysfunction. This was thought to be due to reduced oxidative particles that would otherwise damage molecules and cellular processes. IF diets showed a boost of antioxidant neurotrophic factors (BDNF, FGF2), increased protein chaperones, and lower level of pro-inflammatory cytokines (TNF-α, IL-1B, IL-6). This combination of immunological effects may promote neurogenesis. However, this effect was not seen to be helpful in conditions like inherited Amyotrophic lateral sclerosis, which suggests motor neurons may not adapt well to the metabolic changes IF induces in the body or there is no rescue of phenotypic changes. In humans, Calorie restriction showed improved verbal memory in overweight women and elderly patients.

Inflammation has shown to be a poor prognostic factor in patients of intracerebral hemorrhage (ICH). Neurosurgical clot evacuation is the primary treatment, however clinical trials have not shown a clear benefit to that treatment when compared to conservative methods. After ICH, the RBCs degrade and cause secondary brain injury by microglial activation and further inflammation. Dai *et al*., 2022 took male mice injected with 30 microliters of autologous blood into the right basal ganglia and modeled to have ICH. They were split into groups of control and the other to have IF type of diet. They found that IF ICH mice showed reduced brain edema on day 3 and 7. On day 28, they found IF ICH mice showed reduced striatum atrophy as compared to the control group. This study showed that IF protected against ICH resulting in neurological deficits for short and long term.

Conclusion

This paper reviews how intermittent fasting effects various body systems and the potential benefits. The popularity of intermittent fasting has been steadily rising. With more and more people looking to get started on with this type of diet, a basic information of the protocol and body changes should be learned. Even though there are a multitude of possible advantages, some areas need to be further investigated to have a clear picture on the changes in the body.

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