International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Unlocking the Potential of Intermittent Fasting as a Dietary Intervention for Chronic Inflammatory Diseases

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ARTICLE INFO

Keywords:
Intermittent Fasting
Diet
Chronic inflammatory diseases
Non-alcoholic fatty liver disease
Neurodegenerative diseases
Chronic kidney disease

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Received: May 4, 2025
Revised: July 29, 2025
Accepted: August 5, 2025

ABSTRACT

Chronic inflammation contributes to development of various chronic diseases and is a significant cause of morbidity and mortality worldwide. Certain interventions can improve chronic inflammatory diseases by reducing inflammation and oxidative stress, activating regulatory T cells, and limiting inflammatory responses. Lifestyle and dietary interventions can also help improve disease outcomes. Intermittent fasting (IF) is a dietary intervention that can regulate inflammation and potentially improve chronic inflammatory diseases through metabolic, immunomodulatory, and microbiome-related effects. This literature review aimed to investigate the efficacy of IF in chronic inflammatory diseases and its related mechanisms. This study conducted an extensive review of current literature by searching four databases, including PubMed, Scopus, Embase, and Web of Science. IF was shown to have positive effects on chronic inflammatory diseases, such as non-alcoholic fatty liver disease and cardiovascular disorders. However, caution should be exercised when recommending IF for patients with inflammatory bowel disease and chronic kidney disease. On the other hand, IF has potential neuroprotective effects against neurodegenerative diseases such as Alzheimer's and Parkinson's and may be a safe dietary intervention for asthmatics that can improve symptoms by reducing inflammatory responses. IF can be an effective strategy for the prevention and management of chronic inflammatory diseases, but careful consideration of individual patient needs seems necessary before recommending this dietary intervention.

Please cite this article as: Ghahremani A, Barati M, Namdar Ahmadabad H. Unlocking the Potential of Intermittent Fasting as a Dietary Intervention for Chronic Inflammatory Diseases. Int J Nutr Sci. 2025;10(3): doi:

Introduction

Inflammation is an evolutionarily conserved and defensive mechanism induced by exposure to harmful stimuli such as pathogens, damaged cells, toxic compounds, or radiation. During this process, immune cells such as neutrophils and macrophages and non-immune cells like endothelial cells, epithelial cells, and keratinocytes are activated. They then release cytokines and chemokines, which attract more immune cells to the location of injury or infection (1, 2). Acute inflammation is essential for eliminating harmful stimuli and

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initiating tissue repair processes. However, if acute inflammation is not suppressed; even after the harmful stimuli are removed, it can result in persistent inflammation or chronic inflammation. This is identified by the continuous activation of immune cells and the release of pro-inflammatory cytokines. Additionally, inflammatory and biochemical inducers such as oxidative stress and mitochondrial dysfunction can contribute to chronic inflammation by increasing the production of free radicals and other molecules (3, 4).

Chronic inflammation can cause tissue damage and contribute to the development of chronic diseases, such as cardiovascular diseases, neurodegenerative diseases, stroke, inflammatory bowel disease, arthritis, metabolic syndrome, type 2 diabetes (T2DM), atherosclerosis, etc. (3, 5). Chronic inflammatory diseases, in which chronic inflammation is a significant cause and progression factor, they are the most important cause of morbidity and mortality worldwide while reducing the quality of life of those affected. It has been shown that over 50% of all deaths worldwide are related to these diseases (6). Certain interventions were demonstrated to promote the production of anti-inflammatory cytokines, reduce oxidative stress and the secretion of pro-inflammatory cytokines, activate regulatory T cells, decrease the activity of Th1 and Th17 lymphocytes, limit inflammatory responses, and improve the status of chronic inflammatory diseases (7, 8). Alongside anti-inflammatory drugs, various supplements, immunotherapy and invasive therapeutic procedures that are prescribed to improve the condition of those with chronic inflammatory diseases (9, 10), lifestyle, and dietary interventions can also help improve disease outcomes and reduce complications (11, 12).

Lifestyle factors such as smoking, physical inactivity, stress, harmful alcohol consumption, and unhealthy diet are key risk factors for chronic inflammation, and potential changes in these factors can prevent 70 to 90 percent of various chronic inflammatory diseases. Among these risk factors, dietary behavior plays the most significant role in modifying mortality and years of life with disability (3, 12). Unhealthy dietary habits are controllable factors that accelerate the development of inflammation and related inflammatory diseases. Conversely, targeted dietary interventions and nutritional therapies can modify inflammatory responses (13). Sears *et al*. believed that dietary intervention in an orchestrated systems-based approach can work to reduce, remove, and repair tissue damage resulting from any inflammation-induced injury (14).

Dietary restriction, without malnutrition, is a reliable and effective intervention for increasing lifespan and improving health status. This intervention enhances adaptive mechanisms against stimulating and damaging factors. The dietary restriction includes caloric restriction (CR), ketogenic diets, fasting mimicking diets, and intermittent fasting (IF) (15, 16). IF refers to severe calorie restriction or avoidance for 12 hours to several days, alternating with periods of unrestricted food consumption. Calorie restriction or avoidance may be limited to specific times of day or days of the week. As shown in the Figure 1, different types of IF include alternative-day fasting (ADF), modified alternative-day fasting (ADMF), 5:2 diet, Ramadan fasting, and time-restricted eating (TRE) or time-restricted feeding (TRF). Intermittent calorie intake causes a metabolic shift from glucose to stored lipids, leading to a cascade of metabolic, cellular, and microbiome changes associated with multiple health benefits (17, 18). In this literature review, we would first describe the mechanisms of IF's effects on inflammation. Then, we would examine its impact on chronic inflammatory diseases.

Methods

To investigate the effects of IF on chronic inflammatory diseases, a comprehensive search was undertaken using electronic databases such as PubMed, Scopus, and Web of Science. The search strategy included keywords such as "intermittent fasting," "alternate-day fasting," "modified alternate-day fasting," "time-restricted eating," "time-restricted feeding," "5:2 diet", "16:8 diet", and "Ramadan fasting" combined with terms such as "inflammation," "chronic inflammatory diseases," "non-alcoholic fatty liver disease," "cardiovascular disorders," "inflammatory bowel disease," "chronic kidney disease," "neurodegenerative diseases" and "asthma." The search was limited to articles published in English between 2010 and August 2023. We selected relevant articles and synthesized data to provide an overview of IF's effects on inflammation and chronic inflammatory diseases.

Mechanisms of Intermittent Fasting in the Control of Inflammation

The Effect of Intermittent Fasting on Metabolic Pathways

IF has been shown to have several metabolic effects on the body, including the breakdown of triglycerides into fatty acids and glycerol, which are then converted into ketone bodies by the liver.

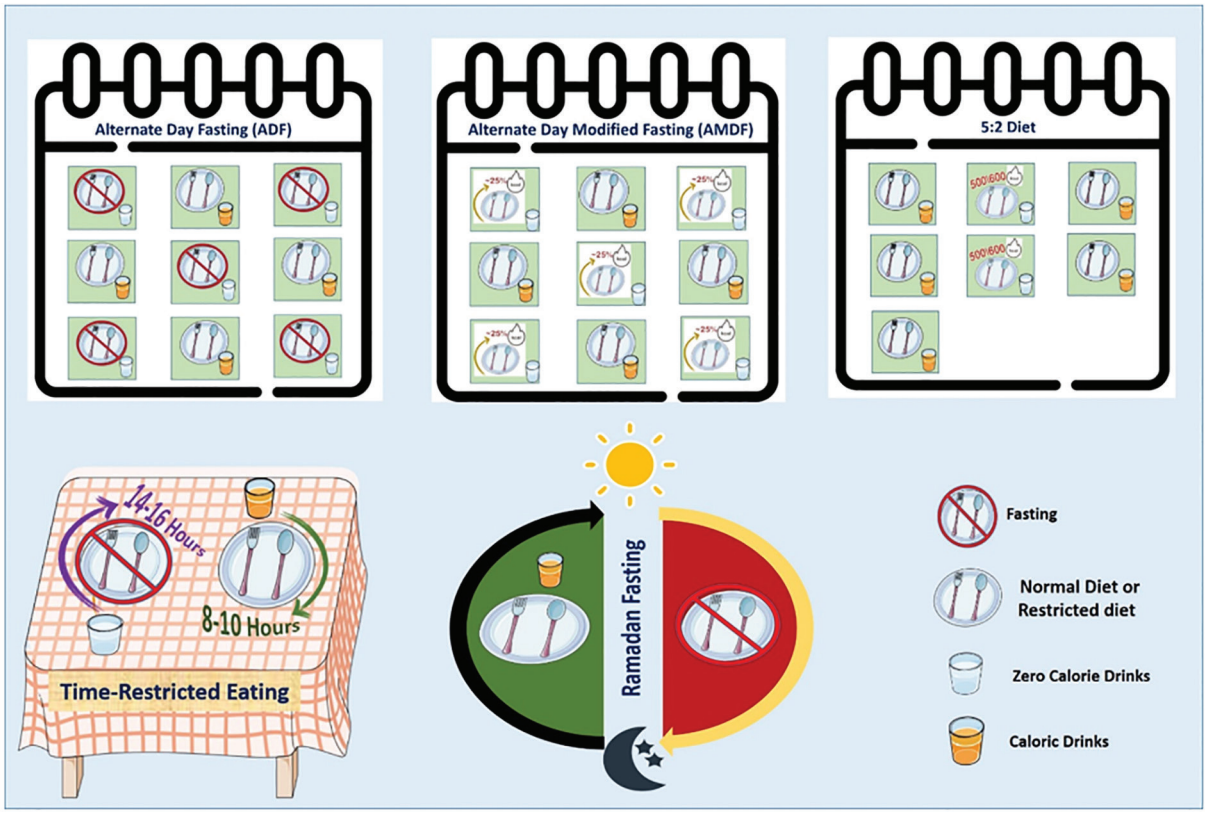

Figure 1: Different types of intermittent fasting. A: Alternate-day fasting: 24-hour fasting periods with unlimited food intake during the following 24 hours, repeated for several days or weeks. B: Modified alternate-day fasting: 24-hour fasting periods with approximately 25% of daily calorie intake from a normal diet, followed by unlimited calorie intake during the next 24 hours, repeated for several days or weeks. C: 5:2 diet: Normal diet five days a week and two consecutive or nonconsecutive days of fasting or restricted calorie intake to 500-600 calories. D: Time-restricted eating: The eating window is restricted to 10-8 hours (early or end of the day), and the fasting window is 16-14 hours. E: Ramadan fasting: No food or drink intake during the day and unlimited food intake at night for one month during Ramadan.

During fasting, these ketone bodies serve as the primary energy source for many tissues, especially for the brain. The increase in ketone bodies leads to a decreased respiratory exchange ratio, indicating greater metabolic flexibility and efficiency in energy production from fatty acids and ketone bodies (19, 20). Ketone bodies also act as signaling molecules that regulate the expression and activity of many proteins and molecules affecting health and disease. They can activate factors that alleviate oxidative stress and control inflammation by inhibiting factors such as NF-kB and NLRP3 and preventing the production of pro-inflammatory cytokines (17).

IF alters the hormonal proteins' leptin and adiponectin concentrations, resulting in increased adiponectin and decreased leptin concentrations and a decreased leptin-to-adiponectin ratio (21, 22). IF can affect immune and inflammatory responses through Leptin and adiponectin level changes, as leptin promotes pro-inflammatory responses while adiponectin inhibits them (23). Although IF may have practical applications in different populations, a research indicated potential sex-specific differences in areas such as body composition and glucose and lipid metabolism. Rius-Bonet *et al.* suggested that further study of these sex-specific responses to intermittent fasting is needed to define the most effective time frames and lengths of fasting periods for men and women (24).

The Effect of Intermittent Fasting on the Immune System

IF has been found to positively affect immune function by regulating the activity of the immune system. It was exhibited that fasting-induced weight loss can regulate lipid and glucose metabolism and positively impact the immune system. IF affects circadian rhythm changes and regulates immune system function in animal and human models (25). During Ramadan, a study on healthy individuals who fasted for 23-30 consecutive days found that serum cytokine levels (IL-1β, IL-6, and TNF-α,) and the number of circulating white blood cells significantly decreased after three weeks (26). Similarly, another study found that plasma cytokine levels (IL-1β, IL-6, and IL-8,) significantly decreased one week after the start of fasting and continued to decrease for two weeks after Ramadan (26). Different types of IF, such as TRE, can lower IGF-1 level (21). This decrease may impact immune

responses due to the immunomodulatory effects of IGF-1 (27). Additionally, IF has been found to inhibit the activation of caspase-1 by NLRP3, preventing the production of pro-inflammatory cytokines IL-1β and IL-18, thus improving inflammatory diseases (28).

The effect of Intermittent Fasting on the Microbiome

IF has been shown to positively affect the gut microbiota by increasing its diversity and promoting the growth of beneficial bacteria. The increase in diversity is attributed to changes in genes related to sirtuin-1, which regulates the gut microbiota and prevents gut inflammation (25). IF also increases anaerobic bacteria such as Lachnospiraceae and Ruminococcaceae that produce butyrate, a process associated with healthy and long-term metabolic effects (29, 30). It was shown that IF can lead to increased anti-inflammatory bacteria, such as *Bacteroides fragilis* and *Akkermansia muciniphila*, and a decrease in pathogenic bacteria (31). The evidence suggests that IF can promote a healthy gut microbiota by creating a favorable environment for beneficial bacteria growth while reducing inflammation (31).

The Effect of Intermittent Fasting on Autophagy

IF has been shown to activate autophagy, a cellular process that plays a crucial role in maintaining cellular homeostasis and preventing inflammation (32). The autophagy process can eliminate pathogens, dead cells, and molecular patterns associated with damage in a non-inflammatory manner. Therefore, a defect in autophagy may cause inflammation and stimulate or exacerbate inflammatory diseases (33). During IF, the decrease in glycogen leads to a shift in metabolism towards fatty acids and ketones, which activates the autophagy process by inhibiting the mTOR pathway. Autophagy helps recycle aggregated proteins and cellular debris and plays a role in the differentiation and survival of immune cells (34). Studies have shown that IF can lead to the expression of autophagy-related genes, including ATG5, ULK1, and BECN1, which may contribute to the beneficial effects of fasting on cellular function and protection against inflammatory diseases (35). In general, IF has been shown to improve cellular function and protect against inflammatory diseases by enhancing autophagy.

Chronic Inflammatory Diseases and Intermitting Fasting

Non-Alcoholic Fatty Liver Disease (NAFLD) and Intermitting Fasting

NAFLD is a metabolic disorder characterized by lipid accumulation, insulin resistance, and inflammation. Lipotoxic metabolites cause mitochondrial dysfunction, oxidative stress, and activation of pro-inflammatory pathways. Free fatty acids contribute to hepatic steatosis and insulin resistance. Inflammation and fibrosis in the liver are driven by gut-derived lipopolysaccharides, translocated gut bacteria, certain metabolites, and injured hepatocytes. Resident hepatic macrophages release proinflammatory cytokines that promote the infiltration of circulating monocytes that differentiate into macrophages, contributing to non-alcoholic steatohepatitis (NASH) progression by activating hepatic stellate cells (36-38). Lifestyle changes, including healthy diet and increased physical activity, are necessary for treating NAFLD as no medication or surgical procedure has been approved (39).

IF as a dietary intervention has received attention in recent years and shows promising results for attenuating the development and progression of NAFLD. IF has been found to have metabolic benefits on the liver, independent of caloric restriction and weight loss, which can improve NAFLD histology. Fasting shifts the metabolic circuitry to increase hepatic lipid oxidation, decrease lipogenesis, and use ketones as the primary energy source. Ketones enhance the efficacy of mTOR and AMPK pathways, improving the liver's ability to break down excess triglycerides (40). During Ramadan, it was found that daily TRF significantly improved non-invasive markers of fatty liver disease, reduced insulin resistance, induced weight loss, and improved inflammatory markers (including IL6 and CRP) (41). A randomized control trial showed that ADF and TRF were effective diet therapies for individuals with NAFLD in a 12-week study. Both ADF and TRF led to significant reductions in body weight and fat mass, as well as improvements in lipid profiles. ADF was particularly effective in reducing total cholesterol levels (42). The study by Varkaneh *et al*. revealed that the 5:2 IF diet decreased inflammatory biomarkers (hs-CRP and CK-18) in NAFLD patients, but did not significantly affect total antioxidant capacity. The reduction in hs-CRP and CK-18 levels suggests that the diet may have a beneficial effect on inflammation in NAFLD patients (43).

A systematic review and meta-analysis by Yin *et al.* (2021) evaluated the effects of IF on NAFLD in 6 studies by including 417 patients with NAFLD who had underwent dietary intervention with ADF and Ramadan fasting. The results showed significant differences in body weight, body mass index (BMI), alanine aminotransferase (ALT), and aspartate transaminase (AST) between the control and fasting groups. However, no significant changes

were observed in hepatic stiffness, fasting blood sugar (FBS), HOMA-IR, an indicator of insulin resistance, total serum triglycerides, total serum cholesterol, low density lipoprotein (LDL), or high density lipoprotein (HDL) levels (44).

Lange *et al.* (2023) in another systematic review and meta-analysis evaluated the effects of IF on anthropometric, biochemical, and hepatic endpoints in patients with NAFLD. The analysis included 14 studies and found that fasting interventions including 5:2 diet, ADF, TRE, and Ramadan fasting led to significant improvements in body weight, BMI, waist-to-hip ratio, ALT, AST, hepatic steatosis, and hepatic stiffness. Total serum triglycerides and HOMA-IR also showed significant reductions. No significant changes were observed in total serum cholesterol or HDL levels (45). IF has been found to have metabolic benefits on the liver, independent of caloric restriction and weight loss, which can improve NAFLD histology. Fasting shifted the metabolic circuitry to increase hepatic lipid oxidation, decrease lipogenesis, and use ketones as the primary energy source. It was shown that IF, including ADF, TRF, and Ramadan fasting, can significantly improve body weight, BMI, hepatic steatosis, ALT, AST, and hepatic stiffness in patients with NAFLD (45) (Figure 2).

Cardiovascular Disorders and Intermittent Fasting

It was found that IF has numerous positive effects on cardiovascular health. It is due to its ability to regulate various risk factors involved in the development of cardiovascular diseases. There are multiple proposed mechanisms by which IF can lead to better cardiovascular outcomes. This dietary pattern reduces the risk of cardiovascular disease by improving weight control, high blood pressure, dyslipidemia, insulin resistance, and diabetes. IF affects various pathways, such as reducing oxidative stress, optimizing circadian rhythm, ketogenesis, and reducing inflammatory markers (46, 47). IF changes the glucose-ketone metabolic pathway, using fatty acids and ketones as the primary energy source, reducing body mass and positively impacting lipid profile parameters. Reduction in total cholesterol (TC), triglycerides, and LDL cholesterol, accompanied by a decrease in the size of these molecules, is one lipid profile change that reduces the risk of cardiovascular diseases. One of the critical changes following IF is the reduction of LDL, which plays a crucial role in preventing cardiovascular disorders. Excess LDL accumulates in the sub-epithelial layer of arterial walls and is oxidized into oxLDL. The combination of oxLDL causes inflammation and the presence

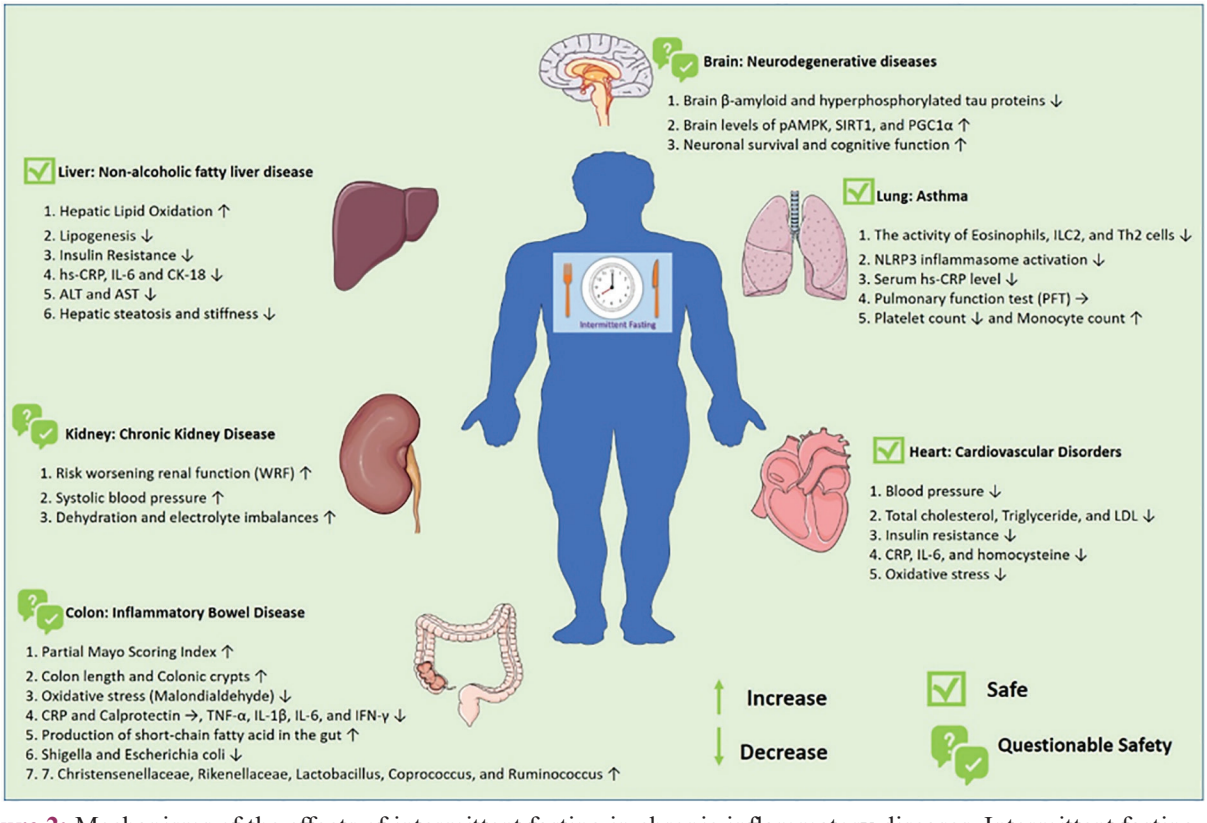

Figure 2: Mechanisms of the effects of intermittent fasting in chronic inflammatory diseases. Intermittent fasting can increase or decrease the number of cells and metabolites involved in inflammation through its effects on autophagy, the immune system, metabolic pathways, and probiotic changes. While intermittent fasting is considered safe for non-alcoholic fatty liver disease and cardiovascular diseases, there are concerns about its safety in chronic kidney disease and inflammatory bowel disease.

of monocytes in the inner membrane of blood vessels, which are internalized by macrophages and transformed into foam cells. Foam cells are associated with the formation of atherosclerotic plaques and cardiovascular diseases (48-50).

IF reduces pro-inflammatory factors such as CRP, IL-6, and homocysteine by decreasing the production of leptin and resistin and increasing the production of adiponectin from adipose cells. The reduction in pro-inflammatory factors reduces platelet accumulation, proliferation of endothelial cells, and migration of monocytes to the inner membrane of blood vessels, and foam cell formation from macrophages. These changes prevent the formation of atherosclerotic plaques in arterial vessels and reduce the risk of atherosclerosis. Since atherosclerosis is responsible for most deaths from cardiovascular diseases worldwide, IF reduces the risk of cardiovascular diseases (47, 48, 51). Human and animal studies have shown that IF decreases systolic and diastolic blood pressure and heart rate after a few weeks (52, 53). The mechanism behind the decrease in blood pressure involves an increase in parasympathetic activity due to brain-derived neurotrophic factor (BDNF), increased elimination of noradrenaline through the kidneys, and increased sensitivity to natriuretic and insulin peptides (47, 54, 55). However, the cardiovascular benefits of decreased blood pressure from IF do not persist beyond the fasting period, and blood pressure levels return to their initial values after the fast (56).

Oxidative stress plays a significant role in myocardial infarction, ischemia/reperfusion injury, or heart failure (57). IF reduces the production of free radicals by mitochondria due to decreased energy intake. The reduction in oxidative stress factors such as nitrotyrosine, 8-isoprostane, protein carbonyls, and increased levels of 4-hydroxynoneal adducts and higher levels of uric acid antioxidants can directly affect the structure and function of cardiac cells and improve protection against cardiovascular diseases (46, 52, 58). IF can improve heart health through circadian rhythm by allowing optimization with the body's peripheral clocks, decreasing insulin levels later in the day, and improving glucose control, lipid levels, hormonal secretion, and inflammation when appropriately timed (59). BaHammam *et al.* reported that diurnal IF during Ramadan may have cardiometabolic benefits, including weight loss, improved lipid profile and glycemic control, lower proinflammatory markers, and reduced oxidative stress (60). Circadian misalignment caused by late dinners and nighttime eating can lead to insulin resistance, obesity, and cardiovascular diseases. Various time-restricted fasting regimens have shown different results based on timing, highlighting the circadian system's influence on this dietary pattern (46, 60) (Figure 2). So IF can be an effective strategy for improving cardiovascular health by managing weight, controlling blood pressure and lipids, reducing insulin resistance, optimizing circadian rhythm, promoting ketogenesis, and lowering inflammation (60).

Inflammatory Bowel Disease and Intermittent Fasting

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract. The two common types of IBD are Crohn's disease and ulcerative colitis. Crohn's disease is characterized by segmental transmural inflammation and granulomas that affect any part of the gastrointestinal tract. Ulcerative colitis presents as inflammation of the mucosal lining of the large intestine and rectum. Negm *et al*. demonstrated that IF during the month of Ramadan does not cause any significant changes in inflammatory markers such as CRP and calprotectin in patients with IBD. However, following IF, there was a significant increase in the Partial Mayo Score, indicating a worsening of clinical status. This effect was more pronounced in older patients and those with higher baseline levels of calprotectin. Nevertheless, there were no adverse effects on quality of life or levels of depression. They suggested that IF should be cautiously recommended for patients with IBD (61). Two randomized controlled trials were conducted by Rangan *et al*. and Song *et al*. to investigate the effect of a fasting-mimicking diet on a murine model of ulcerative colitis. The results of these studies demonstrated that the fasting-mimicking diet increased the frequency of stem cells, improved gut microbial dysbiosis, increased colon length, increased colonic crypt, reduced some inflammatory markers including CD4+, CD8+, and CD11b cells in the intestinal epithelium, and ultimately reduced colonic inflammation (62, 63).

Zhang *et al*. conducted a randomized controlled trial to compare the effects of two types of IF, including TRF and ADF, on a dextran sodium sulfate-induced colitis mouse model. The study showed that TRF was effective treatments for improving colitis compared to ADF. Also TRF increased survival rate, reduced disease activity index score, increased colon length, and decreased histological score in mice with colitis (64). The mechanisms involved in the effectiveness of these dietary interventions included reducing oxidative stress (decreasing malondialdehyde), reducing inflammatory cytokines (TNF-α, IL-1β, IFN-γ and IL-6), improving microbial dysbiosis (increasing Christensenellaceae, Rikenellaceae,

Lactobacillus, Coprococcus, and Ruminococcus and decreasing Shigella and *Escherichia coli*), and increasing short-chain fatty acid production in the gut (64, 65) (Figure 2). IF during Ramadan does not significantly affect inflammatory markers in IBD patients, but may worsen clinical status. However, a fasting-mimicking diet and certain types of IF, such as TRF and intermittent-energy restriction, were shown to improve colitis in animal models by increasing stem cells, improving gut microbial dysbiosis, reducing inflammation and oxidative stress, and increasing short-chain fatty acid production. In general, IF should be cautiously recommended for IBD patients (64, 65).

Chronic Kidney Disease and Intermitting Fasting

Several studies were conducted to investigate the impact of Ramadan fasting on individuals with chronic kidney disease (CKD). The findings revealed that fasting was well-tolerated by these patients and resulted in positive outcomes such as increased glomerular filtration rate (eGFR), reduced proteinuria and urinary sodium levels, and improved lipid profiles. These suggested that patients with CKD should be encouraged to fast during Ramadan (66-68). However, Bragazzi *et al*. expressed in a systematic review that there is no conclusive evidence regarding the safety of Ramadan fasting for patients with CKD, and healthcare professionals should take necessary precautions in this regard (69). Bakhit *et al*. conducted a single-arm prospective observational study including 65 patients with stage 3 or higher CKD. They observed that 33.8% of patients experienced worsening renal function (WRF), with 15 during Ramadan and 7 in the three months after. They also found that advanced CKD stage, higher baseline systolic blood pressure, and younger age were independently associated with WRF. The study suggested that physicians should inform CKD patients about the potential adverse effects of fasting on kidney function and closely monitor their kidney function during Ramadan (70).

In 2021, Malik *et al.* conducted a literature review on the effects of Ramadan fasting on patients with CKD. They found that Ramadan fasting adversely affected patients with moderate to severe CKD, particularly those in stages 4 and 5, at higher risk of renal function deterioration due to dehydration and electrolyte imbalances. However, stable CKD non-dialysis (CKD-ND) patients up to stage 3 may be able to fast safely if closely monitored and adhered to medical advice. Patients with CKD and known cardiovascular diseases should be discouraged from fasting. Hydration after breaking the fast is crucial for patients prone to stone formation and urinary tract infections. According to Malik *et al.*'s study, individuals with CKD who intended to fast during Ramadan should undergo a thorough risk assessment a month prior. This is because fasting may necessitate changes in medication and a monitoring plan for kidney function and electrolyte levels. Sometimes, patients may need to stop or break their fasting (71) (Figure 2). Therefore, while some studies suggest that fasting during Ramadan may have positive outcomes for patients with CKD, there are no conclusive evidences regarding the safety. Patients with moderate to severe CKD, particularly those in stages 4 and 5, are at higher risk of renal function deterioration due to dehydration and electrolyte abnormalities. Therefore, patients with CKD, especially those with CKD and known cardiovascular disease, should undergo a thorough risk assessment before fasting and be closely monitored by healthcare professionals (71).

Neurodegenerative Diseases and Intermitting Fasting

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, frontotemporal dementia, and Huntington's disease, are age-dependent disorders impacting millions globally, particularly the elderly. These conditions involve the progressive loss of neurons and their functions, resulting in debilitating neurological disabilities without cure. The underlying causes of neurodegenerative diseases are multifactorial, involving a combination of genetic, environmental, and endogenous factors. Common pathological mechanisms include abnormal protein dynamics, oxidative stress, mitochondrial dysfunction, DNA damage, neurotrophin dysfunction, and neuroinflammatory processes. Oxidative stress and protein toxicity, in particular, play crucial roles in diseases like Alzheimer's and Parkinson's. The activation and recruitment of immune cells through the TNF cytokine contribute to the propagation of inflammation and oxidative stress, further promoting neurodegeneration. Overall, these diseases pose significant challenges to both human health and society (72, 73).

IF may help protect against Alzheimer's disease by reducing levels of β-amyloid and hyperphosphorylated tau proteins in the brain. Fasting increases ketone bodies, which protect against β-amyloid toxicity. Study on animals demonstrated that IF has a positive impact on brain health by reducing the level of brain β-amyloid through various mechanisms. When assessing the impact of IF on β-amyloid levels in humans, conflicting results were noticed. However, it may be

possible that IF could reduce β-amyloid deposition in cases of late-onset of sporadic Alzheimer's disease (74). Mitochondria are responsible for producing energy and regulating cellular processes, and their dysfunction has been linked to neurodegeneration (75). IF has been found to improve mitochondrial function and protect against neurodegeneration by promoting mitochondrial biogenesis, increasing mitochondrial respiration, and activating adaptive cellular stress responses and signaling pathways. IF also activates autophagy, which clears out toxic proteins that contribute to neurodegeneration. The effects of IF are complex and require sensors of energy metabolism, signaling, and transcriptional pathways that improve mitochondrial bioenergetics, biogenesis, and dynamics. Gut microbiota may also mediate the neuroimproving effects of IF. However, caution should be exercised as IF is unsuitable for specific populations and can cause side effects such as hypoglycemia, dehydration, and malnutrition. Developing therapeutic strategies to ameliorate mitochondrial function may be a possible intervention to delay or prevent neurodegeneration and increase lifespan (76).

IF has been shown to improve mitochondrial function in various organs, including the brain, liver, and skeletal muscle. The mechanism underlying these effects involves the activation of the AMP-activated protein kinase (AMPK), which enhances the level of peroxisome proliferator-activated receptor gamma coactivator1alpha (PGC1α). PGC1α then stimulates sirtuin 1/3 (SIRT1/3), which promotes mitochondrial biogenesis (77, 78). In addition, IF increases the expressions of Mfn1, Mfn2, and Opa1; while decreasing those of Drp1 and Fis1, enhancing mitochondrial dynamics and maintaining the rate of fusion/fission, which improves mtDNA integrity (79). IF also increases autophagy, which enhances the clearance of amyloid-beta (Aβ) and reinforces mitochondrial protein synthesis, producing more ATP for neuronal survival. Moreover, IF promotes lipolysis, leading to more production of β-hydroxybutyrate (β-OHB), which passes through the blood-brain barrier and binds to receptors (GPR109A and Hcar2) in brain cells. GPR109A and Hcar2 elevate the pAMPK, SIRT1, and PGC1α levels and lead to improved neuronal survival and cognitive function (80) (Figure 2). IF has potential neuroprotective effects against neurodegenerative diseases such as Alzheimer's and Parkinson's by reducing β-amyloid and hyperphosphorylated tau proteins, improving mitochondrial function, and activating autophagy. However, caution should be exercised as IF can cause side effects and is unsuitable for specific populations. Developing therapeutic strategies to ameliorate mitochondrial function may be a possible intervention to delay or prevent neurodegeneration and increase lifespan (80).

Asthma and Intermitting Fasting

Asthma is a chronic disease that affects millions of people worldwide and is characterized by airway inflammation, intermittent airflow obstruction, and bronchial hyperreactivity. The pathophysiology of asthma is complex and involves a number of factors including genetic, environmental and immunological factors (81). Changes in dietary patterns may have contributed to the increasing prevalence of asthma over the past few decades. Observational studies suggest that intake of fresh foods, particularly fruits and vegetables, may have a protective effect against asthma. On the other hand, a high-fat diet can increase airway inflammation, while antioxidants found in fruits and vegetables may lower inflammation (82, 83). Alongside various dietary interventions such as ketogenic diets, Mediterranean diets, and others, which have been studied for their effects on the condition of asthma patients (82, 84), while another intervention is IF. Most studies related to the effects of IF on asthma patients have focused on Ramadan fasting, with less research on other types of IF (82-84).

Ramadan fasting does not significantly affect spirometry indices in patients with moderate to severe asthma, according to Ghaffary *et al*.'s study. They suggest that fasting during Ramadan can be considered safe for patients with asthma (85). In another study by Askari *et al*., the effects of Ramadan fasting on patients with asthma were investigated. Their results showed a decrease in platelet count and serum hs-CRP level, as well as an increase in monocyte count after one month of fasting. They reported that pulmonary function test (PFT) values did not change significantly after the month of Ramadan fasting, but some respiratory symptoms, particularly wheezing, decreased. They emphasized that Ramadan fasting is not only safe for patients with asthma but may also have a positive impact on the severity of asthma through reducing inflammatory biomarkers and respiratory symptoms (86). In agreement with this study, Aydin *et al*. also reported that Ramadan fasting is safe for patients with asthma who were taking prescribed medications (87). Suzuki *et al*. investigated the mechanisms involved in IF in asthma and demonstrated that this diet can suppress eosinophils, innate type 2 lymphoid cells (ILC2), effector CD4+ T cells, and Th2 cytokines in the lungs of eosinophilic asthma mice and lead to an improvement in asthma symptoms (88). Han *et al.* showed that modified ADF blunts the NLRP3 inflammasome and Th2

cell activation in steroid-naive asthmatics, reduces airway epithelial cell cytokine production, and potentially regulates inflammation in asthma. They also found that prolonged fasting did not significantly affect pulmonary function testing in subjects with mild asthma (89) (Figure 2). Although further studies are needed to investigate the effects of various types of IF on asthma, based on current research, it appears that IF may be a safe dietary intervention for asthmatics that can improve symptoms by reducing inflammatory responses. It should be noted that this dietary intervention cannot replace prescribed medications for asthma patients (89).

Conclusion

Taken together, IF has emerged as a promising dietary intervention for preventing and managing chronic inflammatory diseases. The metabolic, immunomodulatory, and microbiome-related effects of IF have been shown to improve NAFLD, cardiovascular health, and asthma while potentially providing neuroprotective effects against neurodegenerative diseases such as Alzheimer's and Parkinson's. However, caution should be exercised when recommending IF for patients with IBD and CKD due to potential worsening of clinical status or dehydration and electrolyte abnormalities. IF may be a safe and effective strategy for preventing and managing chronic inflammatory diseases. However, patient needs should be carefully considered before recommending this dietary intervention. Further studies are needed to investigate the effects of various types of IF on other chronic inflammatory diseases.

Acknowledgement

The authors wish to apologize to the all authors whose outstanding study has not been mentioned here due to space limitations. During the preparation of this literature review, we used ChatGPT (OpenAI) in order to improve the quality and accuracy of writing by identifying grammar mistakes and introducing new words and phrases.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contribution

All authors should have made substantial contributions to all of the following: (i) the conception and design of the study, (ii) drafting the article or revising it critically for important intellectual content, and (iii) final approval of the version to be submitted.

Conflict of Interest

The authors declare no potential conflicts of interest.

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