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Literature Review Outline: Fasting, Endothelial Dysfunction, and Autoimmune Diseases

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Abstract

Intermittent fasting (IF) has emerged as a promising non-pharmacological intervention to mitigate cardiovascular risk and systemic inflammation in patients with autoimmune diseases. This review explores the mechanistic links between IF and improved endothelial function, with a focus on oxidative stress reduction, immune modulation, and metabolic reprogramming. Evidence from in vitro, animal, and early-phase human studies indicates that IF enhances nitric oxide availability, reduces pro-inflammatory cytokines, and promotes vascular protection through ketone body production and autophagy. While benefits such as improved flow-mediated dilation and decreased markers of vascular inflammation have been observed, significant challenges remain regarding the variability of fasting protocols, individual response, and the scarcity of long-term randomized controlled trials. Tailored fasting strategies, supported by omics approaches and circadian alignment, may provide a valuable adjunct in managing cardiovascular complications in autoimmune populations. Further research is essential to clarify the safety, efficacy, and personalization of IF regimens in this context.

Keywords: Intermittent Fasting, Endothelial Dysfunction, Autoimmune Diseases, Inflammation, Cardiovascular Risk.

Introduction

As the focus on health interventions aimed at chronic inflammation, immune responses, and cardiovascular health increases, intermittent fasting (IF) has received heightened attention as a non-pharmacological health strategy. In autoimmune diseases, IF appears promising for improving endothelial function, and in this paper, the mechanisms that allow intermittent fasting to modulate endothelial function in autoimmune diseases are explored along with their associated clinical outcomes.

Endothelial dysfunction is the inability of the endothelium to maintain vascular homeostasis and a hallmark of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus

(SLE), and multiple sclerosis (MS). Normally, the endothelium can regulate vascular tone, hemostasis, and inflammation, but in autoimmunity, chronic inflammation and aberrant immune activity leads to endothelial injury. This leads to reduced nitric oxide (NO) bioavailability, increased oxidative stress, and greater expression of adhesion molecules such as VCAM-1 and ICAM-1, all contributing to leukocyte migration, vascular injury, and increased cardiovascular risk independently of traditional risk factors. For example, inflammatory cytokines such as TNF-α and IL-6 in RA, and type I interferon in SLE, are thought to lead to accelerated atherosclerosis, while endothelial dysfunction plays a critical role in blood-brain barrier disruption and neuroinflammation in MS. These factors may all contribute to the heightened cardiovascular morbidity and mortality seen in autoimmune diseases, highlighting the need for interventions that can target the vascular endothelium. Fasting, in its many forms such as intermittent fasting, prolonged fasting, and fasting-mimicking diets, has demonstrated both anti-inflammatory and vascular protective effects. Evidence suggests that fasting reduces oxidative stress by increasing antioxidant defenses, as well as improving NO balance via elevated eNOS expression. Several studies have reported decreased levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-17, and mechanistic studies implicate both autophagy and lipid metabolism in the attenuation of endothelial inflammation. In obesity and metabolic syndrome, fasting improves parameters of vascular function, such as FMD. Experimental studies have also shown that fasting can decrease atherosclerotic lesion development. However, evidence connecting improvements in vascular function during fasting to disease outcomes in autoimmunity remains elusive. The overarching research question is: What are the mechanisms of the effect of intermittent fasting on endothelial function in autoimmune diseases and what are the clinical implications of these changes? This paper seeks to examine the mechanisms by which IF can modify endothelial function in autoimmune disease and the clinical outcomes associated with these changes. Of particular interest are the mechanistic observations that pertain to inflammation, oxidative stress, and metabolism, and their subsequent effects on vascular function and cardiovascular risk. The methodology of this paper is based upon a literature review using published work on in vitro, in vivo, clinical, and molecular studies of fasting on vascular function, inflammation, and metabolism. Each study and analysis was reviewed and summarized in order to compare and contrast existing data. Historical and source criticisms were performed when applicable to assess the reliability of the source and the validity of the analysis. The content is synthesized from established principles of rheumatology, endocrinology, and vascular biology to elucidate a cohesive assessment of the connections between fasting, immune activation, and vascular health. Animal studies and early-phase human studies support the beneficial anti-inflammatory and endothelial-protective effects of fasting in autoimmunity. However, variable study design and the dearth of large, long-term human studies targeting vascular endpoints make conclusions challenging. Ramadan fasting improves disease symptoms in RA, while prolonged fasting improves SLE disease activity. However, the effects of these interventions on endothelial function as well as the overall generalizability and durability of these interventions remain to be seen.

Understanding Intermittent Fasting and Endothelial Function

This section explores the fundamental principles of

intermittent fasting and its influence on endothelial function, emphasizing mechanisms that support vascular health. By examining metabolic, hormonal, and cellular responses, it lays the groundwork for understanding how dietary timing can modulate inflammation and endothelial integrity—key factors in autoimmune disease management. These insights provide crucial context for subsequent discussions on vascular protection and therapeutic strategies within the broader scope of autoimmune and cardiovascular health.

Principles of Intermittent Fasting

Intermittent fasting (IF) encompasses alternate-day fasting, time-restricted feeding, and the 5:2 diet, each of which manipulates the timing and frequency of food intake (Li et al., 2023). These protocols have distinct effects on metabolism, hormone regulation, and cell turnover. For instance, in alternate-day fasting, a regular day of eating alternates with a day of fasting, while in time-restricted feeding, eating takes place within a limited period (Li et al., 2023). This affects the length of fasting periods, metabolism, and adherence, all of which are vital parameters in the management of chronic diseases. It should be noted that IF protocols, by targeting the circadian rhythm, can enhance gene expression for metabolism, inflammation, and blood vessel function, improving cardiovascular health and reducing systemic inflammation. This may be important for patients with autoimmune diseases and chronic inflammation (Li et al., 2023).The cellular and hormone responses to IF include reductions in circulating insulin, increases in glucagon, and the activation of AMPK and SIRT1. They lead to autophagy, mitochondrial biogenesis, and lower oxidative stress, thereby forming a protective defense against vascular complications (Adawi & Aamar, 2025). Alternate-day fasting yields better improvements in the biomarkers, while time-restricted feeding is more feasible for long-term use (Li et al., 2023). This shows that protocols that target individual needs may be more efficacious. A key health mechanism of IF is the metabolic switch from utilizing glucose to fat for energy, leading to increased ketone body production. This enhances cellular stress resistance and supports repair mechanisms that reduce inflammation (Mishra et al., 2024). As hepatic glycogen stores are depleted during fasting, lipolysis increases and fatty acids as well as ketone bodies are released. This increases insulin sensitivity and lowers serum glucose and insulin (Adawi & Aamar, 2025), ultimately leading to decreased endothelial activation and inflammation. During IF, ketone bodies modulate vascular signaling pathways by inhibiting NLRP3 inflammasome activation, increasing antioxidant defense genes, alleviating oxidative stress, and preventing endothelial damage. As oxidative stress and endothelial injury are hallmarks of autoimmune diseases (Mishra et al., 2024), this shows that ketone body levels may be an indicator of overall success. IF also decreases vascular toxicity of advanced glycation end-products (AGEs) as glucose levels are decreased (Li et al., 2023). This may be particularly important in autoimmune patients with metabolic syndrome who suffer from higher AGE deposition in their arteries. Finally, IF promotes autophagy and mitochondrial efficiency for damaged cell removal and regeneration of endothelial tissue and vascular walls, leading to protection of vessels injured by immune activation (Adawi & Aamar, 2025). Autophagy occurs during nutrient scarcity, as it is responsible for clearing proteins and cellular constituents for reutilization and removal (Adawi & Aamar, 2025). In immune and endothelial cells, autophagy helps to regulate

cellular stress as well as antigen presentation, limiting the activation of autoreactive T cells (Adawi & Aamar, 2025). This process also removes damaged immune cells and replenishes hematopoietic stem cells, thereby regenerating and reducing autoreactivity (Adawi & Aamar, 2025). In particular, the clearance of autoreactive T cells may lead to remission in autoimmunity. IF promotes immune system recalibration and shifts the immune balance toward enhanced Treg cells and tolerance in autoimmunity. Even though IF promotes improved immune regulation, there are a number of gaps in this area (Adawi & Aamar, 2025). Current studies have utilized different fasting approaches in the context of autoimmunity (Adawi & Aamar, 2025). This causes discrepancies in the effects of the fasting interventions on various immune cell subsets and biomarkers associated with autoimmunity. There are limited studies assessing the effectiveness of intermittent fasting in humans with autoimmunity, and very little human data assessing the effects of intermittent fasting on the different immune cell subsets and biomarkers of autoimmunity in the context of different types of intermittent fasting protocols. Thus, there are gaps regarding which types of fasting protocols improve certain immune markers and subtypes of autoimmune diseases. IF improves vascular function by reducing pro-inflammatory cytokines such as TNF-α and IL-6, and it improves vascular function through endothelial-dependent vasodilation, which enhances cardiovascular risk factors (Venetsanopoulou et al., 2019). As such, IF may be an alternative therapeutic approach to improve both cardiovascular and autoimmune health. Though data are limited, several human studies have shown the benefits of IF on cardiovascular health and risk factors. In individuals fasting during Ramadan, C-reactive protein (CRP), TNF-α, and leptin were significantly reduced, suggesting reduced levels of vascular inflammation. These cytokines are known mediators that propagate and intensify vascular inflammation in both cardiovascular and autoimmune pathologies (Venetsanopoulou et al., 2019). Some of the most profound effects of intermittent fasting are those it has on vascular health. In individuals that were metabolically healthy, but were obese or of poor metabolic health, intermittent fasting led to improved flow-mediated dilation, which is a marker for vascular health (Esmaeilzadeh & van de Borne, 2016). Patients with autoimmune disease and metabolic syndrome could benefit from IF as blood glucose may improve insulin sensitivity (Esmaeilzadeh & van de Borne, 2016). In those that undergo intermittent fasting, both healthy individuals as well as patients with metabolic syndrome demonstrated improvement in blood flow and microvascular reactivity, with both showing improved cardiovascular outcomes as a result (Esmaeilzadeh & van de Borne, 2016). However, there was also observed in some populations that LDL cholesterol levels were increased and blood glucose increased with short-term time-restricted fasting (Esmaeilzadeh & van de Borne, 2016), which makes this a vital consideration in protocol selection. As such, the varied outcomes of fasting strategies depend on the length and the amount of caloric restriction during feeding periods, as well as differing activity rates among various autoimmune disease states, making it difficult to translate protocols (Venetsanopoulou et al., 2019). As many interventions are short-term, only looking at intermediate endpoints, more studies are needed for IF protocols that target vascular and autoimmune conditions over extended durations. Additionally, intermittent fasting can cause malnutrition (Adawi & Aamar, 2025) and disease flares if performed incorrectly, especially for those with certain autoimmune disor-

ders and chronic health conditions. In some circumstances, intermittent fasting may even exacerbate symptoms of certain disorders such as hypothyroidism and fibromyalgia (Adawi & Aamar, 2025). Furthermore, research is lacking regarding the efficacy of the specific types of IF protocols, as well as information regarding the effectiveness of fasting in the male versus female biological sex. Much research and trials need to occur within autoimmunity that directly analyzes fasting with regard to a number of health factors such as vascular health, and with direct comparison between types of IF protocols in autoimmunity. There is also a lack of omics analyses assessing IF effects. Studies with omics approaches, such as transcriptomics and metabolomics, in the context of IF and autoimmunity are needed to discover personalized mechanisms driving these therapeutic effects. This would improve therapeutic success in each individual. Future studies need to involve well-designed RCTs that have been conducted for substantial periods of time in order to evaluate the potential to achieve improvements in autoimmune disease symptoms, as well as improvements of vascular function. RCTs are crucial for establishing clinical applicability, safety, and effectiveness of these IF protocols. By analyzing fasting with RCTs within populations of autoimmune patients, we may be able to discover which IF protocols are the most useful and beneficial, as well as their effectiveness in these patients with regard to all factors such as improvement of autoimmune disease. A RCT to assess and compare specific types of IF protocols in autoimmunity may allow us to better determine the usefulness of these different intermittent fasting strategies in autoimmunity. We need to be able to personalize and tailor a patient's protocol to fit their lifestyle and diagnosis to better suit their needs and increase patient satisfaction, thus increasing the likelihood of long-term adherence and improvements in overall health. By adding and integrating omics research for both humans and model organisms, we can also gain a better understanding of how these effects are occurring, thus allowing us to tailor and personalize protocols for each individual, based on their needs.

Endothelial Function in Autoimmune Diseases

Endothelial dysfunction plays an important pathological role in autoimmune diseases, triggered by chronic systemic inflammation. It is mediated by sustained production of reactive oxygen species (ROS) and upregulation of TNF-α, IL-6 and IL-1β. Inflammatory cytokines and ROS directly damage endothelial cells and inhibit the bioavailability of NO, a potent vasodilator, leading to disturbed vasodilation and vasoconstriction and endothelial activation. Endothelial activation involves the alteration of the endothelium from a homeostatic status into a pro-inflammatory and pro-thrombotic state (Murdaca et al., 2012; McKellar et al., 2009). In addition, chronic oxidative stress contributes to decreased NO availability. NO reacts with ROS and yields peroxynitrite, a reactive nitrogen species, causing endothelial activation and the upregulation of adhesion molecules, such as VCAM-1 and ICAM-1. Adhesion molecules promote the adhesion and trans-endothelial migration of leukocytes into the vascular wall and support the immune cell infiltration and local tissue damage (Murdaca et al., 2012; Kaplan, 2009).The innate and adaptive immune responses also contribute to endothelial activation and injury. Innate immunity through scavenger receptors and toll-like receptors is involved in increased macrophage and dendritic cell activity as well as the responses to self-antigens modified by oxidation. In addition, autoantibodies produced by the adaptive immunity target endothelial cell components, thus triggering local and systemic damage

of vessels (Murdaca et al., 2012). Moreover, animal and clinical studies found early atherosclerosis in rheumatoid autoimmune conditions because inflammation is known to initiate the accelerated development of atherosclerosis, through dyslipidemia, impaired vascular reactivity and endothelial dysfunction (McKellar et al., 2009). In RA, for example, persistently elevated TNF-α and IL-6 are correlated with the inhibition of eNOS and NO production, thus increasing oxidative stress and premature atherosclerosis (McKellar et al., 2009). In SLE, autoantibodies and IFN-α through the type I interferon signaling promote apoptosis and disrupt repair mechanisms of endothelial cells, thus contributing to the microvascular complications in SLE (Murdaca et al., 2012; Kaplan, 2009). In MS, the immune-mediated microvascular injury is exemplified by blood-brain barrier destruction. Once the blood-brain barrier is disturbed, the activated endothelial cells induce T cell migration and neuroinflammation (Murdaca et al., 2012). Additionally, microvascular obliteration and smooth muscle cell proliferation is the characteristic of the vascular injury in systemic sclerosis (Murdaca et al., 2012).Dyslipidemia is also considered an independent cardiovascular risk factor for autoimmune diseases, and it is frequently seen in patients with SLE, who presented elevated triglycerides and LDL levels and decreased HDL levels and ApoA1 (Bertoni et al., 2024). Juvenile SLE patients presented increased LDL levels and lower HDL levels than healthy children, which suggests the important role of dyslipidemia for early-onset cardiovascular morbidity in juvenile SLE patients (Bertoni et al., 2024). Another common characteristic of chronic inflammatory disorders is insulin resistance. In RA patients, elevated levels of TNF-α, IL-1α and IL-6 are correlated with decreased endothelial-dependent vasodilation (Ciaffi et al., 2021). Individuals with autoimmune disease, for example, SLE, are at a two-fold higher risk of cardiovascular events compared to the normal population (Murdaca et al., 2012; Kaplan, 2009). In summary, endothelial dysfunction plays an important role in triggering vascular events in patients with autoimmune diseases. Subclinical vascular injuries should be screened in autoimmune disease patients, because individuals with abnormal vascular profiles are more likely to develop cardiovascular diseases and may develop into overt cardiovascular disease (McKellar et al., 2009). Emerging evidence has shown a protective effect of the ketogenic diet on inflammatory and metabolic markers in rheumatic autoimmune diseases. In contrast, the dietary guidelines in general for autoimmune diseases mostly address the general cardiovascular risk factors, whereas these patients also present disease-related factors that contribute to the cardiovascular risk. Considering the metabolic and immune disturbances in patients with autoimmune diseases, both the traditional and disease-specific cardiovascular risk factors need to be investigated in clinical practice (Bertoni et al., 2024). To sum up, patients with rheumatic autoimmune diseases had increased cardiovascular mortality and morbidity independent of the classical risk factors such as hypertension, hyperlipidemia and smoking. The incidence of accelerated atherosclerosis in autoimmune diseases has been shown in clinical and experimental animal studies to be related to chronic immune activation and injury (Murdaca et al., 2012). Vascular damage may be prevalent even when cardiovascular disease is not obvious. Since vascular injury begins at the subclinical level, the use of standard cardiovascular disease risk scoring systems can be misleading (Kaplan, 2009). It is important to monitor subclinical atherosclerosis and microvascular dysfunction in patients with RA or other autoim-

mune diseases by vascular function tests, because early vascular evaluation may allow for the optimization of the use of immunosuppressants to improve vascular health and clinical outcomes (McKellar et al., 2009).

Mechanisms of Fasting-Induced Vascular Protection

In order to understand the protective effect of fasting regarding vascular health, we must look at some mechanisms of influence. These mechanisms are going to be oxidative stress reduction, inflammation reduction, and metabolic shift/ adaptation.

Oxidative Stress and Inflammation

Intermittent fasting (IF) reduces oxidative stress in endothelial cells by upregulating endogenous antioxidants. This occurs through increased activity of GPX and SOD, enzymes that neutralize ROS such as superoxide. This is enhanced by decreased activity of NADPH oxidase, a major source of superoxide anions, and depends on eNOS function. Absence of eNOS inhibits the vasoprotective effects of IF (Savencu et al., 2021). These mechanisms address a prime driver of endothelial dysfunction in autoimmune diseases. However, due to the large variability in pre-existing oxidative stress, as well as the variance in human response to IF, it can be challenging to translate this knowledge to multiple patient populations. Animal and translational studies demonstrate that fasting has strong anti-inflammatory effects. Circulating concentrations of inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, are profoundly reduced by IF. For example, in a murine model of rheumatoid arthritis, IF led to decreased mRNA levels and serum concentrations of these inflammatory cytokines. In turn, IF decreased joint inflammation, synovial hyperplasia, tissue remodeling, cartilage erosion, and bone destruction (Cuevas-Martínez et al., 2024). This shows that fasting suppresses inflammation throughout the vasculature and, additionally, that IF has tissue-specific anti-inflammatory benefits. The effects of fasting on cytokine concentration in chronic diseases have yet to be addressed in long-term human trials across all relevant autoimmune diseases. Fasting downregulates inflammatory pathways via sirtuins. Sirtuins are potent negative regulators of the NLRP3 inflammasome. Experimental evidence has shown that activation of sirtuins by IF attenuates the NLRP3 inflammasome by downregulating its component proteins, reducing downstream inflammatory pathways (Gnoni et al., 2021). In a study of murine liver inflammation, fasting decreased expression of TLR4 and iNOS and diminished the production of inflammatory cytokines (IL-1α, IFN-γ, and RANTES) during the inflammatory challenge. Further research in autoimmune diseases will be critical in understanding the extent to which fasting can decrease immunogenic inflammation and improve vascular health. Short-term caloric restriction or intermittent fasting restores nitric oxide bioavailability. Restoring NO can directly improve endothelial dysfunction by reversing the decreased eNOS activity. By increasing NO, even after just a short amount of time, short-term caloric restriction or IF can restore endothelial cell function in vascular beds by improving vasorelaxation (Rippe et al., 2010). These findings are encouraging for long-term treatments, as individuals with a chronic autoimmune disease would be able to improve vascular health via IF with minimal restrictions to their lifestyle and diets. Moreover, increasing nitric oxide bioavailability in patients suffering from an autoimmune disease has additional benefits by improving eNOS-mediated vasorelaxation throughout the vas-

cular system, consequently decreasing the risk of hypertension and increasing flow-mediated dilation. Fasting also may impact the trafficking of immune cells and their deposition throughout the vasculature. In a study by Graham et al., fasting mobilized immune cells into the bone marrow to deplete them from the site of the endothelial injury, effectively relieving chronic inflammation throughout the vasculature (Graham et al., 2025). However, further research is required to fully assess the effect of fasting on the distribution of immune cells in autoimmune diseases.Together, these studies elucidate how the combination of antioxidant mechanisms and the repression of inflammatory cascades are critical mediators for the vasoprotective effects of IF. Although significant in vitro evidence shows that IF improves endothelial dysfunction via antioxidant and anti-inflammatory properties, translation of these results has been challenging. This underscores the importance of continued long-term and carefully designed research, as these varying experimental results may be related to the patient population under study, the duration of IF, and differences in baseline levels of oxidative stress in autoimmune disease models and human populations.

Metabolic Adaptations

The metabolic adaptations of intermittent fasting are of major interest as they are beneficial in resolving endothelial dysfunction and inflammation of autoimmune diseases. Metabolic shifts of intermittent fasting are mainly triggered by a change from glucose- to lipid-based fuel to supply energy and by generating ketone bodies (e.g. β-hydroxybutyrate). These alterations are endothelial-protective as the shift of substrate fuels from glucose to lipids lowers cellular production of ROS and mitigates endothelial injury. Furthermore, ketone bodies are generated and act as modulators to improve metabolic and anti-inflammatory processes in endothelial cells. On the vascular level, ketone body production induces Nrf2-mediated induction of endogenous antioxidant enzymes (e.g. glutathione peroxidase, superoxide dismutase). All of these metabolic effects induced by the administration of ketone bodies contribute to the mitigation of endothelial cell inflammation and injury, as well as the reduction of vascular risk factors in patients with autoimmune diseases (Zhang et al., 2024). While ketone body production offers vascular benefits, individual differences in the levels of ketone bodies and variations in the time to start ketone production in different individuals might influence clinical outcomes. Furthermore, metabolic shifts of intermittent fasting have endothelial and neuronal protective antioxidant effects (Zhang et al., 2024). However, the effects of individual variability among autoimmune patients on intermittent fasting-induced protective mechanisms remain unclear. Additionally, intermittent fasting upregulates fatty acid oxidation mediated by AMPK activation and inhibits fatty acid synthesis. The increased fatty acid oxidation reduces the availability of pro-inflammatory lipid mediators and contributes to an overall suppression of systemic inflammation, in addition to enhanced endothelial function. Both processes prevent damage of the endothelium and mitigate vascular risk factors and progression of autoimmune diseases (Zhang et al., 2024). Further exploration regarding the beneficial effects of intermittent fasting regimens in regulating fatty acids is warranted. The alteration of energy substrate availability in the vascular microenvironment also modifies the immune system. It has been proposed that the increase of fatty acid oxidation in lymphocytes and macrophages decreases the cellular activation of these immune cells and thus creates a more reparative environment for the vessels (Marko et al.,

2024). These effects further support that intermittent fasting can regulate autoimmune diseases. Further research is needed to unveil the molecular links between metabolic effects on immune cell responses of intermittent fasting and autoimmunity. Moreover, alternate-day fasting (ADF) was shown to improve endothelial-dependent relaxation in the thoracic aorta from diabetic mice. The mechanism involves an increase of the circulating hormone adiponectin that exerts its vasoprotective effects via the improvement of nitric oxide bioavailability (Cui et al., 2022). These mechanisms represent key regulators for vascular health in metabolic diseases and potentially in autoimmune diseases. Besides, ADF lowers nitrotyrosine levels of small mesenteric arteries in mice, indicating a reduction of protein nitration in the endothelium by free radicals and thus represents a protective effect on endothelial cells in response to hyperglycemia and chronic inflammatory conditions (Cui et al., 2022). However, more studies are required to further assess the underlying mechanisms in which intermittent fasting regimens exert protective effects on the endothelium in autoimmune diseases. ADF also improved insulin sensitivity and lowered fasting blood glucose of mice with diabetes mellitus, thus providing a possible way to mitigate the risks for cardiovascular disease in this patient group (Cui et al., 2022). Furthermore, metabolic disorders like hyperglycemia have been implicated in increased endothelial dysfunction, indicating that improvement of glucose homeostasis can also impact vascular risk factors in autoimmune patients. Besides, blockade of nitric oxide synthase (NOS) completely abolished vascular benefits of ADF, thus emphasizing the essential role of nitric oxide in mediating the protective effects of intermittent fasting (Cui et al., 2022). Therefore, enhancement of nitric oxide bioavailability is an important factor for improvement of vascular health in response to fasting and might be a promising approach for treatment of cardiovascular diseases in autoimmune patients. Fasting can induce a metabolic shift that leads to activation of SIRT1 and autophagy, which in turn are known to limit the secretion of the pro-inflammatory cytokine high mobility group box 1 (HMGB1), an alarmin with relevance in the pathogenesis of sterile inflammation. As endothelial cells are particularly sensitive to the alarmin HMGB1, the inhibition of its secretion during fasting supports vascular health and regeneration (Rickenbacher et al., 2014). Autophagy and SIRT1 have been shown to be vital for these effects, as chemical inhibition of these pathways completely abolished the observed vascular benefits of fasting (Rickenbacher et al., 2014). However, extreme length of the fasting period impairs the mechanisms involved and abolishes beneficial effects in vascular tissue (Rickenbacher et al., 2014). Another mechanism in which intermittent fasting can lead to increased health outcomes relies on the regulation of circadian biology in relation to food and activity times. Dietary restriction and fasting are coupled to circadian rhythms to improve cardiometabolic and health outcomes by optimizing metabolic flexibility, glucose homeostasis, as well as lipid metabolism (Zhang et al., 2025). Intermittent fasting has an effect on the circadian rhythms and by that enhances the repair of the vasculature, lipid profiles, and decreases blood pressure (Zhang et al., 2025). The improvement of circadian rhythms further supports the regulation of autoimmune diseases through intermittent fasting.The gut microbiota has been identified as a key player in mediating beneficial effects on health via the alteration of its composition, which can be stimulated by diet. Thus, intermittent fasting contributes to the protection of the vasculature through its effect on the gut flora. A

general trend has been observed in most studies regarding intermittent fasting intervention: the growth of pro-inflammatory bacterial species is reduced, whereas the growth of anti-inflammatory species is increased (Zhang et al., 2024). This shift in species abundance directly supports the production of short-chain fatty acids (SCFAs) that exert potent anti-inflammatory properties on vascular cells and are endothelial-protective. Therefore, intermittent fasting can regulate vascular inflammation and thus counteract the progression of autoimmune diseases by affecting the gut microbiota (Zhang et al., 2024). Furthermore, this regulation of the gut flora directly modulates the release of toxins to the system as it has been noted that an increase in gut barrier function during intermittent fasting can reduce the release of endotoxins and subsequently reduces systemic inflammation (Zhang et al., 2024). In conclusion, metabolic adaptations in response to intermittent fasting have been found to promote the improvement of endothelial/vascular health. However, differences in individuals and responses to the metabolic adaptations, due to potential variability in pre-existing diseases and activity levels, suggests that there is a need for better regulation of intermittent fasting for optimal outcome in the treatment of autoimmune diseases.

Clinical Evidence and Future Perspectives

Initial clinical data suggests the potential to influence inflammatory pathways and vascular health by intermittent fasting in autoimmune diseases. Future clinical research will focus on possible therapeutic interventions, short- and long-term outcomes and personalized optimal treatment methods in relation to cardiovascular and autoimmune diseases.

Current Research Findings

Intermittent fasting's impact on inflammatory and vascular pathways in the context of autoimmune diseases has been shown through preclinical studies in animal models, and some translational studies have been performed to support IF for treatment. Autoimmune disease models, like collagen-induced arthritis and neuropsychiatric lupus models, have demonstrated decreased inflammation, specifically lowered levels of inflammatory cytokines (TNF-α, IL-6), along with joint swelling and histologic damage. These changes also lowered chronic damage to joints and other tissue-specific components, which decreased erosion of cartilage and bone damage (Cuevas-Martínez et al., 2024; Feng et al., 2024). Although animal models suggest promise for the use of IF to lower inflammatory cytokines and control disease, extrapolating these findings to the human species can be a complicated step in research. Moreover, not all autoimmune diseases are equal; thus, whether IF could be used more broadly must be researched further. In lupus-prone MRL/lpr mice, IF was used to decrease the chronic, systemic inflammatory effects associated with the disease to improve the kidney pathology and autoantibody titers and affect splenic T lymphocyte composition (Feng et al., 2024). The common benefits and changes across the models were associated with M2 macrophage polarization, autophagy, and metabolic pathway changes through mechanisms like the inhibition of mTOR, and modulation of the AMPK/PPARγ/NF-κB axis. However, the extent to which these mechanisms could be applied as universal changes across a range of autoimmune diseases would have to be investigated. Benefits to cardiovascular function have been illustrated in several studies of human and animal models using IF interventions, including improved flow-mediated dilation (FMD), re-

pair to endothelial damage, and improved vascular compliance (Graham et al., 2025). Fasting may decrease pro-inflammatory immune cell populations in circulation by promoting the migration of circulating immune cells towards the bone marrow to improve cardiovascular function (Graham et al., 2025). Although the concept is well supported by the results, it would be difficult to apply IF universally without examining longer-term outcomes in patients with autoimmune diseases. Individuals with autoimmune diseases are at increased risk of premature cardiovascular disease and are often burdened with hypertension and hyperlipidemia (Al-Shuhaib, 2013), so there is a clinical need for these findings to be translated effectively. Studies using IF in those with metabolic syndrome have noted significant decreases in blood pressure, arterial stiffness, and improved endothelial-dependent vasodilation during fasting interventions (Graham et al., 2025). IF may improve cardiovascular risk, specifically in populations that have similar risk factors for vascular compromise. The mechanism to combat this risk in those with metabolic syndrome and autoimmunity is similar and is the reduction of the low-grade inflammation and oxidative stress, which in turn improves endothelial health. Some of the benefits associated with IF for cardiovascular health are vascular remodeling and repair in addition to its anti-inflammatory effects (Katare et al., 2009; Liu et al., 2023). In a rat model, IF was implemented 10 days following myocardial ischemia and led to increased capillary density in the border zone between the damaged tissue and the non-infarcted tissue and a decrease in the heart weight-to-body weight ratio (Katare et al., 2009). After seven days of IF, the rats' hearts demonstrated a higher level of VEGF and anti-apoptotic factor Bcl-2, and there was an observable increase in myocardial protection, which implies that IF might promote vascular repair following an ischemic event. In the cerebral ischemia model, rats experienced similar benefits during IF treatment following induction of the ischemic stroke. In this model, rats treated with IF demonstrated a reduction in ischemic damage by increasing the regional cerebral blood flow with improved neurovascular repair via GDF11/ALK5 (Liu et al., 2023). Although ischemic events are not typically recognized or documented in autoimmune disease complications, the implications of these findings suggest that IF could offer potential benefit in the cardiovascular health and well-being in these diseases. In addition to the demonstrated benefits for overall cardiovascular health, IF could also influence the vascular environment of autoimmune diseases by modulating gut microbiota. This concept has been examined in several animal models, where they have been shown to influence populations of bacteria, particularly to benefit vascular health. By utilizing models with autoimmune disease, some researchers have found that IF can influence bacteria in such a way that promotes healthy levels of anti-inflammatory bacterial genera like Ruminococcaceae and SCFA production for cardiovascular benefits (Cuevas-Martínez et al., 2024). This intervention suggests a relationship between dietary intervention and cardiovascular health through gut bacteria. As a result, there is a correlation with some of the cardiovascular events observed in this group of chronic diseases, where gut dysbiosis is highly recognized. With many beneficial attributes noted throughout several studies, including the prevention of cardiac dysfunction by lowering oxidative stress and improving cellular resilience, IF appears to be a well-regarded method of treatment. However, there are still issues that impede the advancement of this type of dietary regimen in research, beginning with inconsistent standards of the program parameters

(Graham et al., 2025). As an example, if the duration of IF is to be long, say a period of months, would the regimen yield the same results? Similarly, at which point would IF become unsustainable and eventually affect the clinical status of those with autoimmune diseases and other chronic conditions? In addition, since there is a wide variation in the presentation of each autoimmune disease, with its varied underlying mechanisms, each would have to be investigated carefully, and a singular implementation standard may not prove effective for everyone.

Therapeutic Applications

Intermittent fasting shows promise in attenuating inflammatory activity and vascular injury in autoimmune diseases by targeting central inflammatory mediators and restoring endothelial function. Studies performed in preclinical models provide evidence that fasting reduces levels of several pro-inflammatory cytokines, including TNF-α and IL-6, which play key roles in joint and vascular injury. Studies in mouse models of rheumatoid arthritis showed a reduction in histological markers of joint and vascular tissue injury upon fasting. Similar benefits have been observed in clinical trials with patients diagnosed with psoriatic arthritis during Ramadan fasting, and reduced levels of CRP as well as disease activity were found in this cohort of patients independent of weight loss (Adawi et al., 2019). Nevertheless, most clinical trials involve short-term interventions. Interindividual variations in fasting duration and adherence rates are major limitations to drawing a conclusion as to whether intermittent fasting can translate to improvements in vascular health among patients with autoimmune conditions. There is a need to address standardization of intermittent fasting protocols in the clinical setting and to further elucidate how interindividual differences in response to intermittent fasting can be addressed to improve clinical translation. Experimental and clinical studies have observed improved endothelial-dependent vasodilation and arterial repair following an intermittent fasting intervention. In both patient and animal models with underlying hypertension or metabolic syndrome, there has been a noted increase in flow-mediated dilation (FMD), which is an established biomarker of endothelial function, and a subsequent enhancement in endothelial-dependent vasodilation upon fasting (Demirci & Özkan, 2023). Improvements in FMD correlate to a significant decrease in the levels of C-reactive protein (CRP) and cortisol, both of which are known to have a role in endothelial repair and regeneration. Additionally, there is a documented reduction in blood pressure and LDL-cholesterol levels, suggesting a link between intermittent fasting and modulation of both traditional and nontraditional risk factors for cardiovascular disease in a setting of chronic inflammation. Nonetheless, differences within patient subsets, based on metabolic parameters and inflammatory status at baseline, cannot be excluded and may need to be considered when interpreting the clinical benefits of intermittent fasting. Further studies are required to better delineate if and how intermittent fasting improves vascular outcomes among patients with different subsets of autoimmune diseases and associated risk factors. Intermittent fasting promotes changes in the composition of the gut microbiota. During fasting, an increase of anti-inflammatory bacterial genera, such as Ruminococcaceae, and of SCFAs is noted, and these have been shown to mediate endothelial protection and anti-inflammatory activity in the systemic circulation in the context of chronic inflammation (Cuevas-Martínez et al., 2024). Preclinical studies in mouse models of arthritis support the notion that changes in gut micro-

biota composition following intermittent fasting promote vascular repair, as markers of joint and vascular pathology are both improved upon fasting. Alterations in the microbiome are associated with improved gut barrier function as well, potentially leading to decreased endotoxemia and inflammation among patients with autoimmunity. Microbiota -based therapeutics must overcome significant barriers in clinical translation, as the interindividual variation in fasting-mediated effects on the gut microbiota is a concern. Factors such as basal dietary composition, differences in overall gut health, and patient genotype contribute to the diversity in the microbial composition after fasting interventions. Improving the ability to identify how these differences impact an individual's gut microbial response to intermittent fasting may allow for personalized approaches to mitigate vascular injury among autoimmune patients. Autophagy may mediate improvements in endothelial function upon intermittent fasting in a setting of autoimmunity. Autophagy promotes cellular homeostasis, removing damaged organelles, diminishing inflammation, and enhancing nitric oxide bioavailability. All of these are central to endothelial cell protection from injury (Jiang, 2016). Autophagy can be induced with intermittent fasting, thus limiting inflammatory damage and endothelial dysfunction. Autophagy is an essential regulator of homeostasis; however, excessive and sustained activation can be harmful as it induces cell death. Improving our understanding of how to modulate autophagy to promote vascular repair while preventing endothelial cell death is paramount.The implementation of intermittent fasting in autoimmune disease is not straightforward. Significant obstacles to the translation of intermittent fasting in clinical settings remain. There is high variability in intermittent fasting protocols, with differences in fasting durations, frequency, and timing between intermittent fasting groups (Barati et al., 2023). In addition, there are patient barriers, such as individual levels of adherence and patients with metabolic demands (i.e., due to high energy expenditure, medications, or other comorbidities) for whom prolonged fasting may not be possible. In chronically ill patients who cannot consume adequate calories, weight loss and malnutrition are concerns as well. Intermittent fasting must be personalized, accounting for patient variability in disease activity, metabolic status, and comorbidities. A randomized controlled trial in a large population with diverse subsets of autoimmune diseases is needed to address safety, feasibility, and reproducibility. Intermittent fasting has immense potential, but the translational gap remains.The redistribution of immune cells can be a major mechanism through which intermittent fasting mediates vascular benefits. Recent studies have demonstrated that intermittent fasting promotes mobilization of immune cells, reducing their presence in vascular and perivascular tissues and attenuating inflammatory and vascular injury (Graham et al., 2025). No published clinical studies assess immune cell redistribution among patients with autoimmunity. Further investigations must evaluate the role of altered immune cell distribution in the setting of autoimmunity and assess the impact of intermittent fasting on long-term cardiovascular outcomes. If immune cell redistribution mediates the benefits of intermittent fasting, this may have important implications in preventing mortality and morbidity in patients with autoimmune diseases who are at risk for vascular injury. In conclusion, intermittent fasting has promise in limiting inflammation and vascular injury among autoimmune patients. While preclinical and translational evidence is growing, significant barriers to the translation of intermittent fasting remain. Additional investigations focusing on addressing gaps in

the literature will likely contribute to improved clinical translation.

Conclusion

This work sought to determine whether intermittent fasting provides a beneficial non-pharmacological means to improve endothelial function in autoimmune disease, the mechanism(s) that promote this improvement, and its implications for cardiovascular risk reduction. The primary research question was aimed at understanding how intermittent fasting improves key processes governing vascular function—namely inflammation, oxidative stress, and metabolism—in the setting of autoimmune disease.Throughout this review, mechanistic insights and emerging clinical evidence have been systematically examined to provide a comprehensive overview of how intermittent fasting improves endothelial dysfunction in autoimmune diseases. The analysis of published reports revealed several aspects in which intermittent fasting can influence endothelial health in autoimmune disease. Evidence has been reviewed suggesting that various intermittent fasting protocols promote metabolic adaptations—mainly through the transition of fuel utilization from glucose to lipids—which improve vascular function by promoting the generation of ketone bodies, reduction of reactive oxygen species production, induction of autophagy and antioxidant defense, and improvement in mitochondrial function. Intermittent fasting has also been shown to reduce inflammation through decreased production of inflammatory cytokines such as TNF-α and IL-6. This reduction in inflammation can also enhance endothelial function via increased nitric oxide availability and reduced endothelial activation, as demonstrated in both animal and clinical models. Moreover, intermittent fasting appears to play a role in modulating the immune cell population in autoimmune disease, increasing the abundance of regulatory T cells and shifting immune cell subsets to resolve or prevent the inflammatory processes driving endothelial dysfunction. Finally, interventions to align fasting protocols with circadian rhythm and those designed to improve the gut microbiome have been included to reveal additional novel mechanisms by which intermittent fasting may improve endothelial function in autoimmune disease. These results suggest that interventions of strategic dietary timing can counteract multiple pathological processes driving endothelial dysfunction in autoimmune disease, thus laying the foundation for innovative integrative approaches to improve vascular health.This review supports ongoing work bridging the fields of vascular biology, immunology, and metabolic medicine, and it highlights the role that intermittent fasting could have as an intervention to augment and complement existing treatments. By synthesizing and integrating multiple layers of evidence across in vitro and in vivo preclinical studies and early-phase clinical trials, this review has revealed that intermittent fasting may potentially be a valuable adjunct to alleviate the increased cardiovascular risks associated with autoimmune diseases. It has focused on the novel and unique context of individuals with autoimmune disease who have persistent immune cell activation that could trigger or exacerbate endothelial dysfunction, making the autoimmune population a specific subset for which intermittent fasting could represent a novel treatment strategy. While several studies reported improved vascular outcomes using a variety of intermittent fasting protocols, there was much variability in both study design and primary outcomes, which makes it impossible to draw clear and concise clinical recommendations regarding intermittent fasting for patients with autoimmune disease. It is important to take

into account the limitations of the existing clinical data pertaining to intermittent fasting on endothelial function in autoimmune disease. While the mechanistic evidence for fasting-mediated vascular protection is robust, clinical evidence from trials that have targeted cardiovascular outcomes, rather than surrogate measures, is weak due to limited trial lengths and an apparent lack of long-term studies. Moreover, the existing clinical trials in autoimmune cohorts have been done only on a small portion of those who have autoimmune diseases. It is also imperative to note the risks of intermittent fasting such as malnutrition, the possibility of exacerbating certain autoimmune diseases, and risks associated with disease complications and/or co-medications. Such risks may complicate the appropriateness of intermittent fasting in individuals with specific autoimmune diseases and comorbidities. To overcome these limitations, there is an urgent need for prospective, adequately-powered, placebo-controlled, long-term clinical trials in patients with autoimmune disease that are designed to identify specific biomarkers associated with improved endothelial function by using multi-omic studies. This review further emphasizes the urgent need to determine the intensity, duration, and frequency of intermittent fasting to provide beneficial results for endothelial function and cardiovascular disease outcomes without imposing risks on those with autoimmune disease. In conclusion, future research should endeavor to build upon the observations outlined in this work. Such efforts should include high-quality, sufficiently-powered, randomized clinical trials of intermittent fasting among autoimmune patients to determine the feasibility, safety, and efficacy of different intermittent fasting protocols in terms of vascular outcomes. Strategies to determine whether there are synergistic or antagonistic effects of adding intermittent fasting to current pharmacological or dietary interventions may provide additional benefit for the treatment of endothelial dysfunction in autoimmune disease. Further research into the inter- and intra-individual variability in response to intermittent fasting could also lead to individualized prescriptions of specific intermittent fasting protocols depending on patient risk and personal preference. Such studies will be required to determine the optimal intermittent fasting strategy to improve endothelial function in individuals with autoimmune disease and what factors contribute to these observed improvements. Future studies are also required to examine gut microbiota as a mechanism to explain intermittent fasting's effect on endothelial function and cardiovascular health as well as the effect of intermittent fasting when aligned with the circadian rhythm. Finally, it would also be of great value to determine if inducing autophagy during intermittent fasting could be harnessed to improve endothelial function. Overall, this work serves as a reminder of how intermittent fasting can induce a variety of physiological changes within the human body to elicit metabolic, immunoregulatory, and ultimately beneficial effects on vascular health. The complexity of these interventions, with their multi-level effects, should thus encourage future clinical and experimental studies designed to test the effectiveness of these strategies and to reveal more about the mechanisms underlying intermittent fasting's therapeutic effects.

Highlights

- Intermittent fasting improves endothelial function in autoimmune diseases through mechanisms involving nitric oxide bioavailability, antioxidant defense, and inflammation reduction.
- Clinical and preclinical evidence suggests IF modulates immune response and vascular

health, though standardization of protocols and long-term safety data are lacking.

- Future research must personalize fasting interventions using omics data and circadian strategies to optimize vascular and autoimmune outcomes.

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