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INTERMITTENT FASTING - ITS BENEFITS AND RISKS

Jakub Prosowski[1] ✉, Szczepan Pośpiech[1],
Jessika Schendzielorz[2], Michał Piotrowski[2],
Piotr Serwicki[2], Jakub Początek[3],
Bartosz Zabrzeński[4], Karolina Paks[4]

[1] Upper Silesian Medical Center of the Medical University of Silesia in Katowice, Poland
[2] Provincial Specialist Hospital No. 5 named after Saint Barbara in Sosnowiec, Poland
[3] District Railway Hospital in Katowice, Poland
[4] Independent Public Healthcare Institution of the Ministry of Internal Affairs and Administration in Katowice named after Sergeant Grzegorz Załoga, Katowice Poland

✉ ***jakubprosowski@gmail.com***

ABSTRACT

BACKGROUND:

Intermittent fasting (IF) is a dietary approach increasingly studied for its potential benefits in metabolic regulation, hormonal balance, and the prevention or management of chronic diseases. It includes several protocols such as alternate-day fasting (ADF), time-restricted feeding (TRF), the 5:2 method, and periodic fasting. These regimens differ in fasting–feeding cycles and may influence weight loss, insulin sensitivity, lipid metabolism, and disease progression through mechanisms involving hormonal modulation, reduced inflammation, and enhanced autophagy. The aim of this review is to evaluate the efficacy and mechanisms of these IF protocols, with a focus on their metabolic, endocrine, and disease-specific outcomes.

AIMS:

The aim of this study is to examine the efficacy and mechanisms of the following IF protocols: alternate-day fasting (ADF), time-restricted feeding (TRF), the 5:2 method, and periodic fasting. The study focuses on their metabolic, endocrine, and disease-specific outcomes.

METHODS:

A literature search was conducted in PubMed, Scopus, and Google Scholar for peer-reviewed studies evaluating the effects of IF on metabolic, endocrine, and disease-specific outcomes. Inclusion criteria comprised studies with clearly defined IF protocols and measurable endpoints such as changes in body weight, fat mass, lean mass, insulin sensitivity, lipid profiles, hormonal markers, and disease-related outcomes. Human studies were prioritized over animal data where available.

RESULTS:

The evidence indicates that IF can reduce body weight, fat mass, and insulin resistance while preserving lean

mass. Additional benefits include improved lipid profiles, decreased systemic inflammation, and enhanced autophagy. These effects may contribute to lowering the risk or slowing the progression of type 2 diabetes, cardiovascular disease, cancer, and Alzheimer's disease. Comparative data suggest that in the long term, IF may be as effective as continuous calorie restriction, with patient adherence and individual health status being key determinants of success.

CONCLUSIONS:

Intermittent fasting is an effective dietary strategy with potential to improve metabolic flexibility and reduce the risk of chronic diseases. However, its application should be individualized, taking into account comorbidities, genetic variability, and lifestyle factors. Further long-term, high-quality clinical trials are required to refine protocols, assess safety, and compare outcomes with other dietary strategies across diverse populations.

Keywords: intermittent fasting, caloric restriction, obesity, weight loss, inflammation, type 2 diabetes, Alzheimer's disease, neurodegenerative diseases, metabolic health.

INTRODUCTION

Despite the long-standing knowledge of intermittent fasting (IF), recent studies have provided new insights into its metabolic, hormonal, and disease-specific effects. This review is relevant as it summarizes current evidence, compares different IF protocols, and highlights their potential role in modern clinical practice. Intermittent fasting (IF) is a diet in which a person alternates between defined periods of eating and fasting during the day [1, 2]. Recently, it has been gaining attention, because of its potential to improve metabolic health [3], aid in weight management [37, 38], and address chronic diseases such as type 2 diabetes, cardiovascular disease, and neurodegenerative disorders [4, 7, 9]. IF focuses on meal timing rather than daily caloric reduction, in contrast to continuous calorie restriction. It has historical roots in cultural and religious practices but has recently been studied for its physiological effects, such as enhancing insulin sensitivity, improving lipid metabolism, and modulating hormones. [6, 12, 18] This review examines the various protocols of IF, its effects on metabolic and hormonal regulation, and its potential therapeutic applications.

Intermittent fasting (IF) can be compared and potentially integrated with other dietary strategies such as low-calorie diets, low-carbohydrate regimens, and high-fat (e.g., ketogenic) diets. Unlike continuous calorie restriction, IF focuses on the timing of food intake, which can be combined with macronutrient-specific approaches to optimize metabolic outcomes. For example, ketogenic diets share with IF the capacity to promote shifts toward fatty acid utilization, but achieve this through macronutrient composition rather than fasting duration [40]. Low-carbohydrate diets can enhance glycemic control and reduce insulin levels [41], potentially complementing the insulin-sensitizing effects of IF. Low-calorie diets remain effective for weight loss [14], but IF may improve adherence by providing structured eating–fasting cycles instead of continuous restriction.

In clinical practice, IF can also be integrated with physical activity to improve body composition and cardiovascular health markers. Combining IF with pharmacotherapy, such as metformin or GLP-1 receptor agonists, may provide additive benefits in glucose regulation and weight reduction [30], although such combinations require careful monitoring to avoid hypoglycemia. Comparative studies evaluating IF alongside and in combination with these approaches are still limited, but mechanistic overlaps suggest potential for synergistic effects.

AIM

The aim of this review is to evaluate the efficacy and mechanisms of various intermittent fasting protocols, with a focus on their metabolic, endocrine, and disease-specific outcomes, and to compare their potential clinical applications with other dietary strategies.

METHODS

This narrative review was based on a literature search of peer-reviewed articles indexed in PubMed, Scopus, and Google Scholar. The search covered the period from January 2005 to June 2024 and was limited to publications in English. The following search terms and their combinations were used: "intermittent fasting," "alternate-day fasting," "time-restricted feeding," "weight loss," "metabolic health," "insulin sensitivity," "cardiovascular health," "type 2 diabetes," "neurodegenerative diseases," and "cancer."

RESULTS OF SELECTION

Inclusion criteria were as follows:

1. Peer-reviewed original research articles or reviews with clearly defined intermittent fasting (IF) protocols (alternate-day fasting, time-restricted feeding, 5:2 method, or periodic fasting).

2. Studies reporting measurable outcomes related to metabolic, endocrine, or disease-specific effects, including changes in body weight, fat mass, lean mass, insulin sensitivity, lipid profile, hormonal markers, and disease progression.
3. Human studies were prioritized, although relevant animal studies were included where human data were insufficient.

Exclusion criteria were:

1. Non-peer-reviewed publications, conference abstracts, letters to the editor, case reports, and opinion pieces.
2. Studies without clearly defined IF protocols or measurable outcomes.
3. Articles not available in English.
4. Studies with insufficient sample sizes, lack of control groups, or inconsistent fasting definitions.

FINDINGS AND DISCUSSION

CHANGES IN HORMONE LEVELS DUE TO IF

Intermittent fasting (IF) directly impacts hormonal regulation by aligning endocrine function with circadian rhythms and modulating metabolic and reproductive hormones. Studies demonstrate that IF significantly reduces plasma insulin levels, with decreases of over 50% observed during fasting periods [18]. This reduction improves insulin sensitivity and lowers fasting glucose levels [27]. Furthermore, IF affects the circadian rhythm of insulin secretion by shifting the acrophase (peak secretion time) and reducing daily fluctuations [27]. In animal models, prolonged alternate-day fasting has been shown to decrease insulin secretion independently of caloric intake. This highlights mechanisms beyond simple energy restriction [5].

Thyroid hormones are notably influenced by fasting. Reductions in triiodothyronine (T3) levels of up to 55% within 24 hours of fasting have been documented, correlating with suppressed thyroid-stimulating hormone (TSH) secretion and reduced hypothalamic-pituitary-thyroid (HPT) axis activity [17]. Evidence suggests that leptin, which decreases during fasting, modulates TSH production through hypothalamic pathways [5]. Despite reductions in T3, short-term studies indicate no significant impairment of basal metabolic rate, suggesting compensatory mechanisms [14].

Reproductive hormones are similarly affected, particularly in individuals with hormonal imbalances. In women with polycystic ovary syndrome (PCOS), IF reduces androgen levels, including the free androgen index (FAI), while improving ovulatory function and reducing visceral fat [5]. These changes are attributed to enhanced insulin sensitivity and lipid metabolism [6]. In men, fasting reduces testosterone levels, although this does not appear to compromise muscle mass or strength [6].

Glucocorticoids, particularly cortisol, are elevated during fasting, reflecting increased gluconeogenesis and energy mobilization [8]. Fasting also shifts the circadian rhythm of cortisol secretion, potentially counteracting some anti-inflammatory benefits if levels remain elevated for extended periods [39]. Additional hormones, including growth hormone, melatonin, and leptin, also demonstrate systemic adjustments in response to restricted feeding schedules [7].

These findings indicate that IF broadly affects hormonal regulation, improving insulin sensitivity and modulating reproductive, thyroid, and glucocorticoid hormones. However, fasting-induced reductions in thyroid hormones and shifts in cortisol secretion highlight the need for individualized IF protocols to maximize benefits while minimizing potential risks.

WEIGHT LOSS

Various intermittent fasting (IF) protocols, including alternate-day fasting (ADF), time-restricted eating (TRE), and intermittent energy restriction (IER), have demonstrated effectiveness in reducing body weight, body mass index (BMI), and fat mass while preserving lean body mass [28]. A meta-analysis of randomized controlled trials showed that TRE resulted in an average weight loss of 0.9 kg over a 6–12 week period, with larger reductions observed in longer-duration studies [13]. Similarly, ADF consistently outperformed continuous calorie restriction (CCR) in reducing fat mass, with decreases ranging from 3% to 7% of baseline weight among overweight and obese participants [38].

One of the primary mechanisms driving weight loss through IF is the creation of a sustained energy deficit. During fasting periods, glycogen stores are depleted, prompting a metabolic shift to lipolysis and mobilization of triglycerides for energy. This process facilitates fat loss, enhances insulin sensitivity, and improves metabolic flexibility [36]. TRE, by restricting eating to a 6- to 10-hour window, aligns food intake with circadian rhythms,

further optimizing metabolic processes [43]. Studies indicate that individuals practicing TRE lose 3-5% of their body weight within 12 weeks, with concurrent improvements in fasting glucose and lipid profiles [10].

IF also influences appetite-regulating hormones. Fasting reduces leptin levels, which are often elevated in obesity, and suppresses ghrelin, the hunger-stimulating hormone [2]. These hormonal adaptations contribute to reduced caloric intake during eating windows and improve adherence to IF regimens over time [14].

A unique advantage of IF is its ability to preserve lean body mass during weight loss. Unlike traditional calorie restriction, which often results in muscle loss, IF protocols such as ADF and TRE maintain lean mass due to intermittent increases in growth hormone secretion during fasting periods [27]. Growth hormone promotes muscle protein synthesis and minimizes muscle catabolism, supporting the preservation of skeletal muscle [18].

DIABETES TYPE 2

A 12-week randomized controlled trial demonstrated that three non-consecutive fasting days per week significantly reduced HbA1c levels in insulin-treated individuals with type 2 diabetes mellitus (T2DM) by an average of 7.3 mmol/mol, compared to negligible changes in the control group [30]. This reduction was accompanied by a 9-unit decrease in daily insulin requirements in the IF group, while the control group exhibited an increase [4]. Additionally, participants practicing IF lost an average of 4.77 kg, predominantly from fat mass, with no adverse effects on lean body mass or basal metabolic rate [10].

On a cellular level, IF induces several metabolic adaptations that counteract the mechanisms driving diabetes. By reducing glycogen stores and enhancing fatty acid oxidation, IF increases ketone body production and shifts metabolism toward fat utilization. These changes not only reduce glucose levels but also improve insulin receptor sensitivity, facilitating glucose uptake by peripheral tissues [1]. IF also stimulates autophagy, clearing damaged organelles and proteins, which enhances pancreatic β-cell function and preserves insulin secretion capacity [21].

IF modulates inflammatory pathways critical in diabetes progression. Studies report reductions in systemic markers of inflammation, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), during fasting, improving vascular and metabolic health [3]. Lipid profiles also benefit from IF, with reductions in triglycerides and LDL cholesterol, alongside increases in HDL cholesterol, likely mediated by enhanced lipolysis and reductions in systemic oxidative stress [21].

Despite its benefits, IF requires careful management in T2DM patients, particularly those on insulin therapy, to minimize hypoglycemia risks. Adjusting insulin doses on fasting days and employing continuous glucose monitoring systems effectively mitigate these risks [8]. IF has proven sustainable for most participants, with adherence rates exceeding 90% in structured clinical trials [31].

CARDIOVASCULAR HEALTH

Intermittent fasting (IF) has emerged as a promising strategy for preventing and managing cardiovascular disease (CVD) by improving metabolic regulation, reducing systemic inflammation, and enhancing endothelial function [22]. By inducing metabolic adaptations, IF targets critical risk factors such as dyslipidemia, hypertension, and oxidative stress, which play pivotal roles in the pathogenesis of CVD [32].

A key cardioprotective mechanism of IF is its impact on lipid metabolism. During fasting, glycogen depletion triggers lipolysis and fatty acid oxidation, leading to a reduction in circulating triglycerides and low-density lipoprotein cholesterol (LDL-C), while increasing high-density lipoprotein cholesterol (HDL-C). Studies report LDL-C reductions of 10–15% and significant triglyceride declines, contributing to a less atherogenic lipid profile [14]. These changes reduce the risk of atherosclerotic cardiovascular disease by improving lipid homeostasis and reducing oxidative stress [2].

In addition to lipid regulation, IF demonstrates robust anti-inflammatory effects. Fasting suppresses pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while lowering C-reactive protein (CRP), a biomarker linked to atherogenesis and plaque instability [2]. This systemic anti-inflammatory response stabilizes atherosclerotic plaques, reducing the risk of acute cardiovascular events such as myocardial infarction and stroke [24].

IF also enhances endothelial function through increased nitric oxide (NO) bioavailability, improving arterial compliance and reducing vascular stiffness [43]. Autophagic processes initiated by fasting aid in removing damaged cellular components, preserving endothelial integrity and mitigating vascular dysfunction [7]. Additionally, IF has been shown to decrease both systolic and diastolic blood pressure by reducing sympathetic nervous system activity and improving insulin sensitivity [38].

At the molecular level, IF modulates signaling pathways implicated in cardiovascular health. Downregulation of the mechanistic target of rapamycin (mTOR) pathway and activation of AMP-activated protein kinase (AMPK) promote cellular energy homeostasis and reduce inflammation. These adaptations collectively enhance mitochondrial

function, providing resilience against stress-induced cardiovascular damage and delaying vascular aging [42].

CANCER

Intermittent fasting (IF) induces metabolic changes that create an environment detrimental to cancer cells, which depend heavily on glycolysis for energy production. It reduces glucose availability, increases ketogenesis, and activates cellular stress response pathways, IF targets the metabolic vulnerabilities of cancer cells while preserving normal cell functions [25]. Preclinical and clinical studies indicate that IF may inhibit tumor growth, enhance the efficacy of conventional treatments, and alleviate their side effects [7].

A key anticancer mechanism of IF is the reprogramming of cellular metabolism. Cancer cells rely on glucose to fuel their rapid proliferation, a phenomenon known as the Warburg effect. IF reduces glucose levels and suppresses insulin and insulin-like growth factor-1 (IGF-1) signaling, depriving cancer cells of their primary energy source. Fasting promotes ketogenesis, generating alternative energy substrates like β-hydroxybutyrate, which normal cells can use efficiently, but cancer cells cannot due to metabolic inflexibility [20]. These changes lead to metabolic stress and impaired tumor growth.

Inhibition of IGF-1 and mechanistic target of rapamycin (mTOR) pathways is another critical aspect of IF's anticancer effects. IF significantly reduces IGF-1 levels—by up to 50%—and suppresses mTOR activity, slowing tumor progression, inducing cell cycle arrest, and enhancing cancer cells' sensitivity to chemotherapeutic agents [34]. Additionally, fasting activates autophagy, a cellular repair mechanism, which protects normal cells but overwhelms cancer cells, leading to apoptosis. Animal studies demonstrate that fasting enhances tumor cell apoptosis by up to 50% and reduces tumor volume by 40% [42].

Oxidative stress plays a pivotal role in the anticancer effects of IF. Cancer cells, naturally producing high levels of reactive oxygen species (ROS), experience exacerbated oxidative damage under fasting conditions. In contrast, normal cells enhance their antioxidant defenses, such as superoxide dismutase and glutathione peroxidase, further tipping the balance against cancer cells [15]. Chronic inflammation, a driver of cancer progression, is effectively reduced by fasting. IF suppresses inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) by up to 70% in rodent studies [19].

Moreover, fasting enhances immune surveillance by increasing the activity of cytotoxic T-cells and natural killer cells, thereby boosting the immune system's ability to target cancer cells. Fasting also modifies the tumor microenvironment (TME), limiting angiogenesis, improving extracellular matrix integrity, and shifting macrophage polarization to an anti-tumor phenotype. Finally, fasting synergizes with conventional cancer therapies, sensitizing cancer cells to treatments while reducing side effects such as fatigue and nausea, as evidenced in glioblastoma models where fasting combined with temozolomide reduced tumor size by 65% [34].

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) currently affects over 55 million people globally, with projections indicating a tripling of cases by 2050 due to aging populations [33]. Characterized by amyloid-β (Aβ) plaque deposition and tau protein hyperphosphorylation, AD leads to synaptic dysfunction and neuronal death [35]. Emerging evidence suggests that intermittent fasting (IF) may mitigate the pathological mechanisms of AD, offering a potential dietary intervention to address this debilitating condition [22].

IF promotes the production of ketone bodies, which serve as alternative energy sources with neuroprotective properties. Ketones facilitate Aβ clearance across the blood-brain barrier (BBB) and may reduce tau hyperphosphorylation, disrupting neurofibrillary tangle formation [40]. Animal studies have demonstrated significant benefits, including decreased Aβ accumulation and cognitive improvements assessed through Morris water maze and Y-maze tasks [29]. For instance, APP knock-in mice on IF showed a 70% improvement in escape latency, while rats on time-restricted feeding exhibited 50% fewer memory errors compared to controls [11].

Beyond reducing Aβ and tau pathology, IF enhances brain-derived neurotrophic factor (BDNF) levels by 25–40%, supporting hippocampal neurogenesis and synaptic plasticity [24]. IF also reduces neuroinflammation by lowering pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [44]. Additionally, fasting improves cerebrovascular integrity, which is crucial in AD pathology, by promoting endothelial function and glymphatic clearance [16].

Human studies, though limited, suggest IF's potential for cognitive health. A three-year study of elderly participants practicing 2-day/week IF showed a 24.3% rate of successful aging compared to 3.1% in non-fasting counterparts [9]. However, adherence challenges persist, with dropout rates ranging from 18% to 34% in clinical trials. These findings highlight the multifaceted benefits of IF in targeting Aβ clearance, tau pathology, neuroinflammation, and cerebrovascular health, albeit with variable efficacy based on genetic background and disease stage.

Table 1 summarizes the main intermittent fasting (IF) protocols discussed in the article and their reported effects across different clinical domains. It is intended to provide a concise reference for comparing the potential benefits and limitations of each protocol based on the available evidence.

Table 1. Structured comparison of intermittent fasting (IF) protocols with reported clinical effects based on evidence presented in the article

IF Protocol	Weight Loss	Diabetes Type 2	Cardiovascular Health	Cancer	Alzheimer's Disease
Alternate-Day Fasting (ADF)	Produces significant reductions in body weight and fat mass; sometimes superior to continuous calorie restriction	Can improve insulin sensitivity and reduce fasting glucose; caution with medication adjustments	May improve lipid profiles and reduce inflammatory markers	Limited human evidence; some preclinical data suggest potential benefits	Preliminary evidence from animal models indicates possible neuroprotective effects
Time-Restricted Eating (TRE)	Leads to modest weight loss (3–5% in 12 weeks) and fat mass reduction	Improves fasting glucose and insulin sensitivity; safe if eating window aligns with medication timing	May improve blood pressure and lipid parameters	Limited evidence; human trials lacking	Some studies suggest improved cognitive performance in animal models
5:2 Method (Caloric Restriction Days)	Reduces weight and fat mass while preserving lean mass	Can improve insulin sensitivity; low risk of hypoglycemia if medications adjusted	Potential to improve cardiovascular risk factors; evidence limited	No strong evidence in cancer prevention/ treatment	No specific evidence reported
Periodic Fasting (24–48 h)	Produces larger energy deficit; requires careful refeeding to avoid deficiencies	May improve glycemic control; caution in insulin-treated patients	Potential improvements in lipid profile; data limited	Some preclinical evidence of reduced tumor growth; human data scarce	Limited evidence from animal studies

CONSIDERATIONS AND LIMITATIONS OF INTERMITTENT FASTING

Despite its many benefits, intermittent fasting (IF) is not suitable for everyone. Individuals with advanced diabetes, particularly those on insulin or glucose-lowering medications, face an increased risk of hypoglycemia during fasting periods and should only consider IF under close medical supervision [4]. Similarly, those with eating disorders, such as anorexia nervosa or bulimia, may experience deterioration in eating behaviors due to the restrictive nature of fasting regimens [14]. Populations requiring consistent energy intake, such as pregnant or breastfeeding women, children, and those with chronic illnesses, are also generally advised to avoid IF [39].

Adherence to IF protocols can be challenging and requires careful planning to ensure nutritional adequacy and long-term sustainability. Studies indicate that up to 30% of participants in IF trials drop out due to difficulty

maintaining the regimen or experiencing side effects such as fatigue, irritability, and headaches [2]. Proper education on nutrient-dense food choices during eating windows is crucial to avoid deficiencies in essential vitamins and minerals [26]. For individuals engaged in high-intensity physical activities, adjusting fasting schedules to align with energy demands is critical to prevent performance decline or injury [37].

While IF holds promise as a dietary intervention, personalized approaches considering an individual's health status, lifestyle, and goals are essential. Continued research into the safety, efficacy, and practical implementation of IF is necessary to expand its accessibility and address its limitations in vulnerable populations [7].

Research on the effects of intermittent fasting on the endocrine system, conducted in both human and animal (mice and rats) models, provides important information about its mechanisms and potential health benefits, which are summarized in the Table 2 and Table 3.

Table 2. Human Data on Hormone Changes due to Intermittent Fasting

Hormone	Key Findings (Humans)	Numerical Data	Potential Implications
Insulin [1, 2, 4, 11, 12, 18, 28, 39,]	Plasma insulin reduced significantly; improved sensitivity; shifted circadian secretion	↓ Plasma insulin by >50%	Improved glucose regulation and metabolic health
Androgens (PCOS) [6]	Reduced androgen levels; improved ovulatory function; reduced visceral fat	FAI reduced; ↓ Visceral fat	Better management of PCOS symptoms and fertility improvement
Testosterone (Men) [6]	Decreased levels; no compromise in muscle mass or strength	↓ Testosterone; no muscle loss	Maintains physical performance despite hormone reduction
Leptin [3, 23]	Leptin levels decrease; improves TSH regulation and appetite modulation	↓ Leptin	Improved appetite control and energy homeostasis
Growth Hormone [24, 25, 26, 27]	Increased secretion during fasting; supports lean mass preservation	↑ Growth hormone levels	Preservation of muscle mass and metabolic activity

Table 3. Animal Data on Hormone Changes due to Intermittent Fasting

Hormone	Key Findings (Animals)	Numerical Data	Potential Implications
Insulin [37]	Prolonged alternate-day fasting decreases insulin secretion independently of caloric intake	↓ Insulin secretion	Improved glucose regulation and metabolic health
Thyroid Hormones (T3, TSH) [1]	T3 reduced significantly; TSH suppression observed with hypothalamic-pituitary-thyroid axis reduction	↓ T3 by up to 55%; ↓ TSH levels	Potential reduction in metabolic rate; endocrine regulation adjustments
Cortisol [15, 41]	Elevated levels during fasting; shifts in circadian rhythm of cortisol secretion	↑ Cortisol	Increased energy mobilization; prolonged elevation may counter anti-inflammatory benefits

Hormone	Key Findings (Animals)	Numerical Data	Potential Implications
Leptin [35]	Leptin levels decrease during fasting, modulating hypothalamic pathways	↓ Leptin	Supports energy homeostasis and hormonal balance
Growth Hormone [40]	Growth hormone levels increase, supporting energy mobilization and tissue preservation	↑ Growth hormone levels	Preservation of lean mass and stimulation of metabolic activity during fasting

By manipulating feeding windows and energy intake in animal models, researchers have observed the effects on hormones, cellular signaling pathways, and gene expression, providing a foundational mechanistic understanding that informs and validates the design of human clinical trials. For instance, preclinical data from mice and rats have shown how intermittent fasting can directly alter insulin secretion [37], reduce T3 levels [1], and elevate cortisol [41, 15]. These animal studies have been indispensable for research on aging and the progression of diseases like Alzheimer's, allowing for the observation of an entire lifespan in a compressed timeframe. They yield data on the preventive potential of long-term dietary strategies and serve as hypothesis-generating tools to be tested in controlled, well-designed human trials.

The combined evidence from human trials and preclinical animal models offers a compelling synthesis, revealing a coherent and well-supported rationale for the efficacy of intermittent fasting. The findings from animal models (as shown in Table 3) provide the mechanistic foundation that validates the clinical observations in humans (as shown in Table 2). The research consistently points to a core biological principle: the "metabolic switch" induced by fasting.

Human trials corroborate and give real-world relevance to these preclinical insights. The practical health benefits, such as significant reductions in plasma insulin [39, 12, 18, 28], improved appetite control linked to lower leptin levels [3, 23], and the preservation of muscle mass supported by increased growth hormone [24, 25, 26, 27], are given deeper meaning by the mechanistic insights from animal models. This convergence of findings across species suggests a virtuous cycle, collectively establishing intermittent fasting not merely as a lifestyle trend but as a powerful, evolutionarily-conserved physiological response with broad therapeutic potential.

These findings have significant practical implications, positioning IF as an evidence-based dietary strategy. However, its application must be highly individualized, considering factors like a patient's health status, comorbidities, and lifestyle. It should be integrated into a broader health plan with patient education and proper monitoring to ensure long-term safety and prevent adverse effects like hypoglycemia or a worsening of disordered eating behaviors.

CONCLUSIONS

Intermittent fasting (IF) demonstrates measurable benefits across multiple domains, including improvements in insulin sensitivity, weight reduction, lipid profile, and potential protective effects against type 2 diabetes, cardiovascular disease, and neurodegenerative disorders. These outcomes are mediated by mechanisms such as hormonal modulation, enhanced autophagy, and improved metabolic flexibility. However, current evidence indicates that, over the long term, IF may yield results comparable to continuous calorie restriction, highlighting the need to individualize dietary strategies. Selection of an IF regimen should take into account clinical context, comorbidities, patient preferences, and potential interactions with pharmacotherapy. Existing limitations include a scarcity of long-duration randomized controlled trials, insufficient data for specific populations, and variable adherence rates.

Future research should focus on head-to-head comparisons with other dietary interventions, evaluation in underrepresented groups, and the development of personalized protocols that incorporate genetic, hormonal, and lifestyle factors.

From a clinical perspective, IF should be regarded as one of several evidence-based dietary strategies rather than a universal solution. When considering IF for a patient, clinicians should assess metabolic status, treatment goals, comorbidities, and potential contraindications such as eating disorders, pregnancy, or specific metabolic diseases. Integration with other lifestyle interventions, including regular physical activity and appropriate pharmacotherapy, may enhance outcomes but requires careful monitoring to prevent adverse effects such as hypoglycemia. Structured follow-up and patient education on gradual implementation and sustainable adherence are essential for maximizing long-term benefits.

DISCLOSURES

AUTHOR CONTRIBUTION

Conceptualization – Jakub Prosowski; methodology – Jakub Prosowski, Szczepan Pośpiech, Piotr Serwicki, Michał Piotrowski; formal analysis, investigation – Karolina Paks, Bartosz Zabrzeński, writing – original draft – Jakub Prosowski, writing – review & editing – Szczepan Pośpiech, Jessika Schendzielorz, Michał Piotrowski, Piotr Serwicki; visualization – Jakub Prosowski, Karolina Paks, Jakub Początek; supervision – Jakub Prosowski, project administration – Karolina Paks, Bartosz Zabrzeński, Jessika Schendzielorz

USE OF AI

AI-based software was applied only for grammar checking and language editing, with all modifications reviewed and approved by the authors.

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CONFLICT OF INTEREST STATEMENT

Authors have declared no conflict of interests.

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