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Intermittent fasting as a metabolic reprogramming strategy: Emerging molecular mechanisms and clinical perspectives

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Abstract
Intermittent fasting (IF) has emerged as a promising dietary strategy for improving metabolic health and preventing chronic diseases. Unlike traditional calorie restriction, IF focuses on cycling between periods of eating and fasting, thereby inducing adaptive metabolic responses. Growing evidence suggests that IF acts as a metabolic reprogramming strategy by modulating nutrient-sensing pathways, mitochondrial function, circadian biology, inflammation, oxidative stress, and autophagy. Various IF regimens, including alternate-day fasting, time-restricted feeding, and periodic fasting, have demonstrated beneficial effects on obesity, insulin resistance, cardiovascular disease, neurodegenerative disorders, and cancer. At the molecular level, IF influences key signaling pathways such as AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), sirtuins, insulin/IGF-1 signaling, and ketogenesis. These mechanisms collectively improve metabolic flexibility and cellular resilience. Clinical studies have shown that IF can reduce body weight, improve glycemic control, enhance lipid metabolism, and promote longevity-associated pathways. However, concerns remain regarding adherence, safety in vulnerable populations, and long-term sustainability. This review summarizes the emerging molecular mechanisms underlying IF-induced metabolic reprogramming and discusses current clinical evidence, therapeutic applications, limitations, and future research directions.

Keywords: Intermittent fasting, metabolic reprogramming, autophagy, AMPK, mTOR, ketogenesis, obesity, insulin resistance, circadian rhythm

Introduction

Intermittent fasting (IF) has gained substantial scientific and clinical interest as a nutritional intervention capable of improving metabolic health and preventing chronic diseases (de Cabo & Mattson, 2019) [7]. Unlike conventional dietary strategies that emphasize caloric restriction or nutrient composition, IF primarily focuses on the timing of food intake (Patterson & Sears, 2017) [48]. The fasting-feeding cycle triggers adaptive physiological responses that influence cellular metabolism, energy homeostasis, and stress resistance (Mattson *et al*., 2018) [53]. Historically, fasting has been practiced for religious, spiritual, and cultural purposes for centuries; however, modern biomedical research has revealed its potential role in metabolic regulation and disease prevention (Longo & Panda, 2016) [31].

The increasing prevalence of obesity, type 2 diabetes mellitus, cardiovascular disorders, and metabolic syndrome has intensified the search for effective dietary interventions (Chiefari *et al*., 2021) [14]. Emerging evidence suggests that IF can promote metabolic flexibility by shifting energy utilization from glucose metabolism to fatty acid oxidation and ketone body production (Anton *et al*., 2018) [2]. These metabolic changes induce molecular adaptations involving nutrient-sensing pathways, mitochondrial remodeling, and cellular repair mechanisms (Di Francesco *et al*., 2018) [16]. Consequently, IF is now considered a metabolic reprogramming strategy capable of modifying systemic physiology and cellular function (Ganesan *et al*., 2018) [19].

Recent studies indicate that IF may exert therapeutic effects beyond weight reduction. Improvements in insulin sensitivity, inflammatory status, oxidative stress, gut microbiota composition, and neuroprotection have been observed in both animal and human studies (Malinowski *et al*., 2019 [32]; Su *et al*., 2021). Furthermore, IF may influence longevity-related pathways and reduce the risk of age-associated diseases (Fontana *et al*., 2010) [18]. Despite these promising findings, variations in fasting protocols, patient adherence, and individual metabolic responses present challenges in clinical application (Horne *et al*., 2020) [24]. Therefore, understanding the molecular basis and clinical implications of IF is essential for optimizing its therapeutic potential.

Types of Intermittent Fasting

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1. Alternate-Day Fasting

Alternate-day fasting (ADF) is a dietary approach in which individuals alternate between fasting days and normal eating days. During fasting days, calorie intake is either completely avoided or significantly restricted, usually to about 20–25% of daily energy requirements (Varady *et al*., 2013) [57]. This fasting pattern promotes a metabolic shift from glucose utilization to fat oxidation, encouraging the body to use stored fat as an energy source. Research has demonstrated that ADF can effectively reduce body weight, improve insulin sensitivity, lower blood glucose levels, and decrease inflammatory biomarkers associated with obesity and metabolic syndrome (Hoddy *et al*., 2014; Stekovic *et al*., 2019) [4, 51]. In addition, ADF may enhance cellular repair processes such as autophagy and improve cardiovascular health markers including blood pressure and lipid profile (Trepanowski *et al*., 2017) [55]. Due to its flexibility and effectiveness, ADF has become one of the most widely studied forms of intermittent fasting.

2. Time-Restricted Feeding

Time-restricted feeding (TRF) is a form of intermittent fasting that restricts daily food consumption to a limited time window, typically between 6 and 10 hours, followed by a prolonged fasting period for the remainder of the day (Catterson *et al*., 2018) [10]. Unlike traditional calorie restriction, TRF focuses more on meal timing than calorie counting. This eating pattern is closely linked with circadian biology, as it aligns food intake with the body's natural metabolic rhythms (Melkani & Panda, 2017) [37]. Studies suggest that TRF can improve glucose metabolism, enhance insulin sensitivity, promote fat oxidation, and reduce body weight even without significant caloric reduction (Moro *et al*., 2016; Wilkinson *et al*., 2020) [42, 61]. Furthermore, TRF may improve sleep quality, regulate hormonal balance, and support mitochondrial function (Jamshed *et al*., 2019) [28]. Early daytime eating windows appear particularly beneficial because they synchronize better with the body's internal biological clock and metabolic activity (Sutton *et al*., 2018) [53].

3. Periodic Fasting

Periodic fasting refers to fasting practices that involve extended fasting periods lasting from 24 to 72 hours and performed weekly, monthly, or at other regular intervals (Long *et al*., 2021) [29]. One of the most common examples is the 5:2 diet, where individuals consume normal meals for five days of the week and restrict calorie intake on two nonconsecutive days (Harvie *et al*., 2011) [22]. Periodic fasting induces profound metabolic adaptations including glycogen depletion, increased ketone body production, enhanced fat metabolism, and activation of cellular stress response pathways (Wei *et al*., 2017) [60]. Research indicates that periodic fasting may contribute to weight loss, improved insulin sensitivity, reduced oxidative stress, and enhanced cellular repair mechanisms (Carter *et al*., 2018) [9]. Additionally, prolonged fasting periods may stimulate autophagy and immune system regeneration, potentially lowering the risk of chronic diseases such as diabetes, cardiovascular disorders, and neurodegenerative conditions (Brandhorst *et al*., 2015) [5].

4. Religious and Cultural Fasting

Religious and cultural fasting practices have been followed for centuries across different civilizations and faith traditions for spiritual, ethical, and health-related purposes. One of the most widely practiced forms is Ramadan fasting, observed by Muslims worldwide, during which individuals abstain from food and drink from dawn to sunset for an entire month (Farooq *et al*., 2019) [17]. Similar fasting traditions exist in Hinduism, Buddhism, Christianity, and Judaism (Trepanowski & Bloomer, 2010) [54]. Scientific studies suggest that properly managed religious fasting may provide metabolic benefits such as reductions in body weight, improved lipid profile, enhanced insulin sensitivity, and decreased inflammatory markers (Adawi *et al*., 2019; Mindikoglu *et al*., 2020) [1, 38]. These fasting practices may also encourage mindful eating, discipline, and improved psychological well-being. However, the health effects of religious fasting largely depend on dietary quality, hydration status, meal timing, and lifestyle habits during non-fasting hours.

Metabolic Adaptations During Intermittent Fasting

During fasting, the body undergoes a metabolic switch from glucose utilization to fat oxidation (Mishra & Mishra, 2025; Mohamed *et al*., 2024) [39, 41]. Initially, glycogen stores in the liver are depleted, leading to increased lipolysis and the release of free fatty acids (Mohamed *et al*., 2024; Wang & Wu, 2022) [41, 59]. These fatty acids are converted into ketone bodies in the liver, providing an alternative energy source for tissues, particularly the brain (Mishra & Mishra, 2025; Wang *et al*., 2026) [39, 58].

Ketone bodies such as beta-hydroxybutyrate (βOHB) function not only as metabolic fuels but also as signaling molecules regulating gene expression, inflammation, and oxidative stress (Newman & Verdin, 2017; Pali, 2024) [44, 46]. IF also improves metabolic flexibility, enabling cells to efficiently adapt to nutrient scarcity and energy demands (Mishra & Mishra, 2025) [39]. Enhanced mitochondrial biogenesis and improved insulin sensitivity are additional hallmarks of fasting-induced metabolic adaptation (Kim *et al*., 2019; Pali, 2024) [28, 46].

Molecular Mechanisms of Metabolic Reprogramming

1. AMP-Activated Protein Kinase (AMPK) Activation

AMPK is a critical energy sensor activated during low-energy states such as fasting. Activation of AMPK stimulates fatty acid oxidation, glucose uptake, and mitochondrial biogenesis while inhibiting anabolic processes (Burkewitz *et al*., 2014) [6]. IF-induced AMPK activation contributes to improved metabolic efficiency and reduced lipid accumulation (Cantó *et al*., 2015) [8].

2. Inhibition of mTOR Signaling

The mammalian target of rapamycin (mTOR) pathway regulates cellular growth and protein synthesis. Excessive mTOR activation is associated with aging, cancer, and metabolic disorders. Fasting suppresses mTOR activity, thereby promoting autophagy and cellular repair processes (Saxton & Sabatini, 2017) [50].

3. Sirtuin Activation

Sirtuins are NAD^+-dependent enzymes involved in mitochondrial regulation, stress resistance, and longevity. IF increases NAD^+ availability, thereby activating sirtuins such as SIRT1 (Imai & Guarente, 2014) [25]. This activation enhances mitochondrial function and reduces oxidative damage (Chang & Guarente, 2014) [13].

4. Autophagy Induction

Autophagy is a cellular recycling process that removes damaged organelles and proteins. IF stimulates autophagy through AMPK activation and mTOR inhibition (Mizushima & Komatsu, 2011) [40]. Enhanced autophagy contributes to improved cellular homeostasis and protection against neurodegenerative diseases (Bagherniya *et al*., 2018) [3].

5. Ketogenesis and Ketone Signaling

Fasting-induced ketogenesis results in the production of ketone bodies, particularly beta-hydroxybutyrate. These molecules regulate inflammatory pathways, oxidative stress responses, and epigenetic modifications, thereby influencing metabolic health and longevity (Newman & Verdin, 2017) [44].

6. Insulin and IGF-1 Pathway Modulation

IF reduces circulating insulin levels and improves insulin sensitivity. Suppression of insulin-like growth factor-1

(IGF-1) signaling is associated with enhanced stress resistance and reduced cellular proliferation, potentially lowering cancer risk (Fontana *et al*., 2010) [18].

Intermittent Fasting and Circadian Biology

Circadian rhythms regulate metabolism, hormone secretion, and energy homeostasis. Disruption of circadian rhythms is associated with obesity, diabetes, and cardiovascular disease (Panda, 2016) [47]. Time-restricted feeding synchronizes food intake with circadian clocks, thereby improving metabolic efficiency (Melkani & Panda, 2017) [37].

Eating during daytime hours aligns with natural hormonal cycles and enhances glucose metabolism. Conversely, late-night eating may impair insulin sensitivity and increase adiposity (Chaix *et al*., 2014) [12]. Therefore, circadian alignment represents a key mechanism underlying the benefits of IF.

Clinical Perspectives of Intermittent Fasting

1. Obesity and Weight Management

Numerous clinical studies demonstrate that IF effectively reduces body weight, visceral fat, and waist circumference (Harris *et al*., 2018) [21]. IF promotes negative energy balance while preserving lean body mass in many individuals (Varady, 2011) [56].

2. Type 2 Diabetes Mellitus

IF improves insulin sensitivity, fasting glucose levels, and glycated hemoglobin (HbA1c) (Barnosky *et al*., 2014) [4]. Reduced hepatic glucose production and enhanced fat oxidation contribute to glycemic control (Grajower & Horne, 2019) [20].

3. Cardiovascular Disease

IF has been associated with reductions in blood pressure, low-density lipoprotein cholesterol, triglycerides, and inflammatory markers (Malinowski *et al*., 2019) [32]. Improved endothelial function and oxidative stress reduction may lower cardiovascular risk (Mattson *et al*., 2017) [34].

4. Neurodegenerative Disorders

Experimental evidence suggests that IF may protect against neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Mattson *et al*., 2018) [35]. Ketone bodies provide neuroprotective effects, while autophagy removes toxic protein aggregates (Phillips, 2019) [49].

5. Cancer Prevention and Therapy

IF may reduce cancer risk by decreasing insulin and IGF-1 signaling, suppressing inflammation, and enhancing cellular stress resistance (Nencioni *et al*., 2018) [43]. Some studies suggest that fasting may improve chemotherapy tolerance and selectively sensitize cancer cells to treatment (Longo & Fontana, 2010) [18].

6. Non-Alcoholic Fatty Liver Disease

IF improves hepatic lipid metabolism and reduces liver fat accumulation. Enhanced fatty acid oxidation and improved insulin sensitivity contribute to liver health (Kadasah *et al*., 2024) [27].

Intermittent Fasting and Gut Microbiota

Emerging evidence indicates that IF modulates gut microbiota composition and diversity. Fasting may increase beneficial bacterial populations associated with short-chain fatty acid production and anti-inflammatory effects (Su *et al*., 2021). Alterations in gut microbiota may contribute to improved metabolic outcomes and immune regulation (Catterson *et al*., 2018) [10].

Potential Risks and Limitations

Despite its benefits, IF may not be suitable for all individuals. Potential adverse effects include fatigue, headaches, irritability, hypoglycemia, and nutrient deficiencies in poorly planned diets (Cabo & Mattson, 2019) [7]. Pregnant women, children, elderly individuals with frailty, and patients with eating disorders require careful medical supervision (Ganesan *et al*., 2018) [19].

Long-term adherence remains a challenge, and clinical outcomes may vary depending on fasting protocol, dietary quality, physical activity, and genetic factors (Horne *et al*., 2020) [24]. Additional long-term randomized controlled trials are necessary to establish standardized recommendations.

Future Directions

Future research should focus on personalized fasting strategies based on genetics, microbiome composition, age, sex, and metabolic status. Understanding the interaction between IF and chrononutrition may optimize therapeutic outcomes. Integration of omics technologies, metabolomics, and systems biology approaches will further clarify molecular mechanisms underlying metabolic reprogramming.

Moreover, combining IF with exercise, pharmacological agents, or functional foods may enhance therapeutic efficacy. Large-scale multicenter clinical trials are required to determine long-term safety, sustainability, and disease-specific applications.

Table 1: Molecular Mechanisms and Clinical Perspectives of Intermittent Fasting-Induced Metabolic Reprogramming (Mattson *et al*., 2018) [35]

Molecular Node / Trigger	Downstream Mechanism / Cellular Actions	Clinical Outcomes & Therapeutic Perspectives
AMPK Activation (High AMP/ATP Ratio)	Downregulates anabolic pathways; phosphorylates and accelerates the degradation of core clock repressors (e.g., CRY proteins).	Enhances dynamic insulin sensitivity, lowers hepatic glucose production, and maintains peripheral clock synchronization.
SIRT1 & NAD^+ Surge	Deacetylates PER2 and BMAL1; works alongside PGC-1α to stimulate mitochondrial biogenesis.	Enhances cellular energy efficiency, mitigates oxidative stress, and counteracts age-related vascular decline.
mTOR Suppression (During extended fasting window)	Activates the ULK1 initiation complex, prompting the clearance of misfolded proteins and dysfunctional organelles.	Clears cellular debris (autophagy), protects against neurodegenerative accumulation, and reduces oncogenic risk.
Metabolic Switching (Glycogen depletion	Promotes the conversion of fatty acids into hepatic ketone bodies (β-hydroxybutyrate); represses	Reduces intrahepatic triglycerides (NAFLD mitigation), reduces circulating visceral adiposity, and lowers

$\rightarrow$ Lipolysis)	de novo lipogenesis.	atherogenic LDL-C.
Circadian Phase Alignment (eTRE Framework)	Aligns nutrient arrival with peak morning insulin sensitivity and optimal biological clock expression.	Enhances dynamic glycemic control, lowers systemic blood pressure, and reduces overall cardiovascular disease risk.
Peripheral Counter-Clock Tuning	Synchronizes local metabolic tissues (liver, white adipose tissue) with central hypothalamic SCN signals.	Mitigates metabolic desynchronization, reduces systemic inflammation, and regulates appetite signaling pathways (ghrelin/leptin).

Conclusion

Intermittent fasting represents a promising metabolic reprogramming strategy with broad therapeutic potential. Through modulation of nutrient-sensing pathways, mitochondrial function, autophagy, ketogenesis, and circadian biology, IF improves metabolic flexibility and cellular resilience. Clinical evidence supports its role in obesity management, diabetes control, cardiovascular protection, neuroprotection, and healthy aging. Nevertheless, individualized approaches and further long-term research are essential for translating mechanistic insights into clinical practice. As scientific understanding continues to evolve, IF may become an integral component of precision nutrition and metabolic medicine.

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