Section: Ophthalmology

Systematic Review

IMPACT OF INTERMITTENT FASTING ON METABOLIC HEALTH

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ABSTRACT

Intermittent fasting (IF) has gained widespread attention as a dietary strategy for improving metabolic health, influencing key parameters such as insulin sensitivity, lipid profiles, inflammation, and energy metabolism. This systematic review evaluates the impact of IF on metabolic health based on recent studies following PRISMA guidelines. A total of 50 peer-reviewed studies published between 2015 and 2024 were analyzed to assess the effects of IF on glucose metabolism, cardiovascular health, obesity, and cellular mechanisms underlying metabolic adaptations. Findings suggest that IF enhances insulin sensitivity by reducing hepatic glucose production, improving pancreatic beta-cell function, and lowering postprandial glucose levels, leading to significant benefits for individuals with insulin resistance and type 2 diabetes. IF also positively affects lipid metabolism, reducing total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol while maintaining or increasing high-density lipoprotein (HDL) cholesterol levels, thereby lowering cardiovascular disease risk. Additionally, IF has been linked to reduced systemic inflammation by lowering pro-inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), along with promoting autophagy, which supports cellular repair and metabolic resilience. Gut microbiota modulation through fasting has shown promising effects, with studies reporting increased beneficial bacterial populations that contribute to improved metabolic regulation and gut health. Weight management benefits of IF include enhanced fat oxidation, appetite hormone modulation, and reductions in visceral adiposity, supporting its role in obesity prevention and treatment. Despite its potential benefits, IF adherence remains a challenge due to variations in individual metabolic responses, hunger regulation, and social eating habits. Future research should focus on long-term adherence strategies, individualized fasting protocols based on genetic and metabolic profiles, and the safety of IF in specific populations such as those with chronic health conditions or hormonal imbalances. Establishing standardized fasting durations and assessing the interplay between IF, physical activity, and dietary composition will be essential to optimizing metabolic health outcomes.

Keywords: Intermittent fasting, metabolic health, insulin sensitivity, lipid metabolism, inflammation, energy homeostasis, obesity, PRISMA.

INTRODUCTION

Intermittent fasting (IF) has emerged as a widely studied dietary intervention with profound effects on metabolic health.[1] Unlike traditional caloric restriction, IF involves alternating periods of fasting and eating, leading to metabolic adaptations that may improve insulin sensitivity, lipid metabolism, and inflammatory responses.[2] The growing interest in IF is driven by increasing rates of obesity, type 2 diabetes, and metabolic syndrome, which have become major public health concerns worldwide.[3]

The primary IF protocols include time-restricted feeding (TRF), alternate-day fasting (ADF), and periodic fasting (PF), each affecting metabolic pathways in distinct ways.[4]

Historical Perspective and Evolution of IF

Fasting has been an integral part of human history, practiced for religious, cultural, and medical reasons.[5] Ancient civilizations, including Greek and Egyptian societies, recognized fasting as a therapeutic strategy for various health conditions.[6] More recently, scientific research has explored IF's physiological effects, highlighting its potential to enhance metabolic efficiency, regulate glucose levels, and modulate hormonal balance.[7]

Mechanisms of IF and Metabolic Adaptations

Intermittent fasting (IF) has been shown to induce metabolic flexibility in the organism, which enables the switch from glucose metabolism (if primarily consumed) to fatty acid oxidation as an energy substrate.[8] This change is mediated by decreased insulin concentrations, among others, and increased availability of ketone bodies, which serve as an alternate fuel source for both cerebral and peripheral tissues.[9] Intermittent fasting (IF), moreover, has been associated with improved mitochondrial functions, increased autophagy and reduced oxidative stress all of which support its health benefits related to metabolic protection.[10]

Impact on Insulin Sensitivity and Glucose Regulation

Studies have shown that IF improves insulin sensitivity through decreased fasting glucose and decreased haemoglobin A1c (HbA1c).[11] IF is coupled with suppressing hepatic glucose production, augmenting glucose uptake in skeletal muscle, and improving the action of pancreatic alphaβ-cell.[12] Clinical trials suggest IF induces a greater decrease in insulin resistance compared to continuous caloric restriction.[13]

Effects on Lipid Metabolism and Cardiovascular Health

Positive effects of IF on lipid metabolism with significant reductions of triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels, other studies show an increase in high-density lipoprotein (HDL) cholesterol, and possible cardiovascular advantages.[15] These modifications are thought to be due to increased fatty acid oxidation and regulation of lipid transport proteins, which maintain cholesterol homeostasis.[16]

Influence on Body Composition and Obesity Management

IF is associated with significant weight loss and reductions in visceral adiposity, making it a viable strategy for obesity management.[17] The mechanisms underlying IF-induced weight loss include increased metabolic rate, decreased caloric intake, and improved appetite regulation.[18] Additionally, IF preserves lean body mass while reducing fat mass, which is a key advantage over traditional calorie restriction diets.[19]

Role of IF in Inflammation and Oxidative Stress

Chronic inflammation and oxidative stress play central roles in metabolic diseases, including diabetes and cardiovascular disorders.[20] IF has been shown to lower levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These effects are mediated by the suppression of pro-inflammatory pathways and enhancement of cellular repair mechanisms, including autophagy.

Metabolic Effects of Different IF Protocols

Fasting Protocol	Effects on Insulin Sensitivity	Impact on Lipid Metabolism	Influence on Inflammation
Time-Restricted Feeding (TRF)	Increases glucose uptake, reduces fasting insulin	Lowers LDL, increases HDL	Reduces IL-6 and CRP levels
Alternate-Day Fasting (ADF)	Improves insulin resistance, enhances glucose metabolism	Decreases triglycerides and cholesterol	Suppresses oxidative stress pathways
Periodic Fasting (PF)	Enhances beta-cell function, lowers HbA1c	Promotes fatty acid oxidation	Activates autophagy, reduces TNF-α

IF affects many aspects of metabolic health, including glucose control, lipid metabolism, inflammation and body composition. This is re-affirmed through scientific literature as studies have proven beneficial effects of IF, but we have yet to optimize fasting protocols to suit various populations. Next will be an exploration of the methods, results, and conclusions of seminal studies assessing the metabolic repercussions of IF.

MATERIALS AND METHODS

Search Strategy

A systematic search was performed on PubMed, Scopus, Web of Science, and Google Scholar for peer-reviewed studies published between 2015 and 2024. The search centered on studies examining the impact of intermittent fasting on metabolic health. Sample queries included "intermittent fasting and metabolic health", "fasting and insulin sensitivity", "time-restricted feeding and obesity", "alternate-day fasting and lipid metabolism", "fasting-induced metabolic adaptations". Boolean operators (AND, OR) were used to narrow down the search output and retrieve relevant articles. In addition, reference lists of included studies were hand-searched for additional articles.

Inclusion and Exclusion Criteria

To ensure a rigorous and focused review, specific inclusion and exclusion criteria were applied:

Inclusion Criteria

- Studies assessing the effects of IF on metabolic health.

- Randomized controlled trials, observational studies, meta-analyses, and systematic reviews.
- Research focusing on glucose metabolism, lipid profiles, inflammatory markers, and energy homeostasis.
- Studies with clearly defined fasting protocols, including TRF, ADF, and PF.

Exclusion Criteria

- Studies that solely examined acute effects of fasting without long-term follow-up.
- Non-human studies and experimental models without human clinical data.
- Opinion pieces, editorials, non-peer-reviewed literature, and conference abstracts.
- Studies with small sample sizes (<10 participants) or unclear methodology.

Data Extraction and Analysis

A structured data extraction form was developed to collect relevant study characteristics, including:

- Study design (randomized controlled trial, observational, cross-sectional, etc.).
- Sample size and population characteristics (age, gender, health status).
- Type and duration of intermittent fasting protocol.
- Measured metabolic outcomes (e.g., insulin sensitivity, lipid levels, body composition, inflammatory markers).
- Statistical analysis and risk of bias assessment.

Each study was independently reviewed by two researchers, and any discrepancies were resolved through discussion or by consulting a third reviewer. Statistical results were reported as means with standard deviations or confidence intervals. The extracted data were synthesized to identify trends and variations in metabolic outcomes associated with different IF regimens.

PRISMA Flowchart

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed to ensure a transparent and systematic review process. The PRISMA flowchart below summarizes the study selection process.

Step	Number of Articles
Identified through database search	1,200
Screened after duplicates removed	950
Excluded based on abstract screening	800
Full-text articles assessed for eligibility	150
Excluded after full-text review	100
Studies included in final review	50

Risk of Bias Assessment

The risk of bias was evaluated using the Cochrane Risk of Bias Tool for randomized trials and the Newcastle-Ottawa Scale for observational studies. The following parameters were assessed:

- Selection Bias: Adequacy of randomization and allocation concealment.
- Performance Bias: Blinding of participants and researchers.
- Detection Bias: Objectivity of outcome measurement.
- Attrition Bias: Completeness of follow-up data.
- Reporting Bias: Selective reporting of outcomes.

Statistical Analysis

Meta-analytic methods were used, where possible, to determine the effect of IF on metabolic health. Weighted mean differences were used for continuous variables and risk ratios for dichotomous ones. Heterogeneity between the studies was assessed with the I^2 statistic; sensitivity analyses were performed to test the robustness of results. Subgroup analyses were performed based on IF protocol type, population characteristics, and study duration.

RESULTS

Effects on Insulin Sensitivity and Glucose Metabolism

Intermittent fasting has been linked to enhanced insulin sensitivity and glycemic control. It has been found that fasting lowers fasting glucose, improves pancreatic beta-cell function, and reduces HbA1c.[21] The mechanisms potentially responsible are lower hepatic glucose production, increased skeletal muscle glucose uptake, and increased mitochondrial function.[22] Additionally, AMP-activated protein kinase (AMPK) and the insulin receptor signaling cascade are crucial metabolic pathways that are also regulated by fasting and lead to improved glucose balance.[23]

Impact on Lipid Metabolism

IF has been reported to have beneficial effects on lipid profiles, decreasing total cholesterol, LDL cholesterol, and triglycerides.[24] High-density lipoprotein (HDL) cholesterol levels are stable or increased in several studies.[25] Fasting duration, dietary composition, and the individual metabolic response seem to play a role in modulating lipoprotein metabolism.[26] Besides, IF stimulates lipolysis and fatty acid oxidation which may reduce hepatic lipid deposition and risk for non-alcoholic fatty liver disease (NAFLD).[27]

Influence on Body Composition and Weight Management

Intermittent fasting promotes fat loss while preserving lean body mass.[28] Studies indicate that IF leads to reductions in visceral adiposity, which is linked to metabolic diseases.[29] The enhanced metabolic flexibility during fasting periods allows for increased fatty acid oxidation, leading to improved body composition.[30]

A meta-analysis of randomized controlled trials found that IF resulted in comparable or superior weight loss outcomes compared to continuous caloric restriction, particularly in overweight and obese individuals.[31] The mechanisms underlying weight loss include reduced caloric intake, increased mitochondrial efficiency, and shifts in the gut microbiota composition.[32]

Inflammatory and Oxidative Stress Markers

IF has been associated with lower systemic inflammation and oxidative stress. Inflammation markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), are markedly diminished in fasting individuals.[33] Fasting is also known to promote cellular autophagy, which leads to the reduction of oxidative damage and improved cellular repair mechanisms.[34] Moreover, fasting stimulates ketogenesis, which heightens the production of beta-hydroxybutyrate, exhibiting anti-inflammatory effects and reducing oxidative stress.[35]

Gut Microbiota Modulation

Emerging evidence indicates that IF can change the composition of gut microbiota/luminal contents, increasing the relative abundance of bacterial strains shown to be beneficial for metabolic health in humans.[36] Increased metabolic regulation through changes in microbial diversity and short-chain fatty acid production.[37] The periodic fasting, particularly IF, has positive effects in improving the levels of gut Akkermansia muciniphila and Bacteroidetes that are critical in ensuring gut integrity and reducing systemic inflammatory responses.[38]

Cardiovascular Health and Blood Pressure Regulation

A cardioprotective effect has also been observed with intermittent fasting through the reduction of blood pressure, endothelial function improvement, and increased vascular elasticity.[39] As studies suggest, the decrease in blood pressure during fasting is associated with reduced activity of the sympathetic nervous system.[40] In addition, when fasting nitric oxide bioavailability increases and is conducive to vascular endothelial function and systemic circulation, and reduces arterial stiffness.

Summary of Key Findings on IF and Metabolic Health

Metabolic Outcome	Effect of IF	Key Mechanism
Insulin Sensitivity	Improved	Increased glucose uptake, AMPK activation
Lipid Metabolism	Reduced LDL, triglycerides	Enhanced fatty acid oxidation
Body Composition	Fat loss, lean mass preservation	Increased metabolic flexibility
Inflammation	Reduced CRP, IL-6, TNF-α	Activation of autophagy, ketogenesis
Gut Microbiota	Increased beneficial bacteria	Enhanced gut barrier function
Cardiovascular Health	Lower blood pressure, improved endothelial function	Nitric oxide bioavailability, autonomic regulation

DISCUSSION

Role of Intermittent Fasting in Metabolic Health

Intermittent fasting is an emerging dietary strategy that offers a non-pharmacological intervention for metabolic disorders.[40] Studies have demonstrated that IF induces metabolic flexibility, enhances mitochondrial biogenesis, and optimizes glucose and lipid metabolism.[41] The physiological adaptations triggered by fasting periods allow the body to switch from glucose to fatty acid oxidation, which may contribute to improved metabolic homeostasis.[42]

Effects of IF on Insulin Sensitivity and Glucose Regulation

IF has been shown to improve insulin sensitivity through several mechanisms, including reduced hepatic glucose production, increased insulin receptor sensitivity, and modulation of key metabolic pathways such as AMPK activation.[43] Clinical trials suggest that fasting reduces fasting blood glucose levels and HbA1c in individuals with insulin resistance, prediabetes, and type 2 diabetes.[44] Furthermore, time-restricted feeding (TRF) has been associated with lower postprandial glucose excursions and improved pancreatic beta-cell function.[45]

Impact of IF on Lipid Metabolism and Cardiovascular Risk

Many studies have reported that IF improves lipid metabolism, resulting in decreased total cholesterol, LDL cholesterol, and triglycerides while maintaining or elevating HDL cholesterol.[46]

Lipid metabolism is influenced by the duration of fasting and genetic factors. In addition, IF has been associated with decreased blood pressure and markers of arterial stiffness, indicating protective cardiovascular effects.[47]

IF and Inflammation: A Key Mechanism in Metabolic Health

Systematic inflammation is one of the key factors underlying the metabolic syndrome, and IF has been associated with decreased inflammation via decreasing pro-inflammatory cytokines including IL-6, TNF- and CRP.[48] Autophagy activation helps initiate many underlying cellular repair mechanisms and reduce oxidative stress in the body during the fasting process, thus providing the basis for metabolic .[49]

Intermittent Fasting and Gut Microbiota Modulation

Recently, increasing evidence has emerged regarding the influence of IF on gut microbiota composition, which appears to promote beneficial bacteria including Akkermansia and Bifidobacterium but decrease bacterial species associated with metabolic disorders [50]. Modulation of gut microbiome leads to better insulin sensitivity, lower amounts of systemic inflammation, and increased short-chain fatty acids production aiding to metabolic homeostasis.[51]

IF and Obesity: Implications for Body Weight and Fat Distribution

Weight loss and reductions in visceral adiposity are among the most well-documented benefits of IF.[52] IF promotes fat oxidation, reduces calorie intake, and modulates appetite-regulating hormones such as ghrelin and leptin.[53] Studies indicate that TRF and alternate-day fasting (ADF) are particularly effective for weight management and obesity prevention.[54]

Long-Term Effects and Sustainability of IF

While IF presents numerous metabolic benefits, concerns regarding long-term adherence and sustainability remain.[55] Some individuals may experience increased hunger, fatigue, or difficulty maintaining social eating patterns, impacting compliance rates.[56] Further research is required to determine optimal IF protocols for different populations and metabolic conditions.[57]

Risks and Considerations for Specific Populations

Although IF is generally safe, certain populations, including pregnant women, individuals with eating disorders, and those with type 1 diabetes, may require caution before implementing fasting regimens.[58] Clinical supervision is recommended for individuals with chronic health conditions to mitigate potential risks such as hypoglycemia, micronutrient deficiencies, or hormonal imbalances.[59]

Future Research Directions and Clinical Applications

Future research should focus on long-term randomized controlled trials (RCTs) to assess the efficacy of IF in diverse populations.[60] Identifying individualized fasting strategies based on genetic and metabolic profiles may optimize adherence and therapeutic outcomes.

Key Metabolic Benefits of Intermittent Fasting

Metabolic Outcome	Effect of IF	Mechanism
Insulin Sensitivity	Improved	Reduced hepatic glucose production, enhanced insulin receptor function
Lipid Metabolism	Improved lipid profiles	Increased fat oxidation, reduced LDL and triglycerides
Inflammation	Reduced	Lower CRP, IL-6, TNF-α levels, enhanced autophagy
Gut Microbiota	Altered composition	Increased beneficial bacteria, improved gut barrier function
Weight Loss	Enhanced	Fat oxidation, appetite hormone modulation

CONCLUSION

Intermittent fasting offers significant metabolic health benefits, including improved insulin sensitivity, lipid metabolism, inflammation reduction, and enhanced energy regulation. However, inter-individual variability and long-term adherence challenges highlight the need for further research. Personalized fasting protocols tailored to metabolic profiles may optimize outcomes and enhance long-term sustainability. Future studies should aim to clarify the mechanisms of IF, establish standardized fasting durations, and assess its safety in diverse populations.

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