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## **Exploring the Impact of Intermittent Fasting on Metabolic Syndrome, Prediabetes and Type 2 Diabetes: a systematic review**

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## **Abstract**

**Introduction:** Metabolic syndrome, prediabetes and type 2 diabetes mellitus represent a growing and interconnected health challenge, gaining significant attention due to their high prevalence and impact they have on individuals' well-being. Intermittent Fasting (IF), involving cycling between periods of fasting and eating, has emerged as a promising dietary approach garnering substantial attention for its potential therapeutic effects on metabolic health.

**Purpose:** This review aims to explore the impact of intermittent fasting on metabolic disease by examining recent studies.

**Methods:** A review of the recent literature was conducted to explore potential positive effects of IF on relevant metabolic parameters.

**Results:** The findings from the reviewed studies demonstrated favorable effects of IF associated with improvements in glycemic control as improved insulin sensitivity and decreased HbA1c levels. Additionally, it led to significant reductions in body weight and waist circumference. Beneficial effects on lipid profiles, such as reduced triglyceride levels, were also observed in some studies.

**Conclusions:** The reviewed studies provide strong evidence supporting the effectiveness of IF regimens in improving metabolic factors, including weight, insulin sensitivity and lipid profiles in individuals with abnormal glucose metabolism. IF offers a promising dietary strategy potentially providing additional benefits beyond conventional dietary interventions. However, further research is needed to elucidate the long-term effects, optimal fasting protocols and potential mechanisms underlying the benefits of intermittent fasting in these conditions.

**Keywords:** intermittent fasting, metabolic syndrome, prediabetes, type 2 diabetes, obesity

## **Introduction**

Metabolic syndrome (MetS), prediabetes and type 2 diabetes are interconnected conditions that share common underlying factors and health implications [1]. Abdominal obesity is the most frequently observed and fundamental pathophysiological component within MetS and a known independent risk factor for type 2 diabetes mellitus (T2DM) [2]. Obesity is a growing public health concern that affects countries worldwide [3]. Multiple factors contribute to the rising obesity rates including changes in dietary habits, increasing sedentary lifestyles and socioeconomic factors [2][3]. This combination of dietary imbalances and decreased energy expenditure has resulted in a consistent and concerning upward trend in prevalence of obesity over the past few decades [4]. According to the 2022 Obesity Report by the World Health Organization (WHO), approximately 59% of adults aged 18 years and older in the WHO European Region can be classified as overweight or obese [5]. Individuals affected by obesity and metabolic syndrome face a significant increase in the risk of developing various health conditions such as cardiovascular diseases, stroke, fatty liver, prediabetes and type 2 diabetes (T2D) [6][7]. Metabolic disorders place a significant burden on the healthcare system, both in terms of direct medical costs and indirect costs associated with decreased productivity and quality of life [8]. Alarming statistics underscore the pressing need for extensive research aimed at identifying the most effective approach to attain and sustain metabolic health. In recent years, intermittent fasting has gained substantial popularity as a method for enhancing overall well-being and managing weight. [9]. Intermittent fasting (IF) is a pattern of eating that involves periodically conducted fasting [10]. The fasting periods typically range from several hours to a few days, depending on the specific protocol being followed [9][10]. One of the advantages of intermittent fasting is that it simplifies the eating routine by focusing on when you eat rather than meticulously counting calories [11]. This review aims through evaluating the available research findings to examine the potential advantages of intermittent fasting in individuals diagnosed with metabolic syndrome, prediabetes and type 2 diabetes. We will explore the effects of IF on crucial components of metabolic syndrome, namely insulin resistance, obesity, hypertension and lipid profiles.

## **Methods**

For the present review PubMed, Medline and Google Scholar databases were searched to find scientific articles concerning the impact of intermittent fasting on metabolic health in individuals with metabolic syndrome, prediabetes, and type 2 diabetes. We conducted a search using the keywords “intermittent fasting,” “time energy restriction,” “alternate day fasting,” “5:2 diet,” “metabolic syndrome,” “prediabetes” and “diabetes.” Articles were carefully reviewed and included based on relevance to our topic. Inclusion criteria consisted of published articles including randomized controlled trials, clinical trials and review articles between the years of 2015 and 2023. The selected articles were required to be in English and accessible in full-text format. Abstracts and non-English articles were excluded from the review process.

## **Metabolic Syndrome, Prediabetes and Type 2 Diabetes**

MetS is characterized by the presence of at least three out of five components: abdominal obesity, elevated serum triglycerides, low HDL-cholesterol, hypertension and hyperglycemia [12]. “Prediabetes” is a practical term referring to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or a glycated hemoglobin (A1C) of 5.7% to 6.4% [1]. Individuals falling under this category face a significantly increased risk of developing diabetes and its associated complications [13]. Type 2 diabetes mellitus is characterized by hyperglycemia due to insulin resistance or insufficient insulin secretion [14]. Insulin resistance is a key metabolic abnormality seen in all three conditions [15]. Cells become less responsive to the effects of insulin, resulting in reduced glucose uptake and increased blood glucose levels [14]. Chronic low-grade inflammation is a common feature in these conditions and is believed to be driven by various factors, including adipose tissue dysfunction, oxidative stress, and immune system dysregulation [16]. Increased levels of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ) are observed and play a role in insulin resistance and the progression of metabolic abnormalities [16]. Dyslipidemia, which includes elevated triglyceride levels, reduced levels of HDL cholesterol and increased levels of small, dense LDL particles, is often observed in MetS, prediabetes, and T2DM [17].

## **What is Intermittent fasting?**

Intermittent fasting encompasses a range of fasting and feeding patterns that have gained popularity in recent years [18]. Among the most widely recognized and practiced methods of intermittent fasting are alternate-day fasting (ADF), the 5:2 diet and time-restricted eating (TRE) [18]. The ADF method involves alternating between fasting days and non-fasting days. On fasting days, individuals may choose to completely abstain from consuming any calories or can follow a modified ADF approach, wherein their calorie intake is significantly reduced to approximately 25% of their daily energy needs [18]. 5:2 diet involves eating normally for five days of the week and restricting calorie intake to about 500-600 calories for the remaining two days [19]. TRE involves restricting the daily eating window to a specified number of hours per day (usually 4 to 10 h) and outside of this period as the prolongation of the overnight fast a person consumes no calories [20].

## **Mechanism of fasting**

Periods of restricted food intake induce the activation of specific metabolic pathways by initiating a 'metabolic shift' within the human body [21]. Cascade of interconnected changes at metabolic, cellular and circadian levels is set off [22]. This shift transitions the body from relying on glucose as its primary energy source to utilizing lipids stored in adipose tissue in the form of triglycerides [23]. The timing of the 'metabolic switch' depends on factors such as the initial glycogen content in the liver and the level of energy expenditure during fasting [24]. Generally, this transition occurs within a timeframe of 12 to 36 hours after the cessation of food consumption [21]. Released lipids are converted into free fatty acids (FFAs), which are released into the bloodstream. These FFAs molecules undergo beta-oxidation within the mitochondria of the liver, leading to the production of acetyl-CoA, which is further converted into ketone bodies, specifically acetoacetate and beta-hydroxybutyrate, through a process termed ketogenesis [25]. Ketone bodies serve as alternative fuel sources for various tissues providing energy when glucose availability is limited [26]. The increased synthesis and utilization of ketone bodies during fasting and periods of low insulin levels can induce oxidative stress within the mitochondria [25]. That initiates a protective response in cells and adaptive adjustments in cellular energy metabolism contributing to the body's ability to cope with the challenges of fasting and maintain optimal cellular function [26]. Many studies investigating the metabolic effects of intermittent fasting have been conducted using rodents as model organisms and provided valuable insights into the mechanisms and effects of IF on various metabolic parameters [27][28][29]. Fasting has been shown to affect bioenergetic

sensors, particularly adenosine monophosphate-activated protein kinase (AMPK) [30]. Enhanced autophagy through AMPK activation helps clear out cellular debris and promotes the removal of damaged components, which can enhance cellular health and function [31]. Fasting-induced AMPK activation can help maintain glucose homeostasis by promoting glucose uptake and utilization in tissues while inhibiting glucose production in the liver, which can contribute to stable blood glucose levels during periods of fasting [31].

Intermittent Fasting has been found to promote the browning and beiging of white adipose tissue, leading to an increase in the number and activity of beige adipocytes [32]. It involves the activation and recruitment of beige adipocytes and increases the expression of uncoupling protein 1 (UCP1). When UCP1 is activated, it uncouples the process of ATP synthesis allowing protons to re-enter the mitochondria without generating ATP, thereby dissipating the energy as heat instead [33]. This process promotes the oxidative metabolism of glucose and fats, redirecting energy expenditure towards heat production rather than energy storage [32]. Intermittent fasting has been shown to reduce inflammation in adipose tissue by modulating immune responses and reducing the secretion of pro-inflammatory molecules [34].

### **Clinical Findings of Intermittent Fasting Protocols in Individuals with Metabolic Syndrome, Prediabetes and Type 2 Diabetic**

In this review section, we will provide a brief overview of recent clinical trials that have examined the effectiveness of Intermittent Fasting regimens in improving metabolic factors in patients with abnormal glucose metabolism conditions. These conditions primarily include metabolic syndrome, prediabetes and type 2 diabetes mellitus. By examining the findings of these trials, we aim to shed light on the potential benefits and outcomes associated with IF interventions in the context of improving metabolic health. Across the five reviewed randomized control trials, a consistent finding was observed regarding the impact of intermittent fasting on anthropometric measurements. Participants who underwent fasting regimes experienced reductions in BMI, weight and waist circumference [36][37][38][39]. Furthermore, the effect of IF on glucose metabolism was assessed in these trials. Serum insulin levels and the homeostatic model assessment of insulin resistance (HOMA-IR) were consistently decreased in the IF group after the intervention [36][37][38][39]. In addition to the effects on weight and glucose metabolism, the impact of IF on blood pressure was also evaluated. Some studies reported reductions in both systolic and diastolic blood pressure

following the IF intervention [35][37]. In some studies, a notable decrease in triglyceride levels was observed in the fasting group [35][36][38].

The health benefits observed in intermittent fasting protocols often overlap with those derived from calorie restriction programs. This overlap can be largely attributed to the common factor of weight loss experienced by individuals following fasting protocols. In the study conducted by Sutton et al. [35] the researchers aimed to determine whether intermittent fasting can yield benefits beyond those solely attributable to weight loss. The findings of the study demonstrated that following an early time-restricted feeding (eTRF) schedule resulted in notable improvements in several key factors related to metabolic health - decreased fasting insulin and decreased insulin levels post-load, pressure regulation and oxidative stress levels [35]. Glucose metabolism measurements also showed positive outcomes in the IF group [35]. Research conducted by Obermayer et al. [39] showed a reduction in the total daily insulin dose required by individuals with insulin-treated type 2 diabetes, which can suggest that intermittent fasting may enhance insulin sensitivity and improve overall insulin utilization in the individuals with T2DM.

For more detailed information about the research, please refer to the following paragraphs.

In an 8-week randomized controlled trial conducted by Guo et al. [36], the study focused on patients diagnosed with metabolic syndrome. The trial included a total of 39 participants, with 21 individuals assigned to the 5:2 fasting regime group and 18 individuals assigned to the control group. The aim of the study was to evaluate the effects of the 5:2 fasting regimen on metabolic parameters and markers of MetS. During the fasting days, participants in the intermittent fasting group reduced their calorie intake by 69% compared to non-fasting days. In the control group there was no observed significant change in anthropometric characteristics or body composition during the study. However, in the IF group, BMI, weight and waist circumference were significantly reduced. Glucose metabolism measurements revealed that serum insulin and HOMA-IR were appreciably decreased in the IF group after the intervention. The results revealed that the fasting regimen did not significantly affect lipid profiles, including serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-c), except for a notable decrease in triglyceride (TG) levels within the Intermittent Fasting group.

In the study conducted by Mindikoglu et al. [37], the 14 participants with metabolic syndrome observed a fasting period from dawn to sunset during the month of Ramadan. They

followed a fasting pattern of more than 14 hours daily and maintained this fasting routine for four consecutive weeks. The aim of the study was to assess the impact of Ramadan fasting on metabolic parameters and markers of metabolic syndrome in individuals with this condition. The study findings revealed significant reductions in several key health parameters following the intermittent fasting period. There were notable decreases in weight, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, and mean arterial blood pressure. Furthermore, one week after completing the four-week intermittent fasting period, significant reductions in insulin resistance, as measured by the homeostatic model assessment of insulin resistance (HOMA-IR), were observed compared to the pre-fasting levels.

In a randomized trial conducted by He et al. [38], the study aimed to investigate the effects of different interventions on individuals with metabolic syndrome. The trial included three groups: an 8-hour time-restricted eating schedule group (n = 44), a low-carbohydrate diet (LCD) group (n = 47), and a group that received a combination of both interventions (n = 44). All participants enrolled in the study met the criteria for metabolic syndrome. The objective of the trial was to assess the impact of these interventions on metabolic parameters and markers of metabolic syndrome in the participants. This trial started with a 2-week weight stabilization and was followed by a 3-month intervention. Following a treatment period, all three interventions resulted in significant reductions in body weight compared to baseline. Only the TRE group induced a more prominent reduction of WHR compared with the LCD and combination group. It was observed that the TRE treatment was effective in reducing visceral fat area, fasting blood glucose levels, uric acid levels and addressing dyslipidemia. All three groups improved fasting insulin levels, C-peptide, HOMA-IR, homeostatic model assessment of insulin sensitivity (HOMA-IS) and quantitative insulin-sensitivity check index (QUICKI). TRE schedule showed significant reductions in triglyceride (TG) levels and the TG/HDL-c ratio. The study demonstrated that although all three treatments led to significant reductions in body weight accompanied by a decrease in subcutaneous fat area, time restricted eating exhibited more pronounced benefits in terms of reducing abdominal visceral obesity and improving metabolic outcomes.

In the RCT conducted by Sutton et al. [35] involving men with prediabetes, participants were assigned to either follow an early time-restricted feeding (eTRF) schedule, which involved a 6-hour feeding period with dinner consumed before 3 pm or a control schedule with a 12-hour feeding period separated by a washout period of approximately seven weeks.

Participants were carefully monitored and provided with controlled meals to ensure consistent caloric intake throughout the experiment. The objective was to evaluate the effects of intermittent fasting on various health markers without the confounding factor of weight reduction. eTRF reduced mean and peak insulin values, leading to a reduction in fasting insulin levels. The study also explored the effects of eTRF on indices of  $\beta$  cell responsiveness and insulin resistance derived from an oral glucose tolerance test (OGTT). Although eTRF did not improve glucose levels, it dramatically lowered insulin levels and improved insulin sensitivity and  $\beta$ -cell responsiveness. Specifically, eTRF improved blood pressure regulation and oxidative stress levels. Serum insulin levels and HOMA-IR were significantly decreased after the intervention, suggesting improved insulin sensitivity. Regarding lipid profiles, the study found no significant effects on total cholesterol (TC) or high-density lipoprotein cholesterol (HDL-c) levels. However, there was a decrease in triglyceride (TG) levels observed in the IF group.

In a 12-week randomized controlled trial conducted by Obermayer et al. [39], the study focused on forty-six participants with insulin-treated type 2 diabetes. These participants were randomly assigned to either the Intermittent Fasting group (n=20) or the control group (n=24). The objective of the study was to evaluate the effects of IF on various outcomes in individuals with insulin-treated type 2 diabetes. The IF group practiced fasting 3 days a week consuming only 25% of the recommended caloric intake. The IF group showed a significant HbA1c reduction compared with the control group. After 12 weeks of intervention, the IF group showed a significant reduction in weight compared with the control group and in fat mass. The IF group had a total daily insulin dose reduction in the intermittent fasting group over 12 weeks by  $9 \pm 10$  IU as opposed to the control group with an increase by  $4 \pm 10$  IU. It was demonstrated that 3 days of nonconsecutive IF per week over the duration of 12 weeks improved HbA1c, reduced body weight and led to a total daily insulin dose reduction in people with insulin-treated type 2 diabetes.

## **Conclusion**

Intermittent fasting regimens have shown promising and beneficial effects on metabolic factors in individuals with abnormal glucose metabolism conditions. Several studies reviewed in this context have reported significant reductions in body mass index (BMI), weight and waist circumference among individuals practicing intermittent fasting. These findings suggest that intermittent fasting may contribute to weight loss and the reduction of abdominal fat,

both of which are crucial for improving metabolic health. It indicates the potential of IF as a strategy for weight management. The positive effects observed in studies on Intermittent Fasting may not be solely attributed to changes in body weight, indicating the potential metabolic benefits of IF independent of weight loss. Intermittent Fasting has been associated with decreased serum insulin levels and improvements in the homeostatic model assessment of insulin resistance (HOMA-IR) scores. These findings suggest a notable enhancement in insulin sensitivity, which is a highly favorable outcome for individuals with metabolic syndrome, prediabetes and type 2 diabetes mellitus. Several studies have reported reductions in triglyceride levels indicating improvements in lipid metabolism among individuals practicing Intermittent Fasting. By lowering triglyceride levels, IF may reduce the risk of cardiovascular disease and its associated complications. Intermittent fasting has emerged as a possible dietary option for individuals with insulin-treated type 2 diabetes, offering potential benefits in terms of glycemic control, insulin dose reduction and weight management. It has been shown that intermittent fasting can lead to improvements in glycemic control, as indicated by reductions in HbA1c levels. Furthermore, intermittent fasting has the potential to decrease total daily insulin requirements. This reduction in insulin dose may be attributed to improved insulin sensitivity and better utilization of available insulin in the body. The ability to decrease insulin requirements is beneficial not only in terms of medication burden but also in terms of potential cost savings and decreased risk of hypoglycemic episodes.

Intermittent Fasting appears to be an easy to apply dietary intervention without the need for continuous caloric reductions, ultimately leading to reduced caloric intake through the time-restricted eating pattern without vigorous documentation or calorie counting. While the current evidence supports the potential benefits of IF on metabolic parameters, many of the existing studies have focused on shorter intervention periods, ranging from a few weeks to a few months. Further research with larger sample sizes and longer durations is needed to establish the full extent of the effects of IF on metabolic parameters and to determine the optimal IF protocols for different patient populations. Longer-duration studies are needed to assess the long-term effects and sustainability of intermittent fasting interventions. Extending the duration of the studies will provide insights into the effects of IF over an extended period and help assess its viability as a long-term dietary strategy.

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