

Editorial

Intermittent Fasting: A Potential Effective Strategy for Preventing Obesity and Type II Diabetes Mellitus

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PREVALENCE OF OBESITY & TYPE II DIABETES

The prevalence of obesity among adults has increased significantly in the past few decades. In the US alone, one in three adults is classified as obese.¹ Most commonly, obesity results from an imbalance of limited energy expenditure to compensate for excess energy intake. However, a number of factors have been identified as possible contributors towards the increasing obesity rates worldwide, therefore acting as a multifaceted problem to resolve.² Obesity is considered a primary contributor towards the development of type 2 diabetes mellitus (T2DM).³ T2DM is characterized by the inability of pancreatic β -cells to produce a sufficient amount of insulin (insulin resistance) in response to necessary levels of glucose uptake. As a result of inhibited insulin secretion, glucose is not taken up into target tissues such as muscle and adipose tissue, leading to elevated blood glucose levels, or hyperglycemia.^{4,5} Hyperglycemia can subsequently lead to vascular damage and other adverse effects.⁶

IMPORTANCE OF INTERMITTENT FASTING RELATING TO OBESITY & T2DM

Intermittent fasting (IF), a form of calorie restriction, has gained popularity in recent years as a methodology for combating obesity and development or progression of type 2 diabetes. IF regimes can vary in fasting durations. Common variations of IF include alternate day fasting (ADF), in which one day consists of a 75% energy restriction followed by a day of *ad libitum* food consumption or 16/8 IF, which includes consuming 100% of energy needs in an 8 hour time period followed by a 16 hour fast.^{7,8} Dysregulated insulin/glucose pathways, shown as glucose tolerance and insulin resistance, is the most frequently reported symptom of T2DM and has been discussed broadly in recent years. Studies

implementing IF have shown normal and overweight human subjects have efficacy for weight loss.⁹ In addition to being an effective method for weight loss, IF can also improve specific health indicators associated with chronic disease in the overweight and obese population, such as insulin resistance.¹⁰ Research on IF's weight loss benefits is aimed at understanding its metabolic effects on many age-related diseases, including type 2 diabetes.¹⁰ However, limited research exists on assessing fasting glucose and insulin levels in patients undergoing IF.

MECHANISM OF IF ACTION

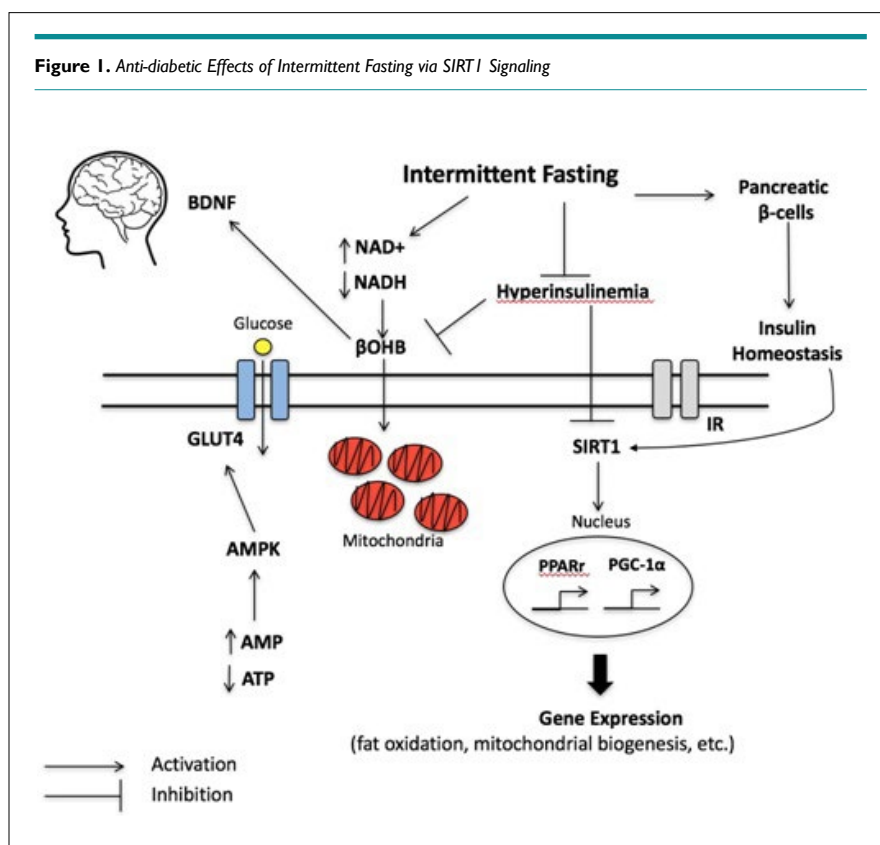
Changes in fasting blood glucose levels have been observed in humans undergoing ADF.^{11,12} As much as a 6% decrease was observed between overweight patients' fasting glucose levels after 8 to 12 weeks of an ADF versus an *ad libitum* diet.¹³ Adversely, a significant insulin reduction of approximately 20% was observed in intermittently fasted overweight and obese adults, respectively.¹⁴ Similar effects of decreased blood glucose and insulin levels resulting from IF have also been observed in human studies. This suggests effects of IF treatment on the insulin transduction pathway, as well as pathways involving cytokine-induced food intake behavior, may be responsible for improving glucose tolerance. A study involving New Zealand obese mice undergoing a calorie-restricted IF diet showed improved blood insulin sensitivity in an oral glucose tolerance test, higher blood glucose clearance in insulin tolerance tests, and lower blood glucose and insulin compared to mice fed an *ad libitum* diet.¹⁵

Improvements in the insulin transduction pathway in response to IF may be a consequence of increased expression of sirtuins (SIRT). SIRT1 is a protein complex involved in cellular energy sensing *via* the ratio of nicotinamide adenine dinucleotide

(NAD⁺) and its reduced form nicotinamide adenine dinucleotide (NAD⁺ + hydrogen (H) (NADH)).¹⁶ The ratio between NAD⁺ and NADH represent overall oxidative phosphorylation capacity within the cell. Higher levels of NAD⁺ in response to fasting and exercise are shown to increase SIRT1 activity.¹⁷ Conversely, SIRT1 activity is reduced during periods of hyperinsulinemia.¹⁸ β -hydroxybutyrate (β OHB), a ketone body, is elevated during fasting.¹⁹ Downstream metabolism of β OHB for acetyl-CoA production requires less NAD⁺ consumption when compared to glucose, thus expression of SIRT1 perpetuates in parallel with the duration of the fast. In addition, β OHB and periods of intermittent fasting upregulate the expression of brain derived neurotrophic factor (BDNF).^{20,21} BDNF, a protein in the hypothalamus, is shown to decrease in response to T2D.^{22,23} Increased expression of BDNF is shown to have protective effects against the development and progression of T2D including: increased energy expenditure, decreased dietary intake, and decreased fasting blood glucose.²⁴ Interestingly, BDNF administration is shown to reduce food intake and correct hyperglycemia in leptin receptor deficient *db/db* mice.²⁵ Increased SIRT1 expression regulates energy expenditure through modulation of cellular respiration. Translation of mitochondrial biogenesis and lipid oxidation are both regulated by peroxisome proliferator-activated receptors (PPARs) and coactivator-1 α (PGC-1 α).²⁶ Both of these proteins are downregulated in response to hyperinsulinemia and insulin resistance.²⁷ Up-regulating their expression through increased SIRT1 activity may serve as a novel approach in combating metabolic abnormalities observed in T2D such as intracellular fat depositions. (Figure 1)

As IF elicits similar effects as calorie restriction, it is worthwhile to test if the expression of adipocyte-specific glucose transporter 4 (GLUT4) is increased as shown in obese mice undergoing calorie-restriction.²⁸ It is believed that IF could induce the secretion of leptin in adipose tissue through up-regulating GLUT4 expression in T2D. The role of the GLUT4 transporter serves as a mediator for improved glucose disposal in response to altered nutrition status. GLUT4 transcription is shown to be tightly regulated in response to energy sensing within the cell. In response to prolonged exercise and calorie restriction, 5' AMP-activated protein kinase (AMPK) activity increases and promotes translocation of GLUT4 to the cell membrane surface. However, the potential of IF influencing this interaction has led to non-correlative results in both human and animal studies.²⁹

Contrastingly, in 2014, Dorighello et al. Reported that wild type mice under IF regimen developed symptoms of diabetes including elevated blood glucose and insulin levels, glucose intolerance, and insulin resistance while reduced food intake was observed. Mechanistic understanding the effects of IF can be beneficial towards attenuating or preventing the increasing prevalence of chronic diseases such as obesity and T2D. However, due to the contradicting evidence in current literature, further research is still needed for understanding the mechanisms of IF on various biomarker responses and appetite control.



CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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