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Intermittent fasting in type 2 diabetes: from fundamental science to clinical applications

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Abstract. – Type 2 diabetes mellitus (T2DM) is a huge challenge for global public health systems. Currently, healthcare policies advocate the prevention of the onset and progression of T2DM by improving individual lifestyles. The increasing benefits of intermittent fasting (IF) as a dietary intervention have been elucidated. However, the beneficial effects of IF in T2DM remain inconclusive. We demonstrated the physiological mechanisms underlying the positive effects of IF in T2DM. IF could trigger metabolic transformation to improve systemic metabolism and induce tissue-specific metabolic adaptations through alterations in the gut microbiota, adipose tissue remodeling, correction of circadian rhythm disturbances, and increased autophagy in peripheral tissues. The efficacy and safety of IF regimens in clinical applications carry a risk of hypoglycemia and require monitoring of blood glucose and timely adjustment of medications. However, there is limited evidence of a positive effect of IF in weight loss and improvement of glycemic variables. Overall, IF serves as a promising therapeutic target for T2DM and needs to be established by a large randomized controlled trial.

Key Words:
Intermittent fasting (IF), Type 2 diabetes mellitus (T2DM), Metabolic transformation, Gut microbiota, Adipose tissue, Circadian biology, Autophagy.

Introduction

The incidence and prevalence of type 2 diabetes mellitus (T2DM) continue to rise globally[1]. T2DM is characterized by hyperglycemia due to insulin resistance (IR) or insufficient insulin secretion[2]. International Diabetes Federation (IDF) estimates that the global prevalence of diabetes in people aged 20-79 years is estimated at 10.5% (536.6 million) in 2021, rising to 12.2% (783.2 million) by 2045[3]. However, current T2DM medications without lifestyle interventions lack comprehensiveness in glycemic control[4]. In light of the limitations of available antidiabetic agents, alternative treatments are highly recommended. In recent years, the dietary intervention has become a hot topic of research.

Intermittent fasting (IF) is a dietary pattern involving energy restriction and time-restricted fasting[5]. Alternative invention of energy intake offers better compliance than continuous energy restriction (CER)[6]. Studies[5,7,8] in animals and humans have shown that IF has a modulating function in a variety of chronic diseases, including obesity, diabetes, cardiovascular disease, multiple sclerosis, neurodegenerative diseases of the brain, and cancer.

In addition to a simple calorie restriction (CR), IF has unique and specific properties, which could trigger systemic metabolic improvements through metabolic transformation and induce tissue-specific metabolic adaptations including changes in the gut microbiome, adipose tissue remodeling, correction of circadian rhythm disturbances, and increased autophagy in peripheral tissues. This review briefly elucidates the positive effects of IF on T2DM in these five aspects. Furthermore, IF may encourage weight reduction to avoid different diabetes risk factors, including lower fasting glucose and fasting insulin and improved insulin sensitivity[9]. Here, we summarized the benefits of IF regimens and explored the efficacy and side effects of IF in prediabetes and T2DM. We intended to provide several suggestions for future research and clinical applications of IF.

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Types of Intermittent Fasting

There are various models of intermittent fasting and three of them have been widely used in clinical practice: alternate daytime fasting (ADF), IF 5:2 (two days of fasting per week), and time-restricted eating (TRE)[10].

ADF consists of a feeding day and a fasting day[11]. Individuals can consume food and beverages without restriction during feeding days and no caloric intake during fasting days. Modified ADF involves individuals consuming typically 20-25% (500-800 kcal) of their energy requirement during fasting days[12]. The IF 5:2 comprises two stages embodying two fasting days (500-1,000 kcal per day) and five other days of free feeding[13]. The two restriction days can be consecutive or nonconsecutive. TRE has a time requirement for the diet, i.e., limiting eating to a specific number of hours per day (usually 4 to 8 hours) and abstaining from water or zero-calorie beverages for the rest of the day[14].

Other forms of fasting are less common, such as B2 and 4:3 IF. In the B2 program, the regime consists of two meals per day, with breakfast from 6 am to 10 am and lunch from 12 pm to 4 pm[15]. 4:3 IF is similar to IF 5:2, except for an extra day of fasting per week[16].

Physiological Mechanisms Associated with Intermittent Fasting

The potential mechanisms for improving T2DM through IF are complex and can be broadly summarized as follows: metabolic transformation, alterations in the gut microbiota, adipose tissue remodeling, improved circadian rhythms, and increased autophagy. These alterations can induce tissue-specific metabolic adaptations that allow for remission or even cure of T2DM. We summarize the limited evidence and describe these alterations in detail from animal experiments as well as molecular mechanisms.

Metabolic Transformation

In the fasting state, triglycerides (TG) are converted to fatty acids and glycerol through lipodieresis. The liver then converts fatty acids to ketone bodies, which provide energy to tissues in various parts of the body[17]. Animals and humans using fasting or IF protocols had significantly higher blood ketone levels, especially β-hydroxybutyric acid[18]. Elevated β-hydroxybutyrate further raises increased autophagy and reduces oxidative stress (Figure 1)[19]. On the other hand, IF-induced metabolic transformation also mediates significant alterations in several metabolic pathways. These include a decrease in rapamycin (mTOR) activity and stimulation of AMP-activated protein kinase (AMPK) (Figure 1)[20]. Reduced glucose and amino acid levels during fasting lead to reduced mTOR pathway activity, and inhibition of mTOR activity decreases protein synthesis and stimulates increased autophagy and mitochondrial synthesis[21]. Fasting affects bioenergetic sensors, especially AMPK, which is activated to promote increased autophagy, thereby eliminating damaged proteins and organelles from the body and improving mitochondrial function[20]. These changes can promote metabolic homeostasis and play a role in maintaining glucose homeostasis and improving insulin sensitivity[19].

Gut Microbiota

The composition of the gut microbiota is remodeled in response to changes in individual dietary habits and nutritional status[22]. IF leads to altered cellular responses, shifting cells from glucose-dependent to using ketone body carbon (KBC), thereby suppressing inflammation and altering the gut microbiota[23,24]. Gut microbiota dominates host health and the pathogenesis of metabolic diseases such as obesity and diabetes[25-30]. The mechanism regulates systemic metabolism by improving inflammation and reducing intestinal permeability[31].

The earliest epidemiology of obesity and T2DM-related inflammation dates back to the 1960s[32,33]. Many studies[34,35] on T2DM and obesity have demonstrated a rise in circulating inflammatory markers. Low-grade inflammation is a vital determinant of obesity and diabetes[36]. Inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) undermine insulin sensitivity and poor glucose tolerance and mediate IR[37-40]. Related studies[41] have shown that obesity and diabetes share an important common feature, namely, an increased proportion of the thick-walled phylum/mycobacterial phylum. A high-fat diet (HFD) can induce changes in the gut microbiota by promoting the development of Gram-negative bacteria, which

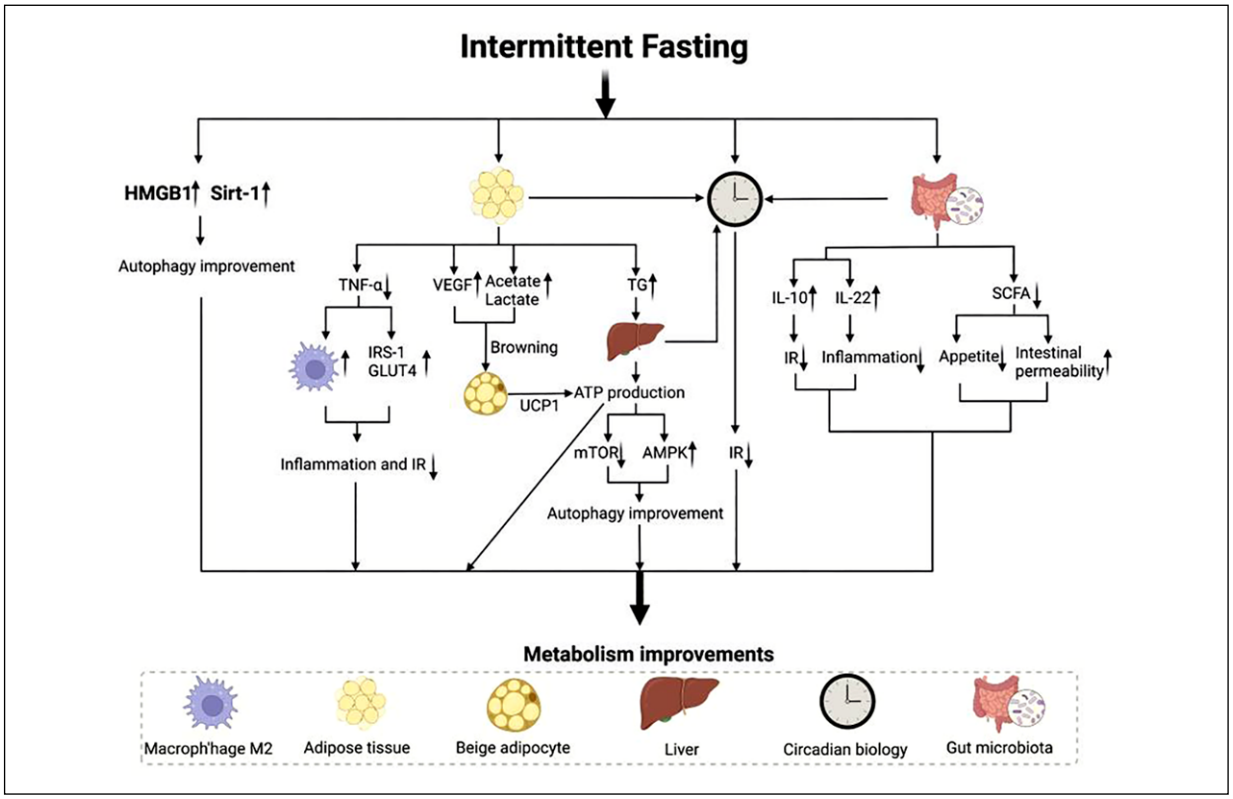

Figure 1. Physiological mechanisms associated with intermittent fasting. Brown to the beige coloration of AT adipose tissue due to elevated acetate and lactate and VEGF cycling. Beige adiposity increases the expression of UCP1, which leads to improved metabolism by promoting the oxidative metabolism of glucose and fat coupled to ATP synthesis. At the same time, a decrease in TNF-α promoted an increase in IRS-1 and GLUT4 and the polarization of macrophage M2. These changes improve insulin resistance and AT inflammation, resulting in improved metabolism. On the other hand, TG increases due to IF, and TG is broken down into ketone bodies in the liver. Ketone bodies increase autophagy in the organism through a decrease in mTOR activity and activation of AMPK. Elevated HMGB and Sirt-1 similarly increase autophagy. Increased autophagy further improves metabolism. IF alters the composition of the gut microbiota, thereby increasing the levels of IL-10, IL-11 and SCFA. IL-10 and IL-22 balance the body's metabolism by improving IR and inflammation, respectively. SCFA, on the other hand, improves body metabolism by reducing appetite and intestinal permeability. Finally, AT, gut microbiota and liver influence the local peripheral clock and regulate the circadian system together with the central clock, thus reducing IR and correcting metabolic disturbances. IF: intermittent fasting; HMGB: high mobility group box 1; Sirt-1: sirtuin-1; TNF-α: tumor necrosis factor-alpha; IRS-1: insulin receptor substrate 1; GLUT4: glucose transporter protein type 4; VEGF: vascular endothelial growth factor; TG: triglycerides; ATP: adenosine triphosphate; mTOR: rapamycin; AMPK: AMP-activated protein kinase; IR: insulin resistance; SCFA: short-chain fatty acid; UCP1: uncoupling protein 1; IL: interleukin.

leads to lipopolysaccharide (LPS) production to trigger systemic inflammation[42]. Furthermore, changes in the gut microbiota brought on by IF may lessen T2DM's inflammatory symptoms[43-45]. For example, interleukin-10 (IL-10) induced by *Roseburia* guts, *Bacteroides fragilis*, *Akkermansia muciniphila*, *Lactobacillus Plantarum*, and *Lactobacillus casei* improves glucose metabolism and prevents aging-related IR (Figure 1)[46-48]. *Enterobacteriaceae* can restore insulin sensitivity and induce transforming growth factor-β (TGF-β) to suppress intestinal inflammation by increasing interleukin-22 (IL-22) production (Figure 1)[49-51]. The anti-inflammatory molecules produced by *Lactobacillus paracasei* and Faecalibacterium prausnitzii can inhibit the activity of nuclear factor-κB (NF-κB)[52,53].

On the other hand, IF treatment significantly increased the levels of the thick-walled phylum while reducing most other phyla and elevating short-chain fatty acids (SCFAs) production, compared to *ad libitum*-fed control animals[54]. SCFAs are the product of gut microbiota fermentation of indigestible foods[55]. The key factor in mucin production (increased mucin expression) and tight junction integrity preservation, SCFAs are crucial for limiting increasing intestinal permeability (Figure 1). A distinctive feature of T2DM is

the increase in intestinal permeability that leads to the transfer of LPS and microbial metabolites into the bloodstream, which in turn causes IR and metabolic endotoxemia[56,57]. Entering circulating LPS interacts with LPS-binding proteins and membrane-bound cluster of differentiation 14 (CD14) receptors. Their complexes interact with toll-like receptor 4 (TLR4) to influence inflammatory signals and insulin signaling pathways[58]. Meanwhile, SCFAs can control energy intake through the gut-brain axis[59]. The gut-derived satiety hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) are mainly secreted by enteroendocrine L cells, with the highest density in the ileal and colonic epithelium[60-63]. SCFAs are a major stimulator of GLP-1 production by endocrine L cells[64]. GLP-1 regulates appetite through its effects on opioid melanocortinogen (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus of satiety (ARC) and is known to inhibit gastric emptying and gastric acid secretion (Figure 1)[65-67]. Thus, there is also a link between GLP-1 and reduced hunger during IF[68].

Overall, IF-mediated changes in gut microbiota alleviate inflammation and maintain intestinal permeability in T2DM. To improve the efficacy of IF in T2DM, further robust preclinical and clinical studies are needed to standardize the optimal regimen for IF.

Adipose Tissue

IF can positively affect T2DM by remodeling adipose tissue (AT), mainly by the browning of white adipose tissue (WAT), increasing thermogenesis of brown adipose tissue, and reducing inflammation (Figure 1)[69-71]. We briefly describe the improvement of AT browning and inflammation.

It was found that IF-induced WAT browning and beiging increased adipogenic thermogenesis and improved HFD-induced obesity and metabolic dysfunction[72-75]. AT browning and beiging increase the expression of uncoupling protein 1 (UCP1), which improves insulin sensitivity by promoting the oxidative metabolism of glucose and fat by uncoupling with adenosine triphosphate (ATP) synthesis, resulting in heat production and energy expenditure (Figure 1)[76,77]. IF-induced browning appears to be largely unrelated to the classical differentiation stimuli β-adrenergic receptor (β-AR) and fibroblast growth factor 21 (FGF21)[78]. Kim et al[72] found IF mice promote selective activation of adipose macrophages *via* the adipose vascular endothelial growth factor (VEGF) cycle and thus increased WAT browning (Figure 1). Li et al[73] demonstrated that IF induces inguinal WAT by altering the abundance of intestinal microbiota and promoting the production of acetate and lactate. The specific mechanism by which IF induces adipose browning needs to be further investigated.

IF ameliorates inflammation in adipose tissue, and some studies[79] have shown that IF reduces pro-inflammatory markers (e.g., macrophages, IL-1, IL-6, TNF-α, etc.) in subcutaneous white adipose tissue (sWAT) of diet-induced obese (DOI) mice. AT inflammation mediated by adipose macrophages and their secreted TNF-α is shown in Figure 1[80,81]. There is evidence that TNF-α can inhibit the activity of peroxisome proliferator-activated receptor-γ (PPARγ) through multiple pathways[82]. The classical pathway blocks the binding of PPARγ to its downstream response elements by activating the NF-κB pathway[83]. HFD-fed mice treated with PPARγ agonists display higher insulin sensitivity and an increase in the anti-inflammatory phenotype of M2 macrophages[84]. In addition, circulating free fatty acid (FFA) levels were increased due to the inhibition of PPARγ downstream signaling[85]. And FFA can promote the polarization of pro-inflammatory phenotype M1 macrophages[86]. TNF-α knockout mice avert HFD-induced IR and show lower FFA levels[87]. In addition, TNF-α significantly downregulates insulin receptor substrate 1 (IRS-1) and glucose transporter protein type 4 (GLUT4) expression and inhibits AMPK activity (Figure 1)[88,89]. Activated AMPK induces polarization of M2 macrophages and inhibits IR (Figure 1)[86,88,90].

Moreover, IF improves insulin sensitivity by decreasing inflammatory collagen IV expression in visceral white adipose tissue (vWAT)[91]. Thus, to further elucidate the specific mechanisms of IF and adipose tissue remodeling numerous preclinical and clinical studies are needed.

Circadian Biology

TRE can increase insulin sensitivity and positively affect systemic metabolic disorders by altering the frequency of eating, correcting circadian rhythm disturbances, and altering the expression of biological clock genes. The circadian biological system consists of a central brain clock in the supraoptic nucleus of the hypothalamus and various peripheral tissue clocks (e.g., similar

clock oscillators found in peripheral tissues such as the liver)[92]. The circadian system plays an important role in metabolic and energetic physiological changes through behavioral interventions[93,94]. Light information and feeding time (Zeitgebers) are the main temporal cues[92]. According to the circadian rhythm disruption hypothesis, synchronization of feeding with the endogenous clock can promote the homeostasis of the clock system[95]. Conversely, it can lead to misalignment of temporal species rhythms, causing circadian rhythm disruption and promoting IR and T2DM development[96].

Several clinical trials[97-99] have confirmed that human glucose tolerance is higher in the morning than in the evening. Dysregulation of circadian rhythms leads to a reduction in glucose tolerance in humans[100]. Shift workers have an increased risk of developing type 2 diabetes mellitus (T2DM) compared to people with normal sleep schedules[101]. The circadian rhythm of glucose tolerance in humans is mediated primarily through the circadian rhythm of systemic insulin sensitivity. The central clock plays a major role in systemic insulin sensitivity through the hypothalamic connection between sleep/wake and food intake[102]. The local peripheral clock further finetunes systemic insulin sensitivity *via* the gut clock[103], muscle clock[104], adipose tissue clock[105], liver clock[106], and pancreatic clock (Figure 1)[107]. Among these, appropriate management of eating behavior, a crucial component of rhythmic behavior, might enhance IR to some amount (Figure1)[108]. Significant changes in peripheral clock gene expression levels in skeletal muscle and subcutaneous adipose tissue (SAT) are observed in obese women[12]. A 5-week randomized crossover-controlled trial[109] of 12 patients with prediabetes found that TRE (6-h feeding period) improved insulin sensitivity and β-cell responsiveness compared to 12-h feeding. Consistent with this finding, after four days of TRE (6-h TRE from 8 am to 2 pm) in 11 obese patients, it was reported[110] that TRE lowered fasting glucose and insulin, reduced 24-hour glucose fluctuations, altered biological clock gene expression, and may also increase autophagy and have anti-aging effects in humans. Notably, however, Lundell et al[111] reported that TRE improved lipid and amino acid rhythmicity but did not interfere with the expression of the core clock. It is undeniable that time-restricted fasting has a positive impact on human metabolism, which requires further research in more clinical applications. However, the precise mechanism by which IF improves metabolic disorders by regulating circadian rhythms needs to be demonstrated by additional studies.

Improved Autophagy

Autophagy, a process of self-degradation and cleanup by organisms, has been demonstrated to play a critical role in T2DM[112,113]. The recovery function of autophagy may be severely compromised in mice on an HFD by IR and T2DM[114,115]. IF has been proven to restore autophagy, attenuate the effects of metabolic diseases such as T2DM on autophagy, and maintain cellular rejuvenation[116]. Similarly, autophagy suppression reduces the interventional impact of IF[117]. In a recent study[118], the light chain 3 (LC3)-II/LC3-1 ratio was higher in mice that followed a 4-month fasting intervention, suggesting enhanced autophagy. On the other hand, IF stimulates sirtuin-1 (Sirt-1) activity and enhances autophagy and serum high mobility group box 1 (HMGB1) levels[119]. The role of HMGB1 and Sirt-1 in the regulation of autophagy has been demonstrated[120] in animals and cell lines (Figure 1). Autophagy is essential for normal β-cell function and survival, and regulation of autophagy, rather than excessive autophagy, may be a possible mechanism to explain the beneficial effects of IF on β-cell function. However, the underlying molecular mechanisms remain unclear[121-123]. IF can result in the remission of β-cell function in T2DM[124] and might improve metabolism by increasing autophagy in humans (Figure 1)[125,126].

Human Intervention Studies

IF is a planned dietary intervention with intentionally prolonged fasting. The focus of research on IF is weight loss. We briefly review some trials conducted in recent years in obese patients (without prediabetes and T2DM) using the three main IF regimens (ADF, IF 5:2 and TRE) (Table I). In addition, we summarize the results of studies with different IF regimens in patients with abnormal glucose metabolism conditions (i.e., prediabetes and T2DM) (Table II).

Results of Studies Using the IF Protocols in Obese Patients (Without Prediabetes and T2DM)

The vast majority of IF outcomes reported in randomized trials of obese patients are primarily weight loss and improved body composi-

Table I. Trials of IF in obese patients.

Participants	Trial weeks	Intervention groups	Body weight	Energy intake	Fat mass	Blood pressure	LDL	HDL	TG	Fasting glucose	Fasting insulin	HOME-IR	HbA1c	Inflammation	Ref.
N=31, men and women, with overweight and without T1DM or T2DM.	8	ADF (500-kcal fast day)	↓[b]	↓ 25%	↓[b]	NT	∅	∅	∅	∅	∅	∅	NT	∅ CRP	[127]
		Exercise (endurance)	∅	∅	↓[b]	NT	∅	∅	∅	↓[b]	∅	∅	NT	∅ CRP	
		ADF with exercise	↓[b]	↓ 20%	↓[b]	NT	∅	∅	∅	∅	∅	∅	∅	∅ CRP	
		Control (*ad libitum* intake, no exercise)	∅	∅	∅	NT	∅	∅	∅	∅	∅	∅	∅	∅ CRP	
N=31, men and women, with overweight and without T1DM or T2DM.	12	ADF (600-kcal fast day)	↓[a]	↓ 35%	↓[a]	∅ SBP ↓ DBP[a]	∅	↓[a]	∅	∅	∅	∅	∅	NT	[128]
N=37, men and women, with overweight and without T1DM or T2DM.	8	ADF (3 nonconsecutive days per week 30% energy requirements 100% energy intake on feasting day)	↓[b]	↓ 30%	∅	NT	NT	NT	NT	∅	↓[b]	↓[b]	NT	NT	[12]
		ADF (3 nonconsecutive days per week 30% energy requirements 145% energy intake on feasting day)	∅	∅	∅	NT	NT	NT	NT	∅	∅	∅	NT	NT	
N = 112, men and women, with overweight and with MS.	46	5:2: Fast day (500 kcal) Feast day (*ad libitum*)	↓[b]	↓ 25%	↓[b]	∅	∅	∅	∅	∅	∅	∅	NT	↓ sCD40L[b] ∅ IL-6 ∅ TNF-α	[13]
		Control (*ad libitum*)	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅	NT	∅ sCD40Lb ∅ IL-6 ∅ TNF-α	

Continued

Table I (*Continued*). Trials of IF in obese patients.

Participants	Trial weeks	Intervention groups	Body weight	Energy intake	Fat mass	Blood pressure	LDL	HDL	TG	Fasting glucose	Fasting insulin	HOME-IR	HbA1c	Inflammation	Ref.
N = 250, men and women, overweight and without T1DM or T2DM.	52	5:2: Fast day (women 500 kcal, men 600 kcal) Feast day (*ad libitum*)	∅	↓ 26%	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅ CRP	129
		Mediterranean	∅	↓ 20%	∅	∅	∅	∅	∅	∅	∅	∅	↓[b]	∅ CRP	
		Paleo	∅	↓ 20%	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅ CRP	
N = 121, women only, with overweight and without T1DM or T2DM.	52	5:2: Fast day (500 kcal) Feast day (*ad libitum*)	↓[a]	↓ 34%	∅	NT	NT	NT	NT	∅	∅	∅	∅	NT	130
		Calorie restriction (1,500 kcal per day)	↓[a]	↓ 25%	∅	NT	NT	NT	NT	∅	∅	∅	∅	NT	
N = 58, men and women, with overweight and without T1DM or T2DM.	8	4-h TRE (3-7 pm)	↓[b]	↓ 30%	↓[b]	∅	∅	∅	∅	∅	↓[b]	↓[b]	∅	∅ IL-6 ∅ TNF-α	131
		6-h TRE (1-7 pm)	↓[b]	↓ 30%	↓[b]	∅	∅	∅	∅	∅	↓[b]	↓[b]	∅	∅ IL-6 ∅ TNF-α	
		Control (no meal timing restrictions)	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅ IL-6 ∅ TNF-α	
N = 58, men and women, with overweight and without T1DM or T2DM.	12	8-h TRE (12-8 pm)	∅	NT	∅	∅	∅	∅	∅	∅	∅	∅	∅	NT	132
		Control (no meal timing restrictions)	∅	NT	∅	∅	∅	∅	∅	∅	∅	∅	∅	NT	
N = 19, men and women, overweight with MS.	12	10-h TRE (self-select)	↓[a]	↓ 10%	↓[a]	↓ SBP[a] ↓ DBP[a]	↓[a]	∅	∅	∅	∅	∅	∅	∅ ∅ CRP	133
N = 20, men and women, with overweight and without T1DM or T2DM.	12	8-h TRE (self-select)	↓[b]	NT	∅	∅	∅	∅	∅	∅	∅	∅	∅	NT	134
		Control (no meal timing restrictions)	∅	NT	∅	∅	∅	∅	∅	∅	∅	∅	∅	NT	

[a]$p < 0.05$, significantly different from baseline (within-group effect). [b]$p < 0.05$, significantly different from the control or calorie-restricted group (between-group effect). When the control group is present, only significant changes versus control are reported. ∅, nonsignificant change; ADF, alternate-day fasting; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; IL, interleukin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MS, metabolic syndrome; NT, not tested (parameter not measured); ND, data not disclosed; SBP, systolic blood pressure; sCD40L, soluble CD40 ligand; TG, triglyceride; TNF, tumor necrosis factor; TRE, time-restricted eating; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; ↓, decrease in the indicated parameter; ↑, increase in the indicated parameter.

Table II. Trials of IF in prediabetes and T2DM patients.

Participants	Trial weeks	Intervention groups	Body weight	Energy intake	Fat mass	Blood pressure	LDL	HDL	TG	Fasting glucose	Fasting insulin	HOME-IR	HbA1c	Inflammation	Ref.
N = 8, men only, overweight with prediabetes.	5	6-h TRE (8 am-2 pm)	∅	∅	NT	↓ SBP[b] ↓ DBP[b]	∅	∅	↑[b]	∅	↓[b]	↓[b]	NT	∅ CRP ∅ IL-6	[109]
		Control (12-h eating window)	∅	∅	NT	∅	∅	∅	∅	∅	∅	∅	NT	∅ CRP ∅ IL-6	
N = 26, men and women, overweight with prediabetes.	12	5:2: Fast day (women 600 kcal, men 650 kcal) Feast day (*ad libitum*)	↓[a]	↓ 24%	↓[a]	NT	∅	∅	∅	∅	∅	NT	↓[a]	∅ TNF-α ∅ IL-6	[151]
		5:2: Fast day (women 600 kcal, men 650 kcal) Feast day (*ad libitum*) *Lacticaseibacillus rhamnosus* probiotic	↓[a]	↓ 25%	↓[a]	NT	∅	∅	∅	∅	∅	NT	↓[a]	∅ TNF-α ∅ IL-6	
N = 97, men and women, with overweight and T2DM.	52	5:2: Fast day (500 kcal) Feast day (*ad libitum*)	↓[a]	NT	↓[a]	NT	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	NT	↓[a]	NT	[152]
		CR (1,500 kcal/day)	↓[a]	NT	↓[a]	NT	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	NT	↓[a]	NT	
N = 51, men and women, with overweight and T2DM.	12	5:2: Fast day (400-600 kcal) Feast day (*ad libitum*)	↓[a]	NT	↓[a]	NT	NT	NT	NT	NT	NT	NT	↓[a]	NT	[153]
		CR (1,200-1,500 kcal/day)	↓[a]	NT	↓[a]	NT	NT	NT	NT	NT	NT	NT	↓[a]	NT	

Continued

Table II *(Continued)*. Trials of IF in prediabetes and T2DM patients.

Participants	Trial weeks	Intervention groups	Body weight	Energy intake	Fat mass	Blood pressure	LDL	HDL	TG	Fasting glucose	Fasting insulin	HOME-IR	HbA1c	Inflammation	Ref.
N = 37, men and women, with T2DM.	12	5:2: Consecutive Fast day (500-600 kcal) Feast day (*ad libitum*)	↓[a]	↓ ND	∅	∅	∅	∅	∅	↓[a]	NT	NT	↓[a]	NT	[154]
		5:2: Non-consecutive Fast day (500-600 kcal) Feast day (*ad libitum*)	↓[a]	↓ ND	∅	∅	↑[b]	∅	∅	↓[a]	NT	NT	↓[a]	NT	
n = 37, men and women, with T2DM.	2	4-6-h TRE (8 am-2 pm)	↓[a]	↓ 18%	NT	∅	NT	NT	NT	ND	ND	∅	NT	∅ CRP	[155]
n = 32, men and women, with MS and T2DM.	1 Analysis after 4 months	Buchinger (300 kcal/day liquid diet) Followed by advice for the Mediterranean diet	↓[b]	NT	NT	↓ SBP[b] ↓ DBP[b]	∅	∅	∅	∅	∅	∅	∅	NT	[156]
		Control (advice about the Mediterranean diet)	∅	NT	NT	∅	∅	∅	∅	∅	∅	∅	∅	NT	
n = 54, men and women, with overweight and T2DM.	12	B2 (500 kcal/day 2 meals per day, breakfast and lunch only)	↓[b]	NT	NT	NT	∅	∅	∅	↓[b]	∅	NT	∅	NT	[15]
		A6 (500 kcal/day 6 meals per day)	∅	NT	NT	NT	∅	∅	∅	∅	∅	NT	∅	NT	
n = 51, men only, with overweight and T2DM.	12	IER (1,400-1,700 kcal/day)	∅	NT	∅	NT	∅	∅	∅	NT	NT	NT	∅	NT	[16]
		PPM (1,400-1,700 kcal/day)	∅	NT	∅	NT	∅	∅	∅	NT	NT	NT	∅	NT	

[a]$p<0.05$, significantly different from baseline (within-group effect). [b]$p<0.05$, significantly different from the control or calorie-restricted group (between-group effect). When the control group is present, only significant changes versus control are reported. ∅, nonsignificant change; ADF, alternate-day fasting; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; IER, intermittent energy restriction; IL, interleukin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MS, Metabolic Syndrome; NT, not tested (parameter not measured); ND, data not disclosed; PPM, proportioned meals; SBP, systolic blood pressure; SSM, self-selected meals; TG, triglyceride; TNF, tumor necrosis factor; TRE, time-restricted eating; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; ↓, decrease in the indicated parameter; ↑, increase in the indicated parameter.

tion[12,13,127-134]. Compared to TRE[131-134], ADF[12,127,128] and IF 5:2[13,129,130] have more clinically significant weight loss effects, suggesting that TRE is safe and well-tolerated. It is relatively easy to accept in elderly or frail patients and there are no weight restrictions[135]. IF failed to help subjects retain a leaner mass compared to CER[130]. However, several studies[136-138] that combined TRE with resistance training found an increase in fat-free mass (FFM), an increase in skeletal muscle, and an improvement in muscle performance along with weight loss. Perhaps this is a direction for future research. The main reason for weight loss in the subjects is a reduction in energy intake. No retaliatory eating was placed while receiving IF therapy, and all IF treatments lowered calorie consumption by more than 10%[13]. According to research[139], IF 5:2 had a high protein, moderate fat, low carbohydrate, and low fiber consumption composition in terms of diet quality. The quality of the diet was consistent with what subjects needed during the weight-loss period. Overall, IF is a beneficial way of weight loss.

As part of the IF trials, blood glucose measurements are frequently evaluated. Fasting glucose usually remains constant during ADF, IF 5:2, and TRE. In normoglycemic subjects, circulating glucose levels are maintained at steady levels, and fasting insulin levels are reduced from baseline in several trials[12,128,130,131,140,141]. In contrast to those whose baseline insulin levels were within the normal range, this impact was seen more often in people with increased baseline insulin levels (>13 uIU/ml)[131]. Elevated fasting insulin levels are a diagnostic criterion for IR[142], suggesting that IF has a better impact on reducing fasting insulin in insulin-resistant patients, which may be related to the metabolic transformation mechanism[17]. The effect of IF on insulin sensitivity varies widely, with some studies showing improvement[12,130,131,141], but most had no effect[43,128,132,134,139, 143-145]. Some studies have reported that prolonged fasting leads to impaired insulin response[146,147], while others have shown that IF140 has a good facilitative function on insulin sensitivity[148,149]. In animal studies[150], IF has been found to improve islet pancreatic β-cell quality by increasing β-cell progenitor cell neurogenin 3 (Ngn3) expression and promoting β-cell neogenesis. It requires more in-depth research in more trials. In those without T2DM, the majority of investigations on glycosylated hemoglobin (HbA1c) have shown no change[128,131,132,134]. Additionally, IF is advantageous for lowering other metabolic disease risk factors, such as lowering blood pressure, controlling blood lipids, decreasing inflammation, and reducing oxidative stress[13,129,133].

In conclusion, IF protocols have a positive effect on obesity. Educational activities and follow-up for patients to maintain an IF diet are necessary.

Results of Studies Using the IF Protocols in Prediabetes Patients

The use of IF procedures in individuals with prediabetes have been positively impacted by recent research. To date, two studies[109,151] have evaluated the impact of IF regimens on individuals with prediabetes. Sutton et al[109] conducted a 5-week trial of TFR (6-h TRE from 8 am to 2 pm) in 8 prediabetic male subjects. The results found that the subjects decreased fasting insulin and blood pressure, improved insulin sensitivity and β-cell responsiveness, and reduced oxidative stress in the absence of weight loss, explaining that IF has benefits which are independent of weight loss. Tay et al[151] obtained similar positive results with a 12-week dietary intervention of IF 5:2 (fasting 2 days per week, 600 kcal per day) in 33 subjects with obesity and prediabetes. Subjects had reduced energy intake, weight loss, less waist circumference, and lower HbaA1c. Subjects complied very well in both trials. However, there was no significant decrease in fasting glucose, which may be related to the short duration of trials. Additionally, these two trials[109,151] lack awareness of fluctuations without glucose monitoring during IF.

Results of Studies Using the IF Protocols in T2DM Patients

Positive outcomes with IF regimens in T2DM patients have been documented[15,16,152-156]. The most used IF regime for T2DM is IF 5:2. A 52-week IF 5:2 trial of 137 patients with both obesity and T2DM yielded positive results[152]. Post-intervention studies[153] showed that weight loss reduced HbA1c levels and improved fasting glucose and lipid levels, which was consistent with the continuous energy restriction (CER) group. The results are coherent with the prior trial using IF 5:2. Both trials[152,153], also performed a medication effectiveness score (MES), which decreased over time indicating that IF would be beneficial for T2DM patients in the decrease of the dose of diabetes medications. Additionally, subjects showed better adherence in the IF group than in the CER group[152]. At the end of the 52-week intervention, Carter et al[157] conducted a 12-month follow-up intervention and found that subjects had a 0.3%

increase in HbA1c levels from the preintervention baseline and a 33% weight recovery from pre-intervention baseline, suggesting that sustained intervention and dietary support are needed to maintain positive outcomes. Corley et al[154] conducted a 12-week trial of IF 5:2 (continuous or noncontinuous fasting) in 37 patients with T2DM and obesity. The results showed a reduction in overall energy intake, weight loss, lower levels of fasting glucose and HbA1c, and improved quality of life in the subjects. Meanwhile, no difference in outcomes between continuous or discontinuous fasting is observed. There was a two-fold increase in the risk of hypoglycemic events during fasting, but no serious hypoglycemic events occurred. Therefore, IF 5:2 is feasible to comply with compliance in patients with T2DM, especially in patients who are diet-controlled and not taking sulfonylureas and insulin.

Additionally, the interventions for IF are varied. Subjects with T2DM who fasted 18-20 hours per day for 2 weeks of metformin intervention experienced weight loss and reduced fasting and postprandial glucose levels[155]. Postprandial glucose variability, a major marker of glycemic control, was also reduced[158]. Fifty-four patients with T2DM underwent a 12-week intervention comparing A6 (three large and three small meals per day) *vs.* B2 (breakfast and lunch) regimen with the same daily energy restriction in both groups. Eating only breakfast and lunch favors weight loss, liver fat content, fasting glucose, C-peptide, glucagon levels, and oral glucose insulin sensitivity (OGIS). These regimens improve insulin sensitivity and β-cell function. Meanwhile, the frequency and timing of eating are as important as energy restrictions. After four months of the Buchinger diet plan intervention (300 kcal per day *via* liquid intake only, followed by gradual reintroduction of solid food), subjects showed weight loss, lower HbA1c levels, lower blood pressure, and improved quality of life[156]. The results of the 12-week 4:3 IF (1,000 kcal per day for 4 consecutive days per week, with the remaining 3 days eating *ad libitum*) were similar to the above results, reducing triglyceride levels. It is worth noting that none of the above dietary interventions reported severe adverse effects.

In conclusion, IF, in any form, leads to significant weight loss and reduction in the whole body and visceral fat[15,16,152-156], and both weight and visceral fat gain are associated with an increased risk of T2DM[159]. Since IF intervention, patients with T2DM have experienced improvements in glycemic parameters and partial reductions in medication intake. IF could improve patient motivation and compliance and reduce medication side effects. As no severe hypoglycemic events and other adverse events have been reported, IF can be considered a relatively safe dietary intervention for T2DM patients.

Safety of Intermittent Fasting

The safety of intermittent fasting has been questioned. Therefore, we tried to find little evidence for the adverse effects of IF regimens. Fasting is barely elite with any long-term gastrointestinal adverse effects such as abdominal pain, diarrhea, nausea, vomiting, or halitosis[131]. A reduction in energy intake was observed without binge eating and other eating disorder symptoms. Psychological disorders such as depressive mood or manic mood are not observed yet[160,161]. Moreover, there is no clear evidence[11,145] of clinically meaningful effects on thyroid hormones or reproductive hormones.

Common adverse effects of IF are gout, muscle wasting, and the risk of hypoglycemia. Prolonged fasting inhibits uric acid excretion, which leads to a rapid increase in serum uric acid[162]. IF usually leads to a decrease in overall energy intake and a deficit in overall protein intake, which may lead to muscle atrophy[163]. However, other studies[136-138] have combined exercise with IF and achieved successful FFM maintenance. IF can avoid hypoglycemic events in normoglycemic subjects, with the main risk being in patients with T2DM. Despite the reduced dose of diabetes medications, fasting increases the incidence of hypoglycemia. Therefore, T2DM patients require close physician monitoring during intermittent fasting.

In conclusion, IF is a safe dietary intervention option and requires robust coordination with the clinician. However, the safety of intermittent fasting remains inconclusive attributed to the lack of large randomized controlled trials to test the long-term efficacy and side effects of IF in patients with well-defined conditions such as metabolic syndrome or mood disorders.

Clinical Implementation Considerations for Patients with T2DM

The clinical implementation of IF in patients with T2DM requires appropriate medical management. Regular glucose monitoring in the

fasting state, two hours before and after each meal and at bedtime on day 7 is recommended. If necessary, anti-diabetic medications are reduced according to physician recommendations to avoid fasting hypoglycemia, such as sulfonamides and insulin[139,164]. The IF intervention should be suspended immediately when a severe hypoglycemic event occurs. Because of the potential for excessive fluid intake (e.g., water and tea) on fasting days, diuretics and SGLT-2 medications may need to be reduced or discontinued to reduce the risk of dehydration and hypotension. The specific medication regimen also relies on the clinical experience of the endocrinologist due to the lack of clinical data. Physicians are advised to work individually with patients on a one-to-one basis 24/7 to minimize the risk of hypoglycemia. Patients are also advised not to adjust their medications privately without physician advice[164].

Conclusions

According to a growing amount of research, IF provides a wide variety of health advantages. Numerous studies have shown that the benefits of IF on glucose homeostasis in T2DM patients and healthy individuals should be further investigated. Almost all kinds of IF exhibited a weight-reduction impact in all population study participants. And in patients with dysglycemia and obesity, IF showed the ability and potential to lower fasting insulin, HbA1c concentrations, and insulin sensitivity index. The specific mechanisms are mainly through metabolic transformation to improve systemic metabolism and induce tissue-specific metabolic adaptations, including changes in the gut microbiota, remodeling of adipose tissue, correction of circadian rhythm disturbances, and increased autophagy in peripheral tissues. IF as a nutritional modifier has a few adverse effects mainly involving the risk of gout, muscle wasting, and hypoglycemia. In conclusion, IF might act as a safe dietary therapeutic target. However, it remains unclear which diets (ADF, IF 5:2, or TRE) are the best regimen. Fortunately, the positive findings so far highlight the direction of future research.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The experimental data used to support the findings of this study are available from the corresponding author upon request.

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