Intermittent Fasting as a Therapeutic Approach for Managing Type 2 Diabetes: A Comprehensive Narrative Review

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Abstract

Diabetes Mellitus (DM) is an increasingly widespread global health issue with an ever-increasing prevalence and serious consequences. While, there are pharmaceutical interventions, the association of comorbidity induced polypharmacy and side effects necessitates for non-pharmacological intervention. Intermittent Fasting (IF) has emerged as an effective strategy to manage this condition but comprehensive evaluation must be carried out. This review employed a narrative approach, collecting and analyzing data from scientiýc databases between 2018-2023 to investigate mechanisms related to DM, various IF methods, clinical trials, drawbacks and future directions of study. Intermittent Fasting (IF) has shown promise for improving insulin sensitivity, decreasing obesity and improving metabolic health in those living with Type 2 Diabetes Mellitus (T2DM). Studies indicate positive effects on weight, glycemic control, lipid proýles and weight management. However, there may be potential hypoglycemia, nutritional deýciencies or adherence issues that hinder long-term sustainability. Therefore, future research must focus on long-term sustainability, tailored approaches and combinational therapies. Intermittent Fasting offers a promising approach for treating T2DM by targeting critical metabolic pathways. While showing potential beneýts, its implementation must be tailored speciýcally for each individual considering patient proýles, medication changes and close monitoring. Future research should examine long-term effects, optimal protocols and combinational approaches. Its inclusion into clinical practice has immense potential to enhance T2DM care and represents an exciting frontier of diabetes care.

Keywords: Intermittent Fasting (IF), Diabetes Mellitus (DM), Glycaemic control, Fasting

Introduction

Diabetes Mellitus (DM) is a prevalent metabolic condition characterized by elevated blood glucose levels, or hyperglycemia. This chronic illness often stems from either insufýcient pancreatic insulin production or impaired ability to utilize this key hormone effectively by the body, ultimately leading to uncontrolled hyperglycemia that damages many bodily systems such as nerves and blood vessels (1-3).

Over time, diabetes prevalence has experienced an exponential rise since 1980; from 108 million worldwide in 1980 to 422 million by 2014 (1). Low- and middle-income countries saw more signiýcant rises than high-income nations(1). Diabetes has far-reaching consequences; it can contribute to blindness, kidney failure, heart attacks, stroke and lower limb amputation (1). Between 2000 and 2019, diabetes-related mortality rates by age saw an upward trend, emphasizing its severity (1). Diabetes caused over an estimated two million deaths worldwide between these years (1).

There are various forms of diabetes, such as Type 1 and Type 2. Type 1 is characterized by inadequate insulin production and requires daily administration, usually beginning early in life (2). Type 2 diabetes affects how the body uses glucose for energy, leading to elevated blood sugar levels if left unmanaged. Lifestyle factors like obesity and physical inactivity, as well as genetic predispositions may play a part in its onset (2). Gestational diabetes may occur during gestation while impaired glucose tolerance or fasting glycemia is an intermediate state between normality and diabetes that poses an increased risk of transitioning to Type 2 (2).

Recent data from Ong et al. demonstrate a startling rise in global diabetes cases. Over 500 million people worldwide currently suffer from diabetes; it's expected that number will more than double by 2023 (3). According to this projection, prevalence rates will experience dramatic increases across all regions; North Africa and the Middle East could experience particularly striking spikes between 2050-2063 of 9.3%-16% (3). Prevalence rates will have seen especially steep spikes (3). Prevalence rates between 9.3%-16.8% by 2050 are projected to increase (3). With such an alarming global surge of diabetes cases necessitating preventative efforts such as early diagnosis and management strategies, urgent measures must be put forth immediately in order to combat diabetes cases and control them effectively.

Living with diabetes can be challenging due to its potential long-term complications that threaten individuals' wellbeing and lifespan. Diabetes has become the leading cause of serious issues such as renal failure, new-onset blindness and non-traumatic lower extremity amputation in the US. Complications associated with this illness can generally be divided into vascular and non-vascular categories. Vascular complications refer to issues related to blood vessels and nerves, impacting areas like eyes, kidneys, heart and limbs. Non-vascular complications cover an array of issues from digestive to skin tone changes to increased infection risks and even sensory impairments such as cataracts or hearing loss (4). Management of type 2 diabetes should aim at protecting patients from its complications while upholding quality of life, according to a consensus report issued by both the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). Lifestyle adjustments like increasing physical activity, losing weight and adopting healthier diet habits are highly encouraged. However, some patients still require medication in order to effectively control their blood glucose levels. As diabetes type 2 is typically characterized by insulin resistance, many medical interventions focus on increasing levels of insulin (5). A variety of drugs and insulin preparations serve this purpose. While they provide effective treatment of hyperglycemia, the increase of insulin alone may create an upward spiral of rising medication dosages over time. A study by Albosta et al. further supports this assertion by showing how intensive insulin therapy - while effective at tight glycemic control - led to increased hyperinsulinemia and weight gain after six months (6).

Even though both the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) emphasize treatment's vital role in avoiding complications, alternative approaches such as intermittent fasting could also prove helpful in managing type 2 diabetes by potentially improving insulin sensitivity. Conducting a comprehensive narrative review on the potential advantages and drawbacks of including intermittent fasting into diabetes mellitus management is of utmost importance in academic research. Intermittent fasting can bring many advantages for those dealing with this disease. Scientiýc studies have documented substantial reductions in blood glucose levels - even 5.6% more efýciently controlling type 2 diabetes cases! There is evidence showing increased insulin sensitivity, an integral component of controlling glycemic levels, which supports intermittent fasting's ability to ameliorate prediabetic conditions. Intermittent fasting combined with weight management strategies has shown immense promise, especially given the rising prevalence of obesity among individuals living with diabetes. This narrative review methodically gathered information by searching scientiýc databases like PubMed and EMBASE for studies published between 2018 and 2023. The study focused on research about how intermittent fasting (IF) can impact type 2 diabetes mellitus (T2DM). It examined various sources, including research articles, clinical trials, systematic reviews, and meta-analyses. The review systematically analyzed key aspects such as the mechanisms of T2DM, different IF methods, clinical trial ýndings, drawbacks of IF, and areas for future research.

Type 1 and Type 2 Diabetes and Mechanisms

Diabetes Mellitus: Understanding Type 1 and Type 2 Mechanisms

Diabetes Mellitus (DM) is a chronic metabolic condition characterized by elevated blood glucose levels due to inadequate insulin secretion or resistance, leading to inadequate blood glucose regulation. There are two primary forms of DM: Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM), each with distinct pathophysiological mechanisms (7).

Type 1 Diabetes Mellitus (T1DM)

T1DM accounts for approximately 5-10% of diabetes cases. It is characterized by an autoimmune response that destroys insulin-secreting beta cells in the pancreas, often due to viral infections or genetic susceptibility. Glutamic acid decarboxylase autoantibodies (GADAs) play an integral part in diagnosing T1DM (7).

Destroying beta cells leads to a decrease in beta-cell mass and, consequently, insulin secretion. When 80-90% of beta cells have been destroyed, hyperglycemia ensues, and diabetes becomes evident. Patients diagnosed with T1DM typically require exogenous insulin therapy to manage blood glucose levels, prevent ketosis from setting in, and stabilize metabolism (7).

Genetic factors, particularly polymorphisms in class II HLA genes like HLA-DR3 and HLA-DR4, play an integral part in T1DM susceptibility. Sensory and autonomic neuropathies often occur from degeneration of axonal pathways and demyelination (7).

Type 2 Diabetes Mellitus (T2DM)

T2DM accounts for 90-95% of diabetes cases and is characterized by peripheral insulin resistance and insufýcient insulin secretion. Insulin resistance develops when cells in peripheral tissues become less responsive to insulin; muscle, liver, and fat tissue become particularly affected, decreasing glucose transport into cells while increasing production from the liver. As a result of decreased transport and increased production from the liver, decreased glucose transport into cells is reduced, along with enhanced fat breakdown (7).

Beta-cell dysfunction is another crucial contributor to T2DM. At ýrst, the body may respond to insulin resistance by increasing insulin secretion, but over time, beta-cell function declines, leading to insulin deýciency, resulting in raised blood glucose levels (7). Obesity, especially visceral obesity, is one of the leading contributors to insulin resistance in T2DM. Increased body fat, particularly in the abdominal region, decreases insulin sensitivity and reduces tissue response to treatment. Other risk factors for T2DM may include increasing age, family history of diabetes, physical inactivity, and ethnic background as potential precursors (7).

Insulin Resistance and Insulin Insufýciency

Insulin resistance is a deýning feature of both types of diabetes. Insulin resistance is particularly inþuential in T2DM due to high levels of free fatty acids and proinþammatory cytokines. This contributes to this resistance and leads to decreased glucose transport into cells, increased hepatic glucose production, and enhanced fat breakdown. While autoimmunity and destruction of beta cells is the primary source, insulin resistance may develop over time (7).

Insulin insufýciency is most evident in T1DM, where beta cell destruction causes signiýcant decreases in insulin secretion. While initially increased secretion may compensate for resistance issues in T2DM, beta-cell dysfunction eventually results in inadequate production and should be monitored closely for signs of inadequate production (7).

T1DM involves genetic susceptibility, viral infections, and autoimmunity as key drivers; polymorphisms of class II HLA genes like HLA-DR3 and HLA-DR4 play an integral part in its progression; obesity, family history, physical inactivity, and ethnic background are also signiýcant contributors in its progression; amino acid metabolism with elevated concentrations has also been associated with an increased risk of future diabetes (7).

Intermittent Fasting and Diabetes Management

As diabetes prevalence soars, effective management and metabolic health strategies are vital. One such strategy that has gained signiýcant attention is intermittent fasting (IF). This dietary pattern involves periods of energy restriction followed by fasting or timed eating windows - providing an alternative approach that may enhance compliance while providing unique metabolic advantages.

There are various popular intermittent fasting regimens:

Alternate Day Fasting (ADF): This regimen alternates between feeding and fasting days. Individuals can consume food and beverages without restriction on feeding days while fasting days entail no caloric intake. Modiýed ADF allows for consuming approximately 20-25% of one's energy requirement (typically 500-800 kcal) during fasting days (8,9).

IF 5:2: This regimen is characterized by two stages: two fasting days per week, during which individuals consume approximately 500-1,000 kcal daily, and ýve days of unrestricted eating. The two restriction days can be consecutive or non-consecutive, offering þexibility in adherence (8).

Time-Restricted Eating (TRE): TRE involves limiting eating to a speciýc window of hours per day, typically ranging from 4 to 8 hours. Individuals abstain from food outside this window and may only consume water or zero-calorie beverages (8).

Other less common forms of intermittent fasting include B2 and 4:3 IF. In the B2 program, individuals have two meals daily: breakfast from 6 a.m. to 10 a.m. and lunch from 12 p.m. to 4 p.m. 4:3 IF is similar to IF 5:2, but with an additional day of fasting per week (10,11).

Intermittent Fasting in Diabetes Management

In the context of diabetes management, intermittent fasting shows substantial promise. It offers a multifaceted approach to improving metabolic health and aiding glucose regulation. Here is how it can be particularly beneýcial for individuals with diabetes:

Enhanced Insulin Sensitivity: Intermittent fasting has demonstrated the potential to enhance insulin sensitivity. This is a critical factor in diabetes management, as improved insulin sensitivity helps cells better utilize glucose, leading to more stable blood sugar levels (6).

Weight Management and Fat Reduction: Intermittent fasting has been associated with effective weight loss and a positive shift in body composition, including a reduction in fat mass. Even modest weight loss can signiýcantly reduce the risk of developing diabetes or help manage the condition in individuals already diagnosed (12).

Glucose and Lipid Regulation: Intermittent fasting has shown promise in inþuencing glucose and lipid homeostasis. Regulating fasting glucose levels and insulin concentrations aids in achieving and maintaining healthy blood sugar levels (13).

Metabolic Adaptations: Beyond calorie restriction alone, intermittent fasting triggers speciýc metabolic adaptations. These include gut microbiome changes, adipose tissue remodeling, and corrections in circadian rhythm disturbances. These adaptations play a pivotal role in comprehensive diabetes management (14).

Complementary Approach: Intermittent fasting can be integrated alongside conventional medication and lifestyle interventions for diabetes. However, it is crucial to do so under the guidance of a healthcare provider to ensure an individualized and safe approach (15).

Intermittent fasting presents a promising adjunct to diabetes management. By incorporating periods of energy restriction and time-restricted eating, individuals may experience notable improvements in insulin sensitivity, weight control, and glucose regulation. As with any dietary modiýcation, it is crucial to consult with a healthcare professional, particularly for individuals with diabetes, to tailor an approach that aligns with their speciýc needs and medical conditions.

Intermittent Fasting and Diabetes Management: Reported Mechanisms

Intermittent fasting (IF) has emerged as a promising approach for managing type 2 diabetes mellitus (T2DM), offering potential beneýts in adiposity reduction, weight loss, improved glucose control, and insulin sensitivity. The relationship between intermittent fasting and diabetes management is underscored by a growing body of research highlighting its positive effects on various clinical manifestations of diabetes.

Adiposity and Weight Loss: Intermittent fasting signiýcantly impacts adiposity and weight loss, pivotal aspects of managing diabetes. Studies conducted by Larson-Meyer et al. and Kim et al. have consistently reported a substantial reduction in triacylglycerol levels in the liver and pancreas following intermittent fasting, with an average weight loss of approximately 3-8% of initial body weight after 3-24 weeks of intermittent fasting(16,17). This decrease in lipid accumulation is paramount as it preserves the health of beta cells, thereby preventing the onset of insulin resistance. Furthermore, Kim et al. noted a lower overall liver weight in mice subjected to intermittent fasting, indicative of reduced lipid accumulation (17).

These ýndings collectively establish that intermittent fasting is critical in diminishing adiposity and promoting weight loss, which holds signiýcant implications for effective diabetes management.

Glycaemic Control: Optimal glycaemic control is a fundamental goal in diabetes management, and intermittent fasting contributes signiýcantly to achieving this objective. Research conducted by Larson-Meyer et al.(16) and Lim et al.(18) has demonstrated that lower triacylglycerol levels in the liver and pancreas correlate with the improved function and return of beta cells, with a signiýcant reduction in HbA1c levels by approximately 0.29% in individuals practicing intermittent fasting compared to those following continuous energy restriction (19). This mechanism is crucial in preventing lipid-induced damage to these vital insulin-producing cells. Saada et al. further support this by establishing a link between lower triacylglycerol levels and heightened insulin sensitivity (20). These ýndings underscore the role of intermittent fasting in enhancing glycaemic control through the modulation of lipid levels and preservation of beta cell function, thereby contributing signiýcantly to the effective management of diabetes.

Insulin Sensitivity: Enhanced insulin sensitivity is a cornerstone of effective diabetes management, and intermittent fasting has demonstrated notable success. Studies conducted by Stockman et al. after practicing intermittent fasting show enhanced insulin sensitivity (21). This improvement is attributed to speciýc mechanisms, including the fasting-induced stimulation of NEUROG3, a progenitor signal responsible for the regeneration of beta cells. Additionally, activating the autophagy-lysosome pathway, as highlighted by Liu et al. and Wei et al. contributes signiýcantly to beta cell survival and heightened insulin production (22.23). Moreover, as demonstrated in Liuûs study, the reduction in autophagic þux and activation of TFEB play a vital role in maintaining beta cells and insulin secretion. Collectively, these mechanisms elucidate how intermittent fasting substantially enhances insulin sensitivity, a critical factor in diabetes management.

Intermittent Fasting and Glycaemic Control And Diabetes

Intermittent fasting (IF) shows promise in improving glycaemic control in individuals with type 2 diabetes mellitus (T2DM). It involves controlled periods of fasting alternated with eating windows. Studies led by Wang et al.,(24) Zaki et al.,(25) and Grajower et al.(26) have examined IF's impact on fasting glucose levels in T2DM individuals. Wang et al. found that IF had similar effects on fasting plasma glucose levels compared to continuous energy-restricted diets, suggesting it as an alternative for glycaemic management (24). Zaki et al. reported comparable impacts on HbA1c reduction, indicating fasting did not signiýcantly alter fasting glucose levels (25). Grajower et al. noted improvements in glycaemic control but with variable responses, possibly due to adherence issues (26). This highlights the potential of IF in inþuencing fasting glucose levels, emphasizing adherence's importance.

Turning to HbA1c levels, an indicator of long-term glucose control, studies by Wang et al., Zaki et al., and Borgundvaag et al. explored IF's impact (24,25,27). Wang et al. reported that IF showed a similar effect on HbA1c reduction compared to continuous energy-restricted diets, suggesting its potential in managing glycaemic control (24). Zaki et al. noted comparable results, indicating fasting did not signiýcantly alter HbA1c levels (25). However, Borgundvaag et al. observed a signiýcant reduction in HbA1c levels in the IF group, suggesting potential sustained beneýts in long-term glycaemic control (27). This collectively supports IF's potential in positively affecting HbA1c levels, offering a promising approach for enhanced glycaemic management in T2DM.

Vitale and Kim's systematic review provides critical insights into IF's effectiveness on glycemic control and body composition in individuals with obesity and type 2 diabetes over 12-24 weeks (28). While their study showed signiýcant improvements, limitations were identiýed, particularly the lack of sustained beneýts over more extended periods (12-18 months) and the similar effectiveness compared to continuous energy restriction.

Choe et al.'s study provided valuable mechanistic insights regarding fasting insulin levels (19). Despite focusing on non-diabetic individuals, their ýndings demonstrated a notable reduction in fasting insulin levels within the IF group, suggesting improved insulin sensitivity—a pivotal factor in glycaemic control, though in non-diabetic individuals, this study offers signiýcant insights into how IF may affect glycaemic control in T2DM.

In conclusion, evidence from studies exploring IF's effects on glycaemic control, spanning fasting glucose levels, HbA1c levels, and fasting insulin, indicates promising potential for this dietary approach in individuals with type 2 diabetes mellitus. Adherence to prescribed fasting protocols is crucial, as individual responses may vary. While short-term beneýts are evident, further research, particularly with larger sample sizes and extended follow-up periods, is imperative to establish IF's long-term effectiveness and safety in individuals with T2DM. The potential beneýts of IF on glycaemic control warrant continued exploration, offering a signiýcant area for future research in diabetes management.

Drawbacks and Considerations of Intermittent Fasting

Intermittent fasting (IF) is an emerging strategy to improve glycaemic control in individuals with type 2 diabetes mellitus (T2DM). While it shows promise, there are important considerations and potential drawbacks, especially for those managing diabetes.

One of the most immediate risks associated with intermittent fasting involves the potential for hypoglycemia, particularly in patients using anti-diabetic medications like insulin or sulfonylureas. These medications can lower blood glucose levels, and extended fasting periods can further exacerbate this risk (15). Close monitoring of blood glucose levels and potential adjustments to medication regimens are crucial to mitigate this risk.

Long-term intermittent fasting also raises concerns about nutritional deýciencies. Extended fasting periods may limit the intake of essential nutrients, potentially leading to deýciencies in vitamins, minerals, and protein. This is particularly critical for individuals with T2DM, as they already face an increased risk of nutrient deýciencies due to metabolic abnormalities (15). Planning well-balanced meals during eating windows and consulting a healthcare provider or registered dietitian is essential.

Adherence to intermittent fasting protocols can be challenging for some individuals due to various lifestyle factors and personal preferences. Inconsistent adherence may lead to less consistent glycaemic control, potentially diminishing the beneýts of intermittent fasting (25). Working closely with healthcare providers to establish realistic and sustainable fasting routines that align with individual circumstances is crucial.

The sustainability of intermittent fasting over the long term is a consideration. While short-term studies have shown promise, the feasibility and effectiveness of this approach in lifelong diabetes management need further investigation. Sustained adherence may be challenging for some individuals, emphasizing the importance of exploring alternative dietary approaches that can be maintained in the long run.

Additionally, unintended weight loss is a concern, particularly for individuals already at a healthy weight or struggling with weight maintenance. Intermittent fasting's impact on body weight can vary depending on factors like the chosen fasting regimen and individual metabolic responses (19). Monitoring body weight and composition is essential to prevent unintended weight loss, and adjustments to the fasting protocol may be necessary.

Speciýc populations, such as pregnant and lactating women, young children, frail older adults, and individuals with speciýc medical conditions, including immunodeýciencies, should be dissuaded from intermittent fasting, especially if they have diabetes. These groups have unique health considerations that fasting may exacerbate (15). Caution and personalized recommendations are essential for these individuals.

Implementing Intermittent Fasting into Clinical Practice

Regular Glucose Monitoring: Individuals with type 2 diabetes (T2DM) who choose to engage in Intermittent Fasting (IF) must undergo regular and comprehensive glucose monitoring. This entails measuring glucose levels in the fasting state two hours before and after each meal and at bedtime on fasting days. Such vigilant monitoring is crucial for timely medication regimen adjustments and for preventing hypoglycemia episodes (29).

Medication Adjustments: Physicians should take a proactive stance in modifying anti-diabetic medications to manage the risk of fasting-induced hypoglycemia effectively. Notably, medications such as sulfonylureas and insulin may need to be judiciously reduced or temporarily discontinued, particularly in patients with T2DM who are being treated with these agents (14).

Caution with Diuretics and SGLT-2 Inhibitors: Given the potential for increased þuid intake during fasting days, it is imperative to exercise caution with diuretics and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. These medications may necessitate adjustment to mitigate the risk of dehydration and hypotension (14).

Individualized Approach: The limited clinical data available on speciýc medication regimens during IF underscores the importance of an individualized approach. Physicians must work closely with patients to tailor treatment plans based on their unique health proýles and responses to fasting (26).

Consultation with a Registered Dietitian: Registered dietitians guide patients undertaking IF. They can furnish tailored dietary plans, offer education on nutritional requirements during fasting periods, and extend ongoing support and monitoring throughout the process (6).

Risk Assessment and Education: Healthcare providers should conduct a comprehensive risk assessment before commencing an IF regimen. This should consider factors such as baseline glucose control, current medication use, and any existing comorbidities. Equally important is educating patients about the potential beneýts and risks associated with IF (6).

Sustainability and Long-Term Adherence: While IF exhibits promise, there is a crucial need for further evaluation of its long-term sustainability and adherence. Healthcare providers must engage in candid discussions with patients, setting realistic expectations and considering alternative approaches if necessary (30).

Collaborative Care Approach: The effective management of IF in patients with T2DM necessitates a collaborative care approach. This entails regular and open communication between the patient, physician, registered dietitian, and other healthcare team members (30).

Monitoring for Potential Complications: Healthcare providers should remain vigilant for any signs of complications arising from fasting. This includes monitoring for electrolyte imbalances, dehydration, and potential adverse effects on kidney function (30).

Incorporating IF into clinical practice for patients with T2DM holds signiýcant potential for improving glycemic control and metabolic health. However, it is paramount that this dietary intervention be approached with caution, utilizing individualized care, and close monitoring to ensure both safety and efýcacy. Furthermore, ongoing research in this area is crucial to reýne recommendations and guidelines for healthcare providers.

Clinical Trials

Research suggests intermittent fasting may provide several advantages to people living with diabetes. Morales-Suarez-Varela et al. found that intermittent fasting is linked to improved lipid proýle, weight loss, and glycemic control for those with obesity and type 2 diabetes (31). Chair et al. conducted a randomized controlled trial that revealed alternate-day fasting and time-restricted 16/8 fasting signiýcantly impacted body weight, blood glucose, and triglyceride levels of overweight and obese adults with prediabetes (32). Corley et al.(33) and Ganesan et al. (34) researched the risk of hypoglycemia among individuals with type 2 diabetes and found that two non-consecutive days of a very low-calorie diet did not increase this risk compared to two consecutive days (Table 1) (33,35-47). Guinto conducted a systematic review that demonstrated improvements in weight, A1C levels, and fasting plasma glucose in individuals who practice intermittent fasting - suggesting it might be a practical approach to managing and improving metabolic markers related to type 1 and 2 diabetes(48). These results point to intermittent fasting as a beneýcial approach to managing and improving these metabolic indicators.

Table 1: Comparative evaluation of clinical trials conducted within the last ýve years

Author(s)	Year	Sample Population	Intervention Arm	Comparator Arm	Results	Remarks
Corley et al.[33]	2018	Type 2 Diabetes Mellitus (T2DM) Patients	Intermittent Fasting (2 Days/Week)	Intermittent Fasting (2 Days/Week on Non-consecutive Days)	Increased rate of hypoglycemia with fasting, regardless of consecutive or non-consecutive days. Improvements in weight, HbA1c, and quality of life.	Fasting, whether consecutive or non-consecutive, increased the risk of hypoglycemia in T2DM patients, but benefits in other aspects were observed with education and medication adjustment.
Obermayer et al.[35]	2023	Insulin-treated Type 2 Diabetes Patients	3 non-consecutive days of intermittent fasting (IF) per week for 12 weeks	Control group with standard care and dietary counseling	IF group showed significant reduction in HbA1c, achieved composite endpoint, no severe hypoglycemia	IF is a safe and feasible dietary option for improving glycemic control and reducing insulin dose and body weight in type 2 diabetes.
Teong et al.[36]	2023	Adults at risk of Type 2 Diabetes	Intermittent fasting plus early time-restricted eating	Calorie restriction and standard care	Improved diabetes remission, weight loss, and reduced medication costs with intermittent fasting	Intermittent fasting can lead to diabetes remission and cost savings in medication.
van den Burg et al.[37]	2020	Type 2 Diabetes Patients	Fasting-mimicking diet (FMD) for 5 consecutive days a month for a year	Usual care	Investigating the effects of FMD on metabolic parameters and medication use	Awaiting the results of the FIT trial to determine the effects of FMD on type 2 diabetes.

Table 1: Comparative evaluation of clinical trials conducted within the last ýve years (continued)

Yang et al.[38]	2023	Type 2 Diabetes Patients	Intermittent calorie-restricted diet	Control group	Achieved diabetes remission in the diet group, reduced medication costs	The study demonstrates the clinical efficacy of the diet in achieving diabetes remission.
Tay et al.[39]	2020	People with Prediabetes	Intermittent fasting supplemented with Lacticaseibacillus rhamnosus probiotic	Intermittent fasting without probiotic	Improved glucose tolerance and psychological benefits in the probiotic group	Probiotic supplementation during intermittent fasting provided psychological benefits and improved glycemic control.
Luo et al.[40]	2022	Type 2 Diabetes Patients	Chinese Medical Nutrition Therapy (CMNT) diet with intermittent energy restriction	Control group with a normal diet	Improved glycemic control and changes in gut microbiota composition with CMNT	CMNT is a promising nutritional intervention in diabetes management.
Gray et al.[41]	2021	Women with a history of gestational diabetes	Intermittent energy restriction (IER)	Continuous energy restriction (CER)	Comparable weight loss between IER and CER groups	IER produces similar weight loss to CER in women with a history of gestational diabetes.
Andriessen et al.[42]	2022	Adults with Type 2 Diabetes	Time-restricted eating (TRE)	Control group with spreading food intake	Improved glucose homeostasis, reduced fasting glucose, and increased time in normoglycemic range with TRE	TRE improved glucose homeostasis but didn't affect insulin sensitivity or hepatic glycogen.
Papamichou et al.[43]	2022	Adults with Type 2 Diabetes	Mediterranean diet (MedDiet) with or without 12-hour time-restricted feeding (TRF)	Standard Australian Dietary Guidelines	Ongoing trial to investigate the efficacy of MedDiet with or without TRF in managing T2DM	Awaiting the results of the MedDietFast trial.

Table 1: Comparative evaluation of clinical trials conducted within the last ýve years (continued)

Berger et al.[44]	2021	Type 1 Diabetes (T1D) Patients	7-day Multimodal Fasting	N/A	- Increased ketone levels without ketoacidosis. - Stable blood sugar levels during fasting. - Improved quality of life. - Slight weight and BMI reduction. - Temporary fasting-related side effects.	Fasting for T1D patients appears feasible, safe, and beneficial, but further research is needed.
de Sire et al.[45]	2021	Type 2 Diabetes Mellitus (T2DM) Patients	MLD and IPC (Experimental)	MLD and Sham IPC (Control)	Significant reduction in lower limb lymphedema. Improved passive range of motion and quality of life.	A multimodal approach (MLD and IPC) shows promise in reducing lower limb lymphedema in T2DM patients, but more research is required.
Dokpuang et al.[46]	2023	Obese Participants with Prediabetes	12-week Intermittent Fasting	Probiotic or Placebo (Randomized)	Significant reductions in subcutaneous, visceral, liver, and pancreatic fat. No difference between probiotic and placebo groups.	Intermittent fasting led to fat loss in various depots, but not correlated with HbA1c or influenced by probiotics, ethnicity, or sex.
Carter et al.[47]	2019	Type 2 Diabetes Mellitus (T2DM) Patients	Intermittent Energy Restriction	Continuous Energy Restriction	Weight loss was maintained, but HbA1c increased in both groups. No significant differences in other outcomes.	Intermittent energy restriction was not superior to continuous energy restriction in terms of glycemic control in T2DM patients.

Intermittent fasting (IF) may beneýt numerous aspects of metabolic syndrome and cardiometabolic risk factors. Yang et al. found that intervention with intermittent fasting (IF) led to substantial improvements in body weight, waist circumference, fat mass, blood pressure, fasting blood glucose, insulin resistance, total cholesterol, and triglycerides compared to control groups (49). Yang et al. reported improvements in weight, waist circumference, fat mass, BMI, blood pressure, total cholesterol levels, triglyceride levels, fasting insulin, and insulin resistance following intensive interventions (49). Ciofý et al. concluded that intermittent and continuous energy restriction showed similar effectiveness for weight loss and metabolic improvement (50). However, Sharma et al. found no signiýcant differences in glycaemic control between IF and control groups for patients with type 2 diabetes mellitus (51). Intermittent fasting has shown promise in improving metabolic syndrome and cardiometabolic risk factors; however, its effect on glycaemic control in these individuals was inconclusive. While these ýndings are encouraging, they may not apply universally to everyone. When making major dietary adjustments for people with pre-existing medical illnesses, it is important to take into account their speciýc health conditions, medications, and lifestyle choices.

Future Research

As intermittent fasting (IF) becomes an integral component of diabetes management, several avenues for future research should be pursued. Longitudinal studies with extended follow-up periods will be essential in understanding its long-term effects on glycaemic control and potential long-term complications associated with type 2 diabetes mellitus (T2DM). Understanding the durability of interventions using IF will offer vital insight into its feasibility and effectiveness as a long-term dietary strategy.

Further exploration into the optimal protocols and regimens for intermittent fasting (IF) among individuals living with T2DM is crucial. Comparative studies evaluating various fasting schedules such as alternate-day fasting, time-restricted eating, or modiýed fasting protocols will help reveal which approach has produced more favorable results regarding blood glucose control, insulin sensitivity, and overall metabolic health beneýts.

Exploring the combined effects of insulin fusion therapy with other interventions, such as physical activity and speciýc dietary patterns, represents another promising ýeld of research. Combinatorial approaches may provide more signiýcant beneýts in managing T2DM and treating its various metabolic abnormalities.

Studies analyzing the impact of IF on speciýc sub-populations within T2DM are also invaluable. Understanding how factors such as age, gender, comorbidities, genetic predispositions, and individual responses to IF can inþuence individual responses can allow practitioners to tailor recommendations speciýcally tailored for patient proýles.

Conclusions

Intermittent fasting (IF) presents a compelling and innovative approach to managing type 2 diabetes mellitus (T2DM) by targeting critical metabolic pathways involved in glycaemic control. The body of evidence demonstrates that IF holds promise in improving insulin sensitivity, reducing adiposity, and enhancing overall metabolic health. However, careful implementation and monitoring are paramount to ensure its safety and efýcacy in clinical practice. In collaboration with healthcare providers and registered dietitians, individualized care is crucial in determining the most suitable IF regimen for each patient. Medication adjustments, particularly for insulin and sulfonylureas, should be made judiciously to prevent fasting-induced hypoglycemia. Regular glucose monitoring, risk assessment, and vigilant monitoring for potential complications are essential components of a comprehensive care plan.

While IF offers a valuable adjunct to diabetes management, it is essential to acknowledge that it may not be suitable for all individuals with T2DM. Consideration of individual health proýles, lifestyle factors, and preferences is imperative in determining the appropriateness of IF as a dietary intervention.

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