https://doi.org/10.46389/rjd-2025-1602
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2025; volume 32, issue 1, pages 105–112

Review

Intermittent fasting: a novel approach for managing type 2 diabetes: systematic review

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Received: 11 October 2024 / Accepted: 14 January 2025

Abstract

The prevalence of Type 2 Diabetes Mellitus (T2DM) has escalated, positioning it as the ninth-leading cause of mortality. Unhealthy lifestyles contribute to the development of cardiovascular disease, including T2DM. This study aims to analyze the effects of intermittent fasting concerning T2DM, synthesizing findings from literature published between 2019 and 2024. Literature was gathered from Scopus, PubMed, and ScienceDirect, focusing on recent studies. Criteria were set to select relevant articles, resulting in the inclusion of 5 studies. The outcomes were analyzed to ascertain the impact of intermittent fasting on various parameters related to T2DM. Intermittent fasting demonstrated a significant effect on several factors associated with T2DM, including HbA1c levels, glucose tolerance, insulin dosage, HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), LDL-C (Low-Density Lipoprotein Cholesterol), MSS (Metabolic Syndrome Score), total leptin and cholesterol levels, HDL (High-Density Lipoprotein Cholesterol), βHB (beta-hydroxybutyrate), body weight, and other anthropometric measurements. The literature review suggests that intermittent fasting can effectively modulate multiple aspects of T2DM. It is proposed as a potential preventive measure for T2DM. However, it is advisable for individuals, especially those with diabetes, to seek medical consultation before adopting intermittent fasting as part of their lifestyle.

Keywords: intermittent fasting, type 2 diabetes, insulin.

Introduction

The incidence and prevalence of type 2 diabetes continue to rise, and it is a leading cause of human suffering and death. In 2017, around 462 million individuals had type 2 diabetes, representing approximately 6,28% of the global population. Among them, 4.4% were aged 15–49, 15% were aged 50–69, and 22% were aged 70 and above. Diabetes emerged as the ninth leading cause of mortality, contributing to over 1 million deaths annually. The prevalence of diabetes mellitus is escalating worldwide, with developed regions like Western Europe experiencing a remarkably rapid increase in its burden [1, 2]. The projected figures for individuals with diabetes are anticipated to rise to 643 million by 2045, constituting approximately 12,2% of the population. It is estimated that about 240 million individuals worldwide have undiagnosed diabetes, indicating that nearly half of adults are unaware of their condition [2].

Type 2 diabetes is a chronic condition characterized by a slow progression that can have life-threatening implications over time. Some of the complications due to type 2 diabetes are retinopathy, causing blindness; nephropathy, causing kidney failure; damage to the vascular system, causing heart attack; foot diseases caused by neuropathy; and ischemia, which can result in leg amputation. Death usually occurs due to complications from kidney disease or heart failure [3]. Diabetes has a plethora of complications in the nervous system, peripheral tissues, retina, liver, and cardiovascular system [4].

Two primary factors cause type 2 Diabetes Mellitus (T2DM). The first problem with pancreatic β-cells leads to defective insulin secretion and insulin resistance

that causes the inability of insulin to respond appropriately to insulin-sensitive tissue. In addition to those factors, T2DM encompasses ethnicity and family history (indicating genetic predisposition), obesity, insufficient physical activity, poor dietary habits, and underlying pathophysiological mechanisms [5]. T2DM occurs due to system dysfunction in metabolic homeostasis [4]. Lifestyle factors contribute to the development of diseases like T2DM. These factors encompass dietary habits, sedentary behavior, sleep patterns, socioeconomic status, and physical activity levels. Factors related to environment and lifestyle can, in one way or another, contribute to the damage of β-cell, which are responsible for insulin production [6]. A sedentary lifestyle and unhealthy eating habits were the main factors related to T2DM [4]. Some of the risk factors of T2DM are modifiable. It means it is possible to reduce the burden of T2DM with appropriate prevention and good therapy for individuals with diabetes to prevent other complications.

Many studies review the benefits of fasting in humans, including its effects on diet, activity, and sleep. In a review of nutrition studies, Patterson (2017) concluded that a single fasting interval in humans, for example, overnight, affects many metabolic biomarkers such as insulin and glucose. Also, overindulgence in eating habits can result in metabolic damage, such as insulin resistance, excessive visceral fat accumulation, and other health complications [7, 8]. Intermittent fasting (IF) is a dietary regimen marked by alternating periods of little or no energy intake, typically lasting from 16 to 48 hours, interspersed with periods regulating eating [8]. Fasting can commence with shorter durations and gradually extend as individuals gain more experience with the fasting process.

Given the rising global prevalence of T2DM and its impact on public health, there is a growing interest in exploring alternative lifestyle interventions to complement existing treatment modalities. Intermittent fasting, characterized by alternating periods of fasting and eating, has emerged as a promising strategy due to its potential to modulate key metabolic pathways implicated in T2DM pathogenesis. By harnessing the body's adaptive responses to fasting, such as improved insulin sensitivity and metabolic flexibility, intermittent fasting can mitigate insulin resistance, promote weight loss, and enhance glycemic control. This study aims to systematically review the latest evidence on the impact of intermittent fasting related explicitly to T2DM, shedding light on its potential as a preventive and adjunctive therapy for this chronic metabolic disorder.

Material and methods

Data sources and search strategy

Search for studies conducted from databases Pubmed, Scopus, and ScienceDirect with keywords "type 2 diabetes" and "intermittent fasting". The selected studies are the latest studies between 2019 and 2024 in English. The systematic review was analyzed using PRISMA (Preferred Reporting Items for Systematic Review) guidelines. Moreover, the articles under study were manually screened based on their titles and abstracts to assess their relevance to the systematic literature review conducted in this study. Figure 1 summarizes the study's literature search process.

Study selection

The inclusion criteria include interventional or observational studies, specifically studies with randomized control trial design and prospective observational studies. In addition, the study's literature analyzed types of intermittent fasting intervention with outcomes relevant to type 2 diabetes. The exclusion criteria were animal studies, review articles, not using the English language, and not accessing the full text.

Data extraction and quality assessment

The reviewer searches for studies in online databases and exports the data to Mendeley Desktop. Duplicate studies are screened and removed. The reviewer performs data extraction and concomitantly analyzes data quality. The study utilized PRISMA recommendations to evaluate the risk of bias within its methodology [9].

Results

Study characteristic

Based on database search results, 1.074 was found after duplicates were removed. Study literature excluded based on title and abstract, review study design, animal study, and non-English based. Afterward, the literature was analyzed based on the study design and primary outcome. A total of 5 studies remained for further analysis. Most of the study literature was randomized control trial study design [10–13], one of which is a prospective observational study [14]. Each literature study experimented with a different type of

https://doi.org/10.46389/rjd-2025-1602

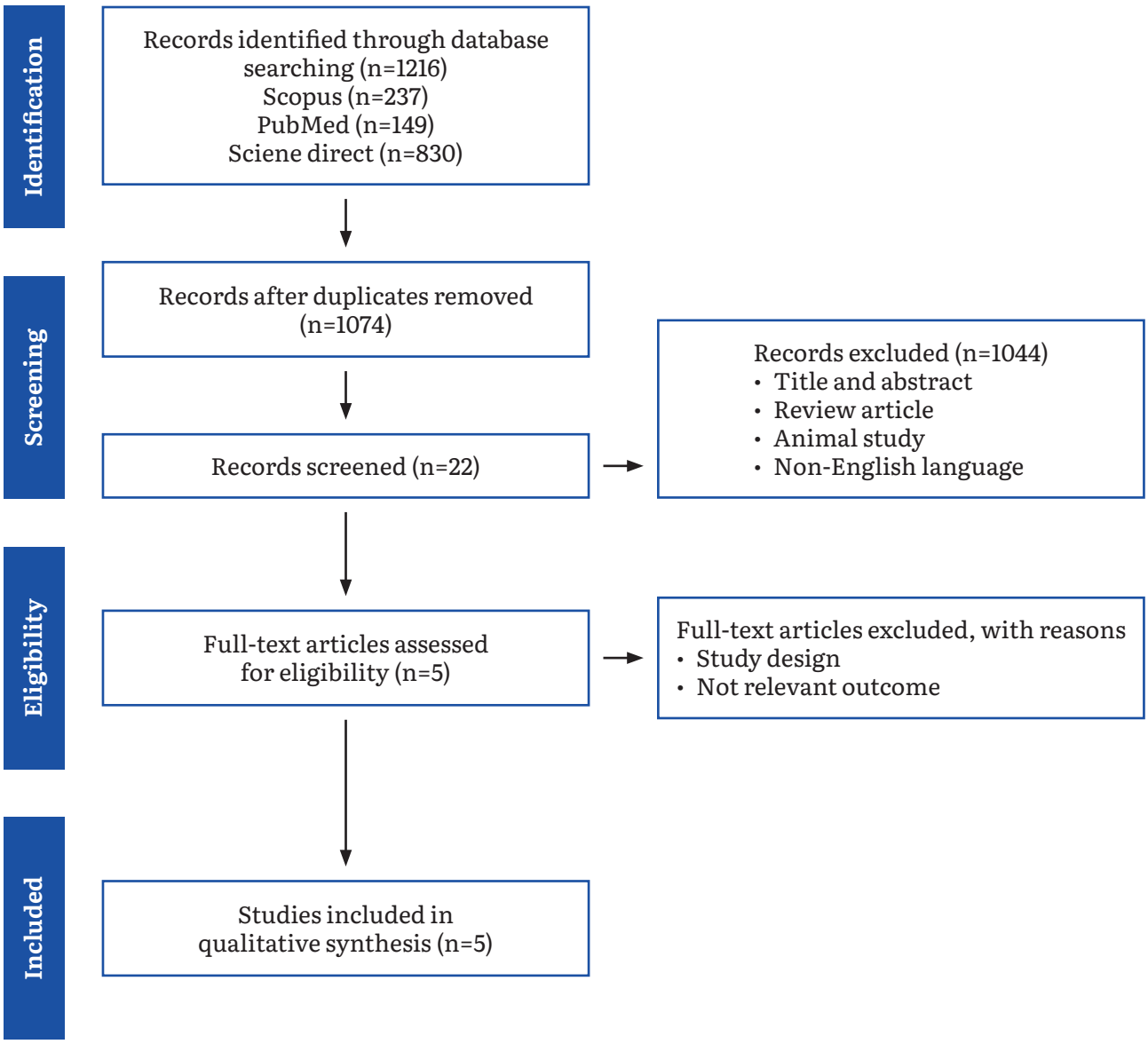

Figure 1: A PRISMA flowchart illustrating the study's literature search process and study selection.

intermittent fasting. Most of the participants of the survey were diabetic patients or at risk of diabetes.

The intermittent fasting intervention was also adopted differently, with two related studies evaluating different changes in HbA1c levels compared with a control group and participants who achieved body weight, insulin dose, and absolute HbA1c reduction at a time [10, 12]. Other studies connect intermittent fasting with LDL-C and other biomarkers such as HOMA-IR, MSS, BDNF, GCPi, lipid biokinetics, and glucose tolerance [11, 13, 14]. Table 1 provides an overview of the study literature.

The NHLBI Quality Assessment Tool for controlled intervention and pre-post studies without a control group was employed to evaluate the quality of the study. This assessment tool focuses on crucial concepts for determining the study's internal validity and identifying potential sources of bias. The reviewer independently assessed each study based on predefined criteria outlined in the NHLBI tool. The criteria evaluated included study design, selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each criterion was rated as "yes", "no", or "cannot determine", indicating whether the study adequately addressed the specific quality aspect.

Additionally, the overall potential for bias was determined based on the collective assessment of individual criteria. According to the NHLBI guidelines, studies were classified as low, moderate, or high based on risk bias. This assessment aims to systematically evaluate the methodological rigor and internal validity of the included studies, thereby enhancing the reliability and credibility of the systematic review findings.

Table 1: Characteristics of included studies literature.

Author (year)	Study design	Total sample	The purpose of the study	Study intervention	Study result
Ciera *et al.* (2021)	Randomized control trial	N=71	To assess the impact of low-frequency intermittent fasting on LDL-C and other biomarkers	Participants were divided into two groups: intermittent fasting and control groups. Intermittent fasting groups have fasting for 24-hour water only two times a week in the first four weeks and continue once a week in the remaining 22 weeks. Meanwhile, in the control group, participants had an ad libitum diet for 26 weeks.	Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Metabolic Syndrome Score (MSS) are improved with participants in intermittent fasting groups. However, LDL-C and markers of cognition (BDNF, GCPi) were unchanged.
Anna *et al.* (2022)	Randomized control trial	N=46	To analyze the effects of intermittent fasting on individuals with insulin-treated type 2 diabetes mellitus over 12 weeks.	Participants were divided into two groups (intermittent fasting and control group) with a 1:1 ratio. Intermittent fasting involves three days per week (Monday, Wednesday, and Friday) with 75% caloric restriction, while the remaining four days allowed for unrestricted eating (0% caloric restriction)	- (conducted in further article study)
Anna *et al.* (2023)	Randomized control trial	N=46	To elucidate the safety and effectiveness of intermittent fasting in managing type 2 diabetes.	Participants were divided into two groups (intermittent fasting and control group) with a 1:1 ratio. Intermittent fasting involves three days per week (Monday, Wednesday, and Friday) with 75% caloric restriction, while the remaining four days allowed for unrestricted eating (0% caloric restriction)	The experimental group showed a significant decrease in HbA1c levels (27.3±12.0 mmol/mol) compared to the control group (0.1±6.1 mmol/mol) over 12 weeks (P=0.012). Eight individuals in the IF group achieved the co-primary endpoint, compared to none in the control group (P<0.001). No instances of severe hypoglycemia were reported.

https://doi.org/10.46389/rjd-2025-1602

Table 1: Continued.

Author (year)	Study design	Total sample	The purpose of the study	Study intervention	Study result
Xia Tong *et al.* (2023)	Randomized control trial	N=137 (final analysis)	To assess the comparative impact of intermittent fasting combined with early time-restricted eating and calorie restriction, standard care in adults at risk of developing type 2 diabetes.	Participants were allocated into three groups (2:2:1) with interventions: iTRE, Calorie Restriction (CR), and standard care. The iTRE and CR group participants received nutritional support for six months and a 12-month follow-up period.	Glucose tolerance exhibited a more pronounced improvement in the iTRE group compared to the CR group, with a reduction of -10.10 mg dl−1 min−1 (95% confidence interval -14.08, -6.11) *versus* -3.57 mg dl−1 min−1 (95% confidence interval -7.72, 0.57) respectively (P=0.03).
Yasmin *et al.* (2024)	Prospective observational study	N=30	To evaluate the effect of IF on lipid metabolism in individuals with T2DM who are overweight or obese.	Participants observed daily fast for 16 hours, from dawn to sunset, as part of their Ramadan fasting regimen. Anthropometric measurements, fasting plasma glucose (FPG), HbA1c levels, lipid profile, leptin levels, beta-hydroxybutyrate (βHB) levels, and high-sensitivity C-reactive protein (CRP) levels were assessed before and three weeks after the fasting period.	There was a notable reduction in post-fasting body weight, Body Mass Index (BMI), waist circumference, hip circumference, LDL-C, total cholesterol, and leptin levels. Additionally, there was a significant increase in post-fasting HDL-C and βHB levels. However, no significant changes were observed in post-fasting levels of HbA1c, FPG, triglycerides, and high-sensitive CRP post-fasting levels.

Impact of intermittent fasting

Two studies assessed the effects of intermittent fasting on insulin resistance and dose. One study compared to the control group considered the enhancement in HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) with a percentage improvement of 32.5% in the fasting group and 3.7% in the control group. This improvement was attributed to an increase in insulin levels (P=0.001), with a 24.0% decrease observed in the fasting group compared to a 2.8% decrease in the control group. Additionally, there was a reduction in glucose concentration to a lesser extent (P=0.039), with a 7.9% decrease in fasting subjects compared to 2.4% in control subjects [13].

Meanwhile, the other study showed a significant reduction in insulin dose within the fasting and control groups. Following the intervention, the IF group showed an insulin dose of 45±19 IU, compared to 63±35 IU in the control group. Before the intervention, the daily insulin dose was 52±19 IU in the fasting group and 59±33 IU in the control group. Following the 12-week intervention period, it was observed that the total daily insulin dose in the fasting group decreased by an average of 9±10 IU. In contrast, the control group experienced an increase of 4±10 IU. This difference was statistically significant (P=0.008) [12].

Intermittent fasting also yielded a notable impact on body weight. Findings from one study revealed a significant weight reduction (4.77±4.99 kg) compared to the control group (10.27±1.34 kg, P<0.001). Additionally, there was a decrease in fat mass, with the intermittent fasting group experiencing a reduction of 3.5±3.3 kilograms compared to 10.1±1.3 kg in the control group (P<0.001) [12]. In another study, anthropometric measurements were taken before and after fasting. In this study it was concluded that there was a significant decrease between pre-post intervention measurements in body weight (98.7±17.6 in pre-fasting and 96.3±17.5 in post-fasting, P≤0.050), BMI (38.29±7.11 in pre-fasting and 37.36±7.11 in post fasting, P≤0.050), WC (120.23±11.96 in pre-fasting and 117±12.81 in post fasting, P≤0.050), and HC (129.9±13.12 in pre-fasting and 127.03±13.45 in post fasting, P≤0.050) [14].

The study's randomized control trial design develops intermittent fasting, added with early Time Restricted Eating (iTRE). Result of the study, there is an improvement in glucose tolerance compared to a control group with only calorie restriction intervention −10.10 (95% confidence interval −14.08, −6.11) *versus* −3.57 (95% confidence interval −7.72, 0.57) mg dl−1 min−1; P=0.03) [11]. In a study comparing 12 weeks of IF with a control group, Glycated Hemoglobin A1c (HbA1c) levels were assessed. The intermittent fasting group decreased HbA1c by 7.3±12.0 mmol/mol, whereas the control group showed an increase of 0.1±6.1 mmol/mol (P=0.012) [12]. Some studies also evaluated the effects of IF on LDL-C and other biomarkers. However, there are two studies with a different result on LDL-C; one considered no significant difference in LDL-C in the control group [13], while the other showed that LDL-C was statistically decreased in post-fasting measurements [14]. Differences in intervention methods may be the reason for these different results.

Other biomarkers assessed in the literature study were total cholesterol, total leptin, HDL, and βHB. There is a significant decrease in total cholesterol (187.03±46.015 in pre-fasting and 178.67±39.69 in post-fasting, P≤0.050) and total leptin (20.19±16.31 in pre-fasting and 14.04±9.5 in post fasting, P≤0.050). At the same time, there is a significant increase of HDL (45.46±6.89 in pre-fasting and 47.233±5.58 in post-fasting, P≤0.050) and βHB (0.799±0.486 in pre-fasting and 1.76±0.826 in post fasting, P≤0.050) [14]. One of the studies assesses the changes in Metabolic Syndrome Score (MSS) with intermittent fasting intervention. The study demonstrated a notable increase in MSS in the control group compared to the fasting group (-0.71±1.72 *vs*. 0.06±1.71, respectively, P=0.056). The improvement in MSS was attributed to reductions in triglyceride, glucose, diastolic blood pressure, and an increase in HDL-C [13]. A summary of the study literature analysis can be seen in Figure 2.

Discussion

Based on the literature analysis, intermittent fasting affects many aspects of the human body. These include reducing LDL-C, HbA1c, insulin dose, HOMA-IR, MSS, total cholesterol, and total leptin and increasing HDL, βHB, and glucose tolerance levels. Additionally, intermittent fasting also affects the physical aspects of body weight, BMI, and waist and hip circumference. Most of the indicators assessed have a significant effect related to type 2 diabetes.

HbA1c is an indicator for evaluating long-term glycemic control, providing insight into the cumulative glycemic status over the preceding two to three months. HbA1c is the gold standard for glycemic control assessment [15, 16]. It also evaluates the risk of long-term diabetes complications [16]. HbA1c significantly correlates

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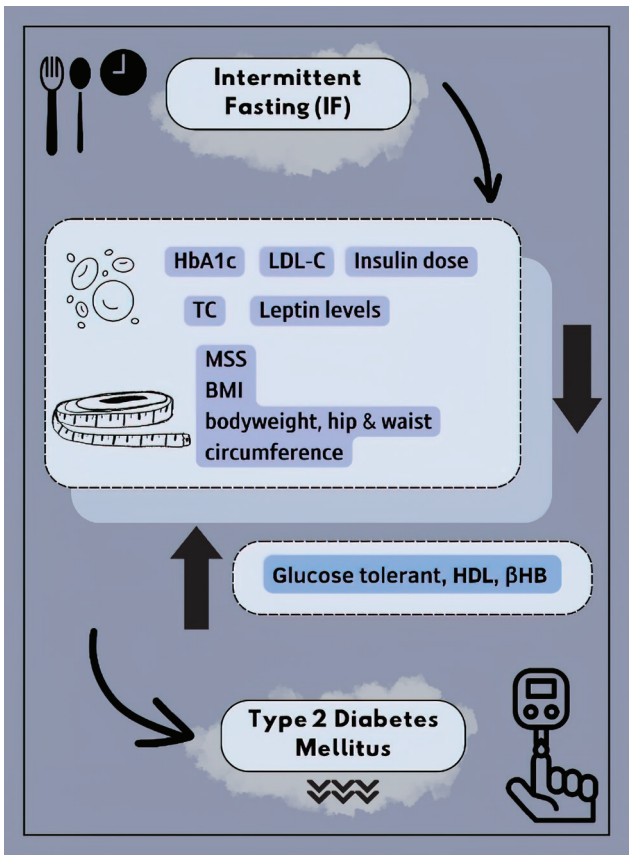

Figure 2: Illustration of the results of the literature study analysis.

with various circulating lipid parameters, such as total cholesterol (TC), LDL-C, and triglycerides (TGs). Individuals with HbA1c levels below 7.0% tend to have a reduced likelihood of experiencing increases in TC, LDL-C, TG, and HDL-C. Maintaining HbA1c levels at or below 7.0% may contribute to a decreased risk of cardiovascular disease [15]. The literature of studies has shown that intermittent fasting decreases the level of HbA1c, which helps stabilize blood sugar levels and reduces the level of insulin resistance for T2DM patients.

Insulin resistance is a critical factor in developing diabetic dyslipidemia, marked by changes in how the body metabolizes lipids. This issue mainly stems from the release of free fatty acids from adipose tissue resistant to insulin [15]. Insulin resistance is the primary cause of type 2 diabetes. Thus, addressing all factors linked to a higher risk of insulin resistance is essential.

Visceral adipose tissue is mainly associated with insulin resistance. Its accumulation is correlated with the buildup of excess lipids in the liver and contributes to cellular impairment in insulin signaling [17]. Addressing visceral adiposity is essential in preventing and managing insulin resistance and T2DM. Obesity leads to adipocyte insulin resistance through cell-autonomous mechanisms. Insulin resistance in adipocytes significantly increases the likelihood of developing T2DM [17, 18].

Overnutrition is a significant contributor to obesity. Overnutrition occurs when there is an imbalance in nutrition due to excessive intake of nutrients, typically calories, which can lead to overweight or obesity [19]. Intermittent fasting can be an effective strategy to combat chronic overnutrition. Prolonged overnutrition contributes to insulin resistance, a key underlying systemic insulin resistance. It also fosters insulin resistance in tissues like skeletal muscle and liver, accompanied by the accumulation of lipids. By promoting periods of fasting, intermittent fasting can help regulate nutrient intake and mitigate the risks associated with chronic overnutrition, potentially reducing the incidence of insulin resistance and related metabolic disorders [20–22].

However, the study has limitations stemming from its literature. The included studies feature short intervention periods, ranging from weeks to months, which may not adequately capture the long-term effects of IF. Additionally, there is considerable variability in IF protocols, including fasting duration and frequency, posing challenges to determining the optimal regimen for managing T2DM. Personalized approaches, collaborative decision-making, and ongoing monitoring are crucial for clinical application. Future research should prioritize long-term studies, standardize IF protocols, investigate underlying mechanisms, and compare IF with conventional T2DM management.

Conclusion

In conclusion, this systematic review highlights the potential of intermittent fasting (IF) as an adjunctive therapy for managing type 2 diabetes mellitus (T2DM). By significantly impacting key parameters, such as HbA1c levels, insulin resistance, and body weight, IF offers a holistic approach to T2DM management. It is recommended that individuals, particularly those with diabetes, consult a medical professional before incorporating intermittent fasting into their routine.

However, it is imperative to acknowledge the limitations of the included studies, such as short intervention periods and variability in IF protocols. Future research should prioritize long-term studies, standardization of IF protocols, and mechanistic investigations to strengthen the evidence base and facilitate the integration of IF into clinical practice.

Additionally, comparative studies between IF and conventional T2DM management approaches can provide valuable insights into IF's efficacy and safety. Ultimately, a collaborative effort between healthcare professionals, researchers, and patients is essential to harness IF's full potential in T2DM management and improve patient outcomes.

Conflict of interest

The authors declare no conflict of interest.

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