Intermittent fasting effects on patients with type 2 diabetes: A scoping review.

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Rapport: *280788 FoU i VGR*, 2023

Litteraturstudie 202*X*
FoU i VGR: [https://www.researchweb.org/is/vgr/project/280788]

Utförd under ST i allmänmedicin, Göteborg/Södra Bohuslän
inom kurs *MFM340 Forskningsmetodik för hälso- och sjukvårdsanställda, 10,5 hp*
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Summary

Background

The global prevalence of diabetes is increasing, leading to rising healthcare expenses for overweight individuals, and type 2 diabetes (T2D). T2D is a chronic disease associated with significant lifestyle changes and reduced quality of life. Non-pharmacological interventions, including dietary modifications and weight loss, are crucial in T2D management. Intermittent fasting (IF) has gained popularity as a dietary pattern due to its perceived ease of adherence and potential positive outcomes.

Purpose

This literature study aims to investigate and compile the research that exists about effects of IF on patients with T2D regarding health outcomes, psychological outcomes, and feasibility.

Method

A scoping review based on searches in the PubMed and SCOPUS databases.

Results

After searching in the PubMed and SCOPUS databases, six articles were included in the final review. The literature review revealed that IF interventions in adults diagnosed with T2D demonstrated positive effects on glycaemic control, with reductions in HbA_{1C} levels ranging from 2 to 16.9 mmol/mol and varied weight loss between 0.8 to 6.8 kg, depending on the specific study and type of intervention. Hypoglycaemic events were lower than expected and primarily occurred at the beginning of the intermittent fasting trials with two days per week of caloric restriction and a regular diet followed for the remaining five days (IF 5:2). The feasibility of both IF 5:2 and time restricted feeding (TRF) interventions was observed, but long-term adherence to the IF 5:2 diet may pose challenges.

Conclusion

IF shows potential as an effective dietary strategy for weight loss, improved glycaemic control, and enhanced psychological well-being in individuals with T2D. It is generally considered safe for individuals with T2D who manage their

condition through diet or take certain medications. However, close monitoring and medication adjustments are necessary for those taking sulfonylureas and/or insulin to prevent hypoglycaemic incidents. Establishing standardized definitions and terminology for IF is crucial to advance research in the field and improve the comparability and reliability of studies. This will enable more rigorous research and enhance our understanding of the potential benefits and risks associated with different fasting protocols.

Keyword

type 2 diabetes, diabetes mellitus type 2, intermittent fasting, time restricted feeding, periodic fasting, glycaemic control, feasibility, psychological outcomes

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Background

Around 1 in 10 adults worldwide live with diabetes and this is predicted to increase to 1 in 8 adults by 2045 (1). As a result of that expenses related to healthcare for overweight individuals, those with obesity, and those with type 2 diabetes (T2D) are on an upward trend (2).

T2D is one of the most common and enfeebling chronic diseases that requires long-term medication use and significant changes to one's lifestyle. In comparison to individuals without chronic conditions, those with diabetes often have a lower health-related quality of life (3, 4). People with diabetes have a comparable level of quality of life as individuals who have other chronic health conditions like chronic respiratory disease, cancer, cardiovascular disease, or visual impairment (5, 6). The quality of life of people with diabetes is mainly determined by the presence of comorbidities and complications (7, 8).

That becomes a big concern in healthcare globally, and as it continues, it is necessary to have treatments that are safe, cost-effective, and easily available (9).

Type 2 diabetes

Diabetes mellitus is a major contributor to morbidity and mortality worldwide, and has significant economic and social consequences (1, 10).

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose, which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation (11).

T2D is the most common form of diabetes, making up approximately 90% of all diabetes cases. It is typically marked by the body's inadequate response to insulin, a condition called insulin resistance. When insulin fails to function properly, blood glucose levels continue to rise, triggering the release of additional insulin. Over time, this can strain the pancreas in some individuals, leading to a reduction in insulin production and ultimately resulting in higher levels of blood sugar (hyperglycaemia) (12).

T2D is typically identified in middle-aged and elderly individuals, but it is becoming more prevalent in children, teenagers, and younger adults due to rising rates of obesity, sedentary lifestyles, and unhealthy eating habits (10, 12-14).

Obesity contributes to the development of insulin resistance and diabetes. Diabesity is a modern epidemic, which indicates the coexistence of both diabetes and obesity (15). A decrease in weight by 1 kg can reduce the risk of diabetes by up to 16% (16, 17).

Different types of oral medications as well as insulin can be used as monotherapy or as combination therapy to treat T2D. The goal of the treatment is to reduce the patient's symptoms and to prevent complications such as vascular and nerve damage. In addition to drug therapy, interventions are also needed regarding smoking cessation, weight loss, diet, physical activity, reduction of frustrating stress, and troublesome sleep problems (11, 12, 18-21).

In addition to medications, there exist numerous treatment options for T2D, with lifestyle interventions forming the fundamental approach to management. (21).

While there are many drugs available that can somewhat effectively manage diabesity, most patients will eventually need insulin to control their diabetes. This can worsen their obesity and lead to further diabesity (22). As a result, it is crucial to prioritize non-pharmacological treatments, such as medical nutrition interventions, lifestyle changes, and bariatric surgery, for all patients with diabesity (18).

Excessive caloric intake is a leading contributor to the rising epidemics of diabesity. However, the quality of one's diet can also have distinct effects (23). Losing a relatively small amount of weight can improve all risk factors for diabetes complications, including increased sensitivity to insulin, lower blood sugar levels, improved blood lipids, and reduction in high blood pressure if present (24). This is why diet is one of the cornerstones of diabetes treatment, but there isn't a single diet that works for all patients. The recommendation must be individualized (24).

There are many different types of diet and nutrition recommendations. Throughout the years new strategies have been presented and both pros and cons for each type of diet have been investigated. It is challenging to maintain adherence to traditional weight loss diets that involve daily caloric restriction over an extended period (25).

Intermittent fasting

Intermittent fasting (IF) has gained popularity as a dietary pattern. A 2022 survey shows that 80.17% of respondents were familiar with IF (26).

People around the world have been practicing periods of voluntary food and drink abstinence since ancient times (27).

IF has seen a surge in popularity as a dietary trend, largely due to its perceived ease of adherence and reported effectiveness in achieving positive outcomes (28, 29). Compared to conventional calorie restriction methods, which many people find challenging, IF is often perceived as being less restrictive by many individuals (30).

The term "Intermittent fasting" refers to a wide range of eating pattern, which restrict food intake for a set period of time to enable the body to enter a fasting state without enduring nutritional deficiency (31, 32). It is not related to a particular type of diet (33).

The IF diet has two basic types, with the most popular being time-restricted feeding (TRF). This type can be implemented in different variations, for example 16/8, 18/6, or 20/4. The 16/8 variant involves a 16-hour fasting period followed by an 8-hour window for consuming food. Alternatively, a stricter approach could involve shortening the nutritional window to just six or four hours (34, 35).

The second type of IF involves alternating between a 24-hour fasting period and a 24-hour eating period, repeated two or three times per week. This method can be implemented in two ways, namely 5:2 or 4:3. The 5:2 system involves two days per week of caloric restriction, with a regular diet followed for the remaining five days and correspondingly 4:3 involves four days of regular diet and three days of fasting. During the fasting period, individuals typically consume around 400-600 kcal/day (35, 36).

Another type of IF includes alternate day fasting (ADF), involving alternating between days with restricted energy intake for 24-h and ad libitum feeding (at one's pleasure) for 24-h (35, 37).

There is even a religious model of IF – Ramadan (called by some Ramadan intermittent fasting, RIF), that happens once per year for a month and includes fasting from dawn to sunset (38, 39).

Purpose

This literature study aims to investigate and compile the research that exists about effects of IF on patients with T2D regarding health outcomes, psychological outcomes, and feasibility.

Research questions

Does IF cause changes in HbA_{1C} (glycated haemoglobin), plasma glucose concentration, body weight, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and glycaemic events on patients with T2D?

Does IF influence any changes in psychological outcomes (e.g., quality of life, cognitive functions, anxiety and stress, eating behaviours), and feasibility in patients with T2D?

Method

Study design

The research was carried out as a scoping review, following the methodology outlined by Arksey and O'Malley (40). The objective of this type of study is to offer a descriptive summary of the existing research in a particular field and pinpoint any areas where further investigation is needed (identify gaps of knowledge). Quality assessment of the included studies is not part of a scoping review.

Selection (eligibility criteria)

Inclusion criteria:

• articles written and published in English
• human subjects
• adults ≥ 18 years of age
• trials, case reports
• T2D, with or without coexisting diseases, with or without obesity, with or without pharmacological treatment
• IF 5:2 or TRF, as these are two basic forms of IF with defined criteria
• studies comparing the intervention to usual care or another dietary intervention
• studies without a control group
• no specific sample size.

Exclusion criteria:

• non-English articles
• any other type of diabetes, prediabetes, prevention of T2D, high risk of T2D and other diseases if not combined with T2D
• other types of diet than IF 5:2 or TRF, if not used as a comparison (for example no ADF and religious models of IF)
• combination of IF with another type of diet
• animal trials
• systematic reviews, narrative reviews, meta-analyses, as they often include other types of fasting and dietary interventions than are included in this scoping review
• letters to the editor, commentary
• articles for which full-text is unavailable
• book chapters

• articles published before 2018 to focus on the most recent knowledge in this area.

PICO criteria for inclusion of studies:

Population	Adult patients with T2D with or without comorbidity, with or without diabetes medications
Intervention	Two types of IF: 5:2 diet and TRF
Comparison	Usual care, different dietary regime, or no control group
Outcome	Primary outcome measures: • Changes in $HbA_{1C,}$ plasma glucose concentration, body weight, BMI • Changes in psychological outcomes and feasibility

Abbreviations: T2D, type 2 diabetes; IF, intermittent fasting; TRF, time restricted feeding; HbA_{1C}, glycated haemoglobin; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Data collection and analysis

To identify relevant articles published between 2018 and 2023, a database search was conducted in PubMed and Scopus the 15th of February 2023. The search strings were developed with the assistance of the Swedish MeSH website. To combine or include keywords in the search Boolean operators “AND” and “OR” were utilized, and the search string was formulated as follows: ("intermittent fasting" OR "periodic fasting" OR "time restricted feeding") AND ("diabetes mellitus type 2" OR "type 2 diabetes" OR "diabetes type 2"). Following the database search, the search results were systematically analysed based on established inclusion and exclusion criteria and the PICO.

Ethics in included studies

Ethical approval was not required for this study, as it was solely based on literature from previously conducted studies. All the included studies declared that they had obtained ethical approval prior to conducting their studies.

Results

The initial database search with a filter for publication years 2018-2023 retrieved 310 studies. The articles were checked for duplicates and analysed based on inclusion and exclusion criteria. The selection process is presented in the flowchart below (Figure 1). A total of 43 abstracts were read, of which 21 articles were excluded. Twenty-two articles were read in full-text, of which only six met the inclusion criteria. The

main reasons for exclusion at this stage were other types of diet interventions, combination of diet interventions, reviews, or commentaries. One article could not be retrieved, and one was not in English.

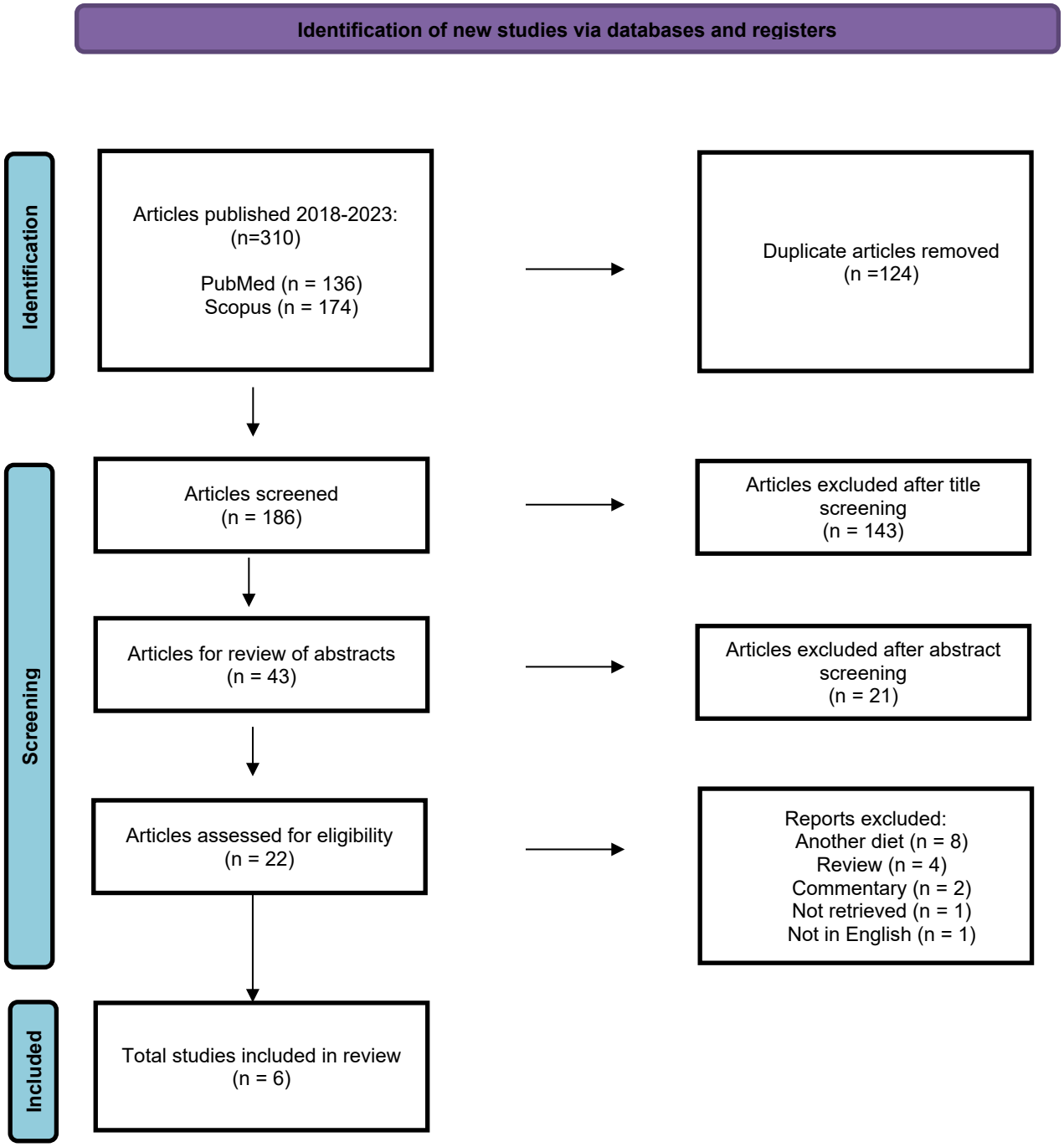

Figure 1. Reporting of data collection

Characteristics of included studies

In total, six studies met the criteria and were included in this review. Three of the studies focused on the effects of the IF 5:2 diet, while the other three investigated the effects of the TRF diet on patients with T2D. Five out of the six studies reported changes in HbA_{1C}, blood plasma glucose, BMI, and weight. One study not only reported changes in plasma glucose and weight but also investigated the effects on hepatic glycogen levels, insulin sensitivity, and mitochondrial activity. Another study focused more on the feasibility of TRF for individuals with T2D, while the other study specifically examined the risk of hypoglycaemia associated with the IF 5:2 diet. The studies varied in terms of their dietary interventions, duration (ranging from 3 weeks to 12 months, with a follow-up assessment at 24 months), the number of participants (ranging from 14 to 137), and participant characteristics. These characteristics included the age of participants (with mean ages in the included studies ranging from 48.8 to 61 years), duration of diabetes (mean durations ranging from 3.4 to 11 years), HbA_{1C} levels (with mean values ranging from 46.1 mmol/mol to 69.4 mmol/mol), and weight (with mean values ranging from 75 to 109 kg). A compilation of the articles is shown in table below.

Reference (year); country	Study design	No. and characteristics of participants (mean values)	Aim/purpose/question	Type of IF; control	Duration of intervention	Outcomes/results/main findings[1]
Carter et al. (2018); Australia (41)	Randomized noninferiority trial	N = 137 (77 M/60 W); age 61.0 y; duration of T2D 8.0 y; BMI 36.0 kg/m^2; weight 101 kg; HbA_{1C} 56.3 mmol/mol (7,3 %); FPG 8.5 mmol/l (153 mg/dl)	Compare the effects of IF versus CER on glycaemic control and weight loss in patients with T2D.	5:2; CER	12 months	↓ HbA_{1C} 3.3 mmol/mol (0.3 %) ↓ FPG 1.0 mmol/l (18.1 mg/dl) ↓ BMI 2.3 kg/m^2 ↓ weight 6.8 kg ↓ MES 0.6 Hypoglycaemic events first 2 weeks: 6 participants. Hyperglycaemic events first 2 weeks: 7 participants. Compliance 97% first 3 months, decreased to 44% at 12 months.
Corley et al. (2018); New Zealand (42)	Randomized, noncontrolled, parallel interventional trial	N = 37 (22M/15 W); age 60 y; duration of T2D 11 y; BMI 36.7 kg/m^2; weight 109 kg; HbA_{1C} 67 mmol/mol (8.3 %); FPG 8.6 mmol/l (155 mg/dl)	Risk for hypoglycaemia of 5:2 IF using consecutive vs non-consecutive fasting days.	5:2 → 2 consecutive and 2 non-consecutive days	12 weeks	Hypoglycaemic events 1.4 over 12 weeks. ↓ HbA_{1C} 6.5 mmol/mol (0.65 %) ↓ FPG 1.2 mmol/l (21.7 mg/dl) ↓ BMI 0.65 kg/m^2 ↓ weight 3.35 kg Improvement of quality of life.[2]
Carter et al. (2019) Australia (43)	Follow-up of a randomised noninferiority trial. Prospective analysis.	N = 137 (77 M/60 W); age 61.0 y; duration of T2D 8.0 y; BMI 36.0 kg/m^2; weight 101 kg; HbA_{1C} 56 mmol/mol (7,3 %); FPG 8.5 mmol/l (153 mg/dl)	24-month follow-up of previous trial, specifically change in HbA_{1C} and weight loss.	5:2; CER	Follow-up at 24 months	Maintained weight loss. ↑ HbA_{1C} 1,1 mmol/mol (0,1 %) from baseline.
Parr et al. (2020) Australia (44)	Observational intervention	N = 19 (9 M/10 W); age 50.2 y; duration of T2D 3.4 y; BMI 34.4 kg/m^2; weight 99.7 kg; HbA_{1C} 59 mmol/mol (7.6 %); FPG 8.4 mmol/l (151 mg/dl)	Feasibility of TRF for individuals with T2D	TRF 15:9 as many days as possible; no control	4 weeks	Compliance to 9 h TRE: 72 % of 28 days. ↓HbA_{1C} 2 mmol/mol (0.2 %) ↓ FPG 0.3 mmol/l (5 mg/dl) ↓ weight 0.8 kg

						↓ time window of energy consumption by 22 %
Che et al. (2021) China (45)	Randomised controlled trial	N = 120 (65 M/60 W); age 48.5 y; duration of T2D 5.0 y; BMI 26.3 kg/m^2; weight 75 kg; HbA_{1C} 69.4 mmol/mol (8.5 %); FPG 9.73 mmol/l (175.3 mg/dl)	Effects of TRF on glycaemic regulation and weight changes	TRF 14:10; normal diet	12 weeks	↓ HbA_{1C} 16.9 mmol/mol (1.54 %) ↓ FPG 1.47 mmol/l (26.5 mg/dl) ↓ BMI 1.64 kg/m^2 ↓ weight 2.98 kg ↓ MES 0.66 No hypoglycaemic events
Andriessen et al. (2022) Netherlands (46)	Randomised controlled trial	N = 14 (7 M/7 W); age 67.5 y; BMI 30.5 kg/m^2; weight 89 kg; HbA_{1C} 46.1 mmol/mol (6.4 %); FPG 7.9 mmol/l (142.3 mg/dl);	Effects of TRF on hepatic glycogen levels and insulin sensitivity	TRF 14:10 daily; food intake ≥ 14 hours	3 weeks	Hepatic glycogen and insulin sensitivity similar in both groups. FPG 7.6 vs 8.6 (TRF vs control) mmol/l ↓ weight 1.0 kg

Abbreviations: IF, intermittent fasting; N, number; M, men; W, women; T2D, type 2 diabetes; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1C}, glycated haemoglobin; FPG, fasting plasma glucose; 5:2, intermittent fasting with energy restriction 2 days per week; CER, continuous energy restriction; MES, medication effect score (calculated as (actual drug dose/maximum drug dose) x drug mean adjustment); Hypoglycaemia, blood glucose level < 4 mmol/l (72mg/dl); TRF, time restricted feeding; 15:9, fasting 15 hours and eating window 9 hours; 14:10, fasting 14 hours and eating window 10 hours

[1] The number and characteristics of participants (mean values) presented in the table apply to all individuals included in the studies. Results presented in the table as outcomes/results/main findings only describe the effects of the implied diet model on the intervention group and do not include information about the control group.

[2] The results are applicable to all participants from both parallel intervention groups.

Intermittent fasting 5:2 and type 2 diabetes

In this review three studies are described that investigate the effects of IF 5:2 on patients with T2D (41-43).

Carter et al. (41) conducted a 12-month clinical trial in which 137 adults with T2D (average age 61 years and diabetes duration of 8 years) were randomized to two diet groups. One group followed an IF 5:2 diet, consuming 500-600 kcal/day for two days every week, and eating ad libitum on the other days of the week. The second group followed a CER (continuous energy restriction) diet, consuming 1200-1500 kcal/day. Participants were closely monitored by a dietitian to ensure compliance with the prescribed diet. Initially, visits with the dietitian were scheduled every two weeks for the first three months, and subsequently, every two to three months for the remaining nine months of the trial. During these visits, blood glucose levels, weight, and diet checklists were assessed. Individual consultations with an endocrinologist were also provided, and a specialized medication management protocol was developed, which underwent modifications throughout the trial. Neither of the participant groups received food or meal replacements, but they were provided with written information about menus, a digital kitchen scale to measure food portions, and a waistband pedometer to monitor daily step count. Participants were instructed to test their fasting blood glucose levels daily and to perform additional tests on days when they practiced IF with limited calorie intake. They were also required to document their medication dosages on a daily basis. Outcome measures were obtained at baseline, three months, and twelve months to assess the effectiveness of the intervention. At the end of the trial, there was decrease in HbA_{1C} levels by around 3.3 mmol/mol (0.3 %), decrease in FPG (fasting plasma glucose) by around 1.0 mmol/l (18.1 mg/dl) and a weight loss of approximately 6.8 kg. Participants with a baseline HbA_{1C} level greater than 8% (63.9 mmol/mol) exhibited the most substantial mean change at 12 months, while participants with HbA_{1C} levels below 6% (42.1 mmol/mol) had minimal change. Notably, significant weight loss was observed within the first three months and was maintained at the 12 months. A small subgroup of participants demonstrated ongoing weight loss throughout the entire study duration, with an approximate weight reduction of 12.5 kg. Participants who fully attended all scheduled visits achieved a significantly greater weight loss compared to those who did not (-7.6 kg versus -4.0 kg). The medication protocol that was developed required the reduction or discontinuation of sulfonylureas and insulin due to their potential to cause hypoglycaemia. Medication adjustments predominantly occurred within the initial three months of the study, with minor modifications observed between three and twelve months. These adjustments were guided by monitoring HbA_{1C} and plasma glucose levels and were quantified as a medication effect score (MES). After undergoing the IF 5:2 diet for a duration of 12 months, there was an observed reduction in MES of approximately 0.6, which was found to be correlated with changes in weight. Furthermore,

participants were advised to promptly contact the study investigators if their blood glucose level dropped below 4 mmol/l (72 mg/dl). Within the initial two weeks, six participants encountered episodes of hypoglycaemia, while seven participants experienced a hyperglycaemic event. All participants who encountered hypoglycaemic events either reported experiencing such events prior to the commencement of the treatment or were uncertain about their occurrence. Compliance was reported to be 97% during the first 3 months but decreased to 44% at 12 months.

Carter et al. (43) continued with 24-month follow-up from baseline (12 months after the end of the trial), participants were not adhering to the diets at 24 months. However, most of them reported following some parts of the diets or principles from the diets. Although the average weight loss was maintained from baseline, the mean HbA_{1C} level increased by approximately 1.1 mmol/mol (0.1%) between 12 and 24 months above baseline. At the follow-up, among the 84 participants, the HbA_{1C} levels remained stable for four individuals (0.05%), increased for 57 participants (68%), and decreased for 22 participants (26%). At 24 months, medication use was still less than at baseline.

Corley et al. (42) conducted a 12-week clinical trial involving 37 adults with T2D (average age of 60 years and diabetes duration of 11 years). The participants were randomly assigned to two parallel interventional groups, both of which involved IF 5:2 as the intervention, which meant consuming 500-600 kcal/day for two days every week and eating ad libitum on the other days of the week. One group followed energy restriction for two consecutive days, while the other group followed energy restriction for two non-consecutive days. Participants were given written sample recipes by a dietitian and were informed about the symptoms and management of hypoglycaemia as well as its common causes. Clinic visits were scheduled at baseline, six weeks, and twelve weeks, during which food diaries were collected, and measurements were taken. Throughout the study, participants were regularly contacted on a weekly basis either through telephone or email communication. The primary objective of the research was to assess the risk of hypoglycaemia, which was defined as a capillary blood glucose level below 4 mmol/l, and to determine the frequency of hypoglycaemic events throughout intervention. Capillary glucose monitoring was maintained, and the doses of sulfonylureas and insulin were reduced either on fasting days or/and on the night before a fast depending on the type of medication. The dose of OHA (oral hypoglycaemic agents) that did not cause hypoglycaemia remained unchanged. Between the 6th and 12th week, continuous glucose monitoring was conducted to record and track the occurrences of hypoglycaemic episodes. While the participants were wearing the monitor, there were a total of seven hypoglycaemic events observed in both groups in five participants. Out of these events, two took place on fasting days, while the remaining five occurred on non-fasting days. In total, 53 hypoglycaemic events were observed during the 84 days of the study, affecting 15 participants. A majority of participants, 22

(59%), did not experience any hypoglycaemic events. During the fasting days, there were 23 hypoglycaemic events out of 851 fasting days, which is a crude rate of one event per 37 days of fasting. On non-fasting days, there were 30 hypoglycaemic events out of 2257 non-fasting days, which is a crude rate of one event per 75 participant-days of non-fasting. No instances of severe hypoglycaemic events were reported. Over the course of 12 weeks, further medication adjustments were deemed necessary in response to hypoglycaemia for nine out of 37 participants (24%). Out of these participants, seven had their medications modified in the first two weeks, one at three weeks, and one at five weeks. Due to hyperglycaemia, the general physician or diabetologist increased the medication dosage of five participants. Weight (↓ 3.35 kg), HbA_{1C} (↓ 6.5 mmol/mol (0.65 %)) and FPG (↓ 1.2 mmol/l (21.7 mg/dl)) were improved from baseline to 12 weeks. The participants also experienced small enhancements in their global quality of life, which were assessed using The Audit of Diabetes-Dependent Quality of Life 19 (ADDQoL) Questionnaire at both the beginning and the 12-week mark (47). The ADDQoL includes a comprehensive evaluation of overall quality of life, ranging from +3 (excellent) to -3 (extremely bad). It also measures the extent to which diabetes affects one's quality of life in general. During the study, participants' perception of the adverse effects of diabetes on their quality of life showed a slight increase. This could be attributed to the dietary restrictions, the need for regular testing, and the focus on body shape and weight due to calorie restriction during the study period.

Time restricted feeding and type 2 diabetes

In this review three studies are described that investigate the effects of TRF on patients with T2D (44-46).

Parr et al. (44) conducted a 4-week observational intervention involving 19 adults with T2D (average age of 50 years and diabetes duration of 3.4 years). None of the participants enrolled in the trial were currently using glucose-lowering medications such as sulphonylureas, insulin, or GLP-1 agonists that require injections. Participants monitored 2-weeks of habitual feeding to establish baseline food intake followed by 4-weeks of TRF intervention, which meant limiting eating to the time window between 10:00 and 19:00 on as many days of each week as possible. Participants were not given any guidance regarding the type of food, its quality, or portion sizes as part of the dietary advice. Participants were instructed to capture photographs during every instance of eating and maintain daily food diaries throughout both the habitual eating and TRF intervention phases. In addition, the participants were required to self-report their adherence to TRF intervention on a daily basis. Participants attended three visits before commencing the 4-week TRF intervention. These visits were conducted to collect blood samples, record dietary information, and conduct psychological and cognitive assessments. Following this, participants visited the laboratory once a week for four weeks (visits 4-6). During these visits, fasting blood samples were taken,

dietary information was recorded, and any potential medical issues were addressed. At the conclusion of the 4-week TRF period (visit 7), additional fasting physiological measurements were performed, and psychological and cognitive assessments were repeated. Finally, at visit 8, which occurred within 0-4 days after the end of the fourth week, a qualitative interview was conducted consisted of 13 open-ended questions. This interview aimed to gather insights into barriers, adherence, and attitudes by utilizing written notations and voice recordings. The main focus was to determine the feasibility of TRF for adults with T2D. Compliance to 9 hours TRF was 20 of 28 days (72 %), which is approximately 5 days/week. Compliance with the 9-hour TRF window resulted in a reduction in daily energy intake by lowering the consumption of carbohydrates and alcohol. Time window of energy consumption was decreased by 22% from 10 h 42 min to 8 h 20 min. Participants demonstrated a compliance rate of 90% in terms of providing either photos or self-reported timing for their meals and snacks. On the days when participants adhered to the time-restriction schedule of 09:45-19:15, there was a significant reduction in total energy intake. Changes in HbA_{1C} (↓ 2 mmol/mol (0.2 %)), plasma glucose (↓ 0.3 mmol/l (5 mg/dl)) and weight (↓ 0.8 kg) were not significant. The implementation of TRF did not have any negative or positive impact on psychological well-being. However, its effects on cognitive function were inconsistent and varied. The main obstacles reported by participants in adhering to the intervention were feelings of hunger, daily stressors, and emotional factors: *"You think 10 a.m. is a long time and then sometimes you didn't have enough the night before and didn't eat a lot and the next day you're like, 'I should've eaten more last night... I am hungry.", "There was always kind of a stress I have to do it in between this time.", "I think some of that accountability of thinking about what you're eating and having to report it all."*. Compared to that, the positive responses included: *"I wasn't hungry at night... I did have a couple of nights where I did feel hungry, but it started to dissipate, and I felt less hungry when I woke up.", "Well at first, I thought I was going to struggle with being hungry, then coming to the conclusion of it, yeah, I was a lot more satisfied and not as hungry and didn't feel like I needed to eat all the time.", "I guess the main thing for me was I could avoid late night snacking... I was always struggling to stop that, but I guess it [TRF] helped me a lot to stop it totally", "Other diets you need to make a choice of what you need to eat and counting everything you want to eat, but this one I just eat what I want to eat and how much. I didn't have to do all the counting."*

Che et al. (45) conducted a 12-week clinical trial in which 120 adults with T2D (average age of 48.5 years and diabetes duration of 5.0 years) were randomized to two diet groups. One group followed TRF diet, with the time eating window 8:00-18:00 and fasting between 18:00-8:00, for 12 weeks. The second group followed their normal diet. The management protocols for drug administration were formulated by endocrinologists. Each participant was provided with capillary blood glucose meters, and they were

instructed to measure their blood glucose levels daily during fasting and before going to bed. To assess adherence to the TRF diet, a daily log was employed, requiring each participant to document the starting and ending times of their caloric intake each day. Compliance with the TRF diet was evaluated based on the number of days per week that adhered to the designated feeding time window. Participants received guidance from a nutritionist on how to accurately estimate portion sizes and maintain meticulous food records to track their dietary intake. They were instructed to utilize household measurement tools to calculate the amount of food they consumed. Baseline and 12-week fasting blood analyses were performed for all participants. The purpose of the trial was to examine the impact of TRF on glycaemic regulation and weight changes in overweight individuals with T2D. Decreased levels of HbA_{1C} (↓16.8 mmol/mol (1.54 %) and plasma glucose (↓ 1.47 mmol/l (26.1 mg/dl)) were observed, as well as weight loss (↓ 2.98 kg) after 12 weeks of TRF. Another finding was changes in beta-cell function and insulin resistance. Reported decrease of MES was 0.66. No adverse events, such as headaches, thirst, or diarrhoea, were reported by participants in the TRF group. In the control group, there was one occurrence of a hypoglycaemic event, while no hypoglycaemic events were observed in the TRF group. TRF intervention resulted in a 9 % enhancement in the overall SF-12 score among participants in the experimental group. The SF-12 is a 12-item health questionnaire utilized to evaluate various aspects of health-related quality of life, encompassing physical health, mental health, and general health perceptions. The TRF intervention implemented in this study positively influenced participants' perception of physical function and daily activity. Moreover, a daily eating window of ten hours resulted in a reduction in caloric intake without the need for conscious calorie counting.

Andriessen et al. (46) conducted a 3-week clinical trial in which 14 adults with T2D (average age 67.5 years, diabetes duration not reported) were randomized to two diet groups. One group followed TRF diet, with the 10 h eating window during the daytime, with the last meal completed no later than 18:00 o'clock. The second group followed their normal diet spread over at least 14 h per day. The purpose of the trial was to investigate the effects of TRF on hepatic glycogen levels and insulin sensitivity in adults with T2D. Results showed that hepatic and peripheral insulin, as well as hepatic glycogen, were not affected by TRF. Secondary findings included decreased FPG and 24-hour glucose levels, as well as weight loss (↓ 1.0 kg).

Discussion

The purpose of this literature review was to examine the available knowledge regarding the effects of IF in adults diagnosed with T2D. The included studies demonstrated positive effects on glycaemic control in

the intervention groups. Depending on the specific trial, there was a decrease in HbA_{1C} levels ranging from 2 to 16.9 mmol/mol. Additionally, weight loss in the intervention groups varied between 0.8 to 6.8 kg. Hypoglycaemic events were lower than expected and primarily occurred at the beginning of the trials. In one trial, hypoglycaemic events were reported during the first twelve weeks of intervention, in another trial, these events were reported during the first two weeks while in the trial focusing on TRF intervention, no hypoglycaemic events were reported. One of the studies, conducted by Carter et al., spanned over a 12-month period, enabling a comprehensive assessment of the effects of IF 5:2 on T2D patients. This longer duration provides valuable insights into the long-term effects and sustainability of the intervention. The same researchers conducted a 24-month follow-up period, providing additional insights into the sustainability of the interventions and their effects on HbA_{1C} levels and medication use over an extended period. The rest of the studies included in the review had shorter follow-up periods. The feasibility of maintaining both IF 5:2 and TRF interventions was observed, indicating that it was possible to sustain them. The correlation between behavioural support and contact with medical professionals was found to improve compliance with the interventions. However, Carter et al., reports a decrease in compliance with the prescribed IF 5:2 diet over the 12-month duration of the study. This declining compliance may impact the interpretation of the results, as participants who did not fully adhere to the diet may have different outcomes compared to those who did. It also raises concerns about long-term adherence to the IF 5:2 dietary intervention. The 24-month follow-up of the same study suggests that the positive effects observed at 12 months may not be sustained in the long term. Further long-term follow-up studies would be valuable to assess the durability of the intervention's effects. It is important to note that these findings are specific to the studies mentioned and may not apply universally. The results suggest that both IF 5:2 and TRF can have positive effects on weight loss and glycaemic control in individuals with T2D, although long-term adherence may be a challenge.

The included studies specifically investigated two basic models of IF, namely IF 5:2 diet and TRF diet. This conscious decision was made considering the wide range of existing IF interventions available. IF 5:2 has been mentioned in diabeteshandboken.se (24), which is a problem-based reference book for patients and all healthcare professionals who interact with patients with diabetes. They comment on this particular method, suggesting that it may be suitable for certain individuals if they are willing to maintain this lifestyle over an extended period. IF has gained significant attention in recent years as a dietary approach with potential health benefits. However, it is important to acknowledge that IF is a heterogeneous concept, making it challenging to define precisely and draw general conclusions. The lack of a standardized definition and terminology poses a significant obstacle in conducting research and interpreting findings related to IF. The heterogeneity of IF is evident in the wide range of fasting

protocols employed in different studies. These protocols vary in terms of fasting duration, frequency, and pattern, making it difficult to compare and synthesize results across studies. For instance, some studies adopt ADF, while others utilize TRF or periodic fasting. As an example, *Yang et al.* (48) developed a novel dietary approach that consisted of five fasting days followed by ten-day period of gradually reintroducing regular food items. This issue needs to be addressed to facilitate a clearer understanding of IF and its effects on various health outcomes. The lack of consistency in IF protocols complicate the interpretation of findings and limits our ability to make comprehensive conclusions regarding its effects on health. In addition to the variability in protocols, the terminology associated with IF is also inconsistent. Terms such as TRF, intermittent energy restriction, and modified fasting are often used interchangeably, further contributing to the confusion surrounding IF. This inconsistency hinders effective communication and collaboration among researchers, as well as confusing the general public who are interested in adopting IF as a dietary approach. To overcome these challenges, it is crucial to establish standardized definitions and terminology for IF. Consensus among researchers, healthcare professionals, and relevant organizations is needed to develop a unified framework that can be widely accepted and applied. This framework should clearly define the parameters of fasting duration, frequency, and pattern, providing researchers with a common ground for conducting studies and comparing results. Moreover, establishing standardized terminology for different types of fasting regimens can help clarify the differences between various approaches. Consistent and precise terminology will improve communication and understanding among researchers, enabling better synthesis of findings and more accurate interpretation of results.

Among studies included in this scoping review, those focusing on the IF 5:2 diet demonstrated effects on HbA_{1C}, plasma glucose levels, weight reduction, and a decreased requirement for diabetes medication (41, 42). It raises the question of whether the changes in HbA_{1C}, plasma glucose and weight would be even more pronounced if the medication dosage remained unchanged. However, researchers aimed to prevent hypoglycaemic episodes that could potentially pose risks to patients, necessitating a reduction in medication dosage, particularly for its hypoglycaemic effects. Article found on SBU (Statens Beredning för Medicinsk och Social Utvärdering), addressing dietary approaches for diabetes (49), highlights the lack of systematic reporting on potential negative health effects of different diets in studies, with variations observed between studies. Most of the studies examined in this report did not extensively investigate serious adverse effects of the interventions, with the exception of studies specifically focusing on IF and carbohydrate counting (50). As mentioned in the studies conducted by *Carter et al.* (41, 43) and *Corley et al.* (42) the IF 5:2 approach demonstrated a clinically acceptable risk of hypoglycaemia, and it can be considered safe for patients who are not using glucose-lowering medications that are known to

increase the risk of hypoglycaemia. However, for patients who are taking sulfonylureas and/or insulin, regular monitoring is of utmost importance. In both studies, researchers developed a specialized medication protocol aimed at decreasing the occurrence of hypoglycaemic events and ensuring the safety of the participants. The trial conducted by *Che et al.* (45) which focused on TRF intervention, reported that no hypoglycaemic events were recorded during the TRF intervention. However, it is important to note that adjustments in diabetes medications were still made during the trial.

Notably, an article with case report showcased three patients with T2D who were able to discontinue insulin therapy, with two of them ceasing all diabetes medication while maintaining diabetes control. This achievement was accomplished through interventions such as the IF 4:3 diet or ADF diet, coupled with educational seminars, dietary adjustments, and medication modifications (51). Additionally, those patients were closely monitored every other week in the clinic until discontinuation of insulin therapy. The question arises as to whether such outcomes are feasible for a larger group of patients and other types of IF interventions. Another significant aspect to consider is the impact of monitoring and support. The literature acknowledges the advantages of behavioural support (52), particularly the support provided by a dietitian (53), along with the effects of lifestyle interventions. The trials discussed in this review indicate that participants who had increased contact with medical professionals, received behavioural support, and attended scheduled visits demonstrated improved outcomes in terms of glycaemic control and feasibility. *Carter et al.* (41) mentions 97 % compliance first 3 months while using IF 5:2 diet, with drop to 44 % at 12 months. Initially, visits with the dietitian were scheduled every two weeks for the first three months, and subsequently, every two to three months for the remaining nine months of the trial. The decrease in compliance observed in the participants could potentially be attributed to less frequent visits after three months, thereby highlighting the importance of ongoing behavioural support. Some suggestions have been made that due to the reduced burden of dietary restriction and its potential for achieving weight loss goals, the IF 5:2 method could serve as a valuable alternative to conventional continuous weight loss diets (34, 54, 55). Participants in *Carter at al.* (41) reported that it was easier to prevent weight gain and to follow the IF 5:2 intervention because it only involved 2 days of calory restriction compared to the continuous calorie restriction in the control group (CER).

Only the study by *Parr et al.* (44), investigating TRF diet strategy, strictly focused on feasibility. The effectiveness of TRF has been suggested as a straightforward and feasible behavioural approach that can decrease calorie consumption among individuals with obesity or metabolic syndrome (56, 57). Compliance to 9 hours TRF mentioned by *Parr et al.* (44) was 20 of 28 days (72 %), which is approximately 5 days/week. Gaining insights into people's experiences with adopting TRF is crucial. This involves receiving feedback on their ability to stick to the designated eating window, their overall

acceptance of this dietary approach, and the potential psychological impacts that arise from emphasizing meal timing. Furthermore, it is necessary to determine the optimal and realistic time frame for energy intake that promotes healthy eating habits and improves metabolic well-being. *Albosta et al.* (58) wrote a review of the literature and a guide for primary care physicians regarding the role of IF in the treatment of diabetes. The researchers reached the conclusion that although ADF and periodic fasting have shown effectiveness in enhancing metabolic risk factors, convincing individuals to completely forego or significantly limit calorie intake for a full 24-hour period might pose challenges. They further concluded that a more suitable approach would be to gradually introduce IF in the form of TRF. For instance, clinicians could initially recommend that patients limit their food intake to a 12-hour period each day, typically through an overnight fast (e.g., from 19:00 to 7:00). As patients become more accustomed to this eating pattern, the feeding window can be progressively reduced (e.g., a 16-hour fast followed by an 8-hour feeding period, or a 20-hour fast followed by a 4-hour feeding period). This approach provides patients with some flexibility in choosing when to consume calories on a daily basis, thereby increasing the likelihood of adherence. These specific recommendations are not officially endorsed by organizations such as the World Health Organization (WHO), Diabetes Federation, or Swedish guidelines. As patients may approach physicians with questions regarding IF it is important for healthcare professionals to be knowledgeable about the aspects of this dietary approach.

Strengths and Weaknesses

STRENGTHS

The scoping review includes three studies investigating the effects of IF 5:2 and three studies investigating TRF on patients with T2D. The inclusion of multiple studies enhances the reliability and generalizability of the findings. However, a larger pool of studies would provide more robust evidence and allow for stronger conclusions.

The review provides detailed descriptions of each study, including information about the study design, participant characteristics, intervention protocols, and outcome measures. This level of detail helps the reader understand the methodology and results of each study.

Various outcome measures were assessed in the studies, such as changes in HbA_{1C} levels, FPG, weight loss, medication adjustments, and hypoglycaemic events. These measures provide valuable information on the effectiveness and safety of IF 5:2 and TRF in managing T2D and suggest that IF 5:2 and TRF may have beneficial effects on glycaemic control and weight management in individuals with T2D.

The review also provides information on participant adherence and compliance with the prescribed diets, which helps evaluate the feasibility and practicality of implementing IF 5:2 and TRF in patients with T2D.

WEAKNESSES

The scoping review includes studies with different intervention protocols, such as variations in calorie intake, fasting days, and feeding time windows. This heterogeneity makes it challenging to draw definitive conclusions about the specific effects of IF 5:2 and TRF and difficult to compare and generalize the findings.

The limited sample size in the included studies, ranging from 14 to 137 participants, may be relatively small for drawing definitive conclusions. A larger sample size would enhance the statistical power and generalizability of the findings.

More long-term data would provide a better understanding of the sustained effects and potential relapse of the interventions over time.

The duration of the included studies, ranging between three weeks to twelve months, makes it challenging to directly compare the results and consistently assess the long-term effects of the interventions.

This scoping review has several strengths, including the inclusion of multiple studies, a long-duration study, and detailed monitoring. It provides valuable insights into the effects of IF 5:2 and TRF on patients with T2D. However, it also has some weaknesses that should be acknowledged. These weaknesses include limited sample size, and limited long-term follow-up. The limited number of studies, heterogeneity of interventions, varying durations, and other weaknesses should be taken into account when interpreting the findings. Therefore, further research with larger sample sizes and longer follow-up periods is needed to strengthen the evidence base in this area.

Suggestions for future research

Future research in the field of IF and its effects on adults with T2D could focus on several key areas.

Firstly, conducting larger-scale studies with a diverse range of participants would strengthen the evidence base for IF in managing T2D. By including a larger sample size, studies would have increased statistical power and greater generalizability of findings. Additionally, assessing the effects of IF on different populations within the T2D spectrum would help understand its impact across various subgroups.

Long-term follow-up studies are crucial to evaluate the sustained effects and potential relapse of IF interventions over time. Extending the duration of follow-up periods would provide insights into the long-term feasibility and adherence to IF as a dietary strategy for individuals with T2D. This information is vital in determining the practicality and effectiveness of IF in the real world.
Comparative studies that directly compare different IF protocols, such as IF 5:2, IF 4:3, TRF, and ADF, would shed light on the relative effectiveness and feasibility of each approach in managing T2D. Comparisons with other dietary interventions, would further contribute to understanding the superiority of IF in terms of glycaemic control, weight loss, and long-term adherence.
Establishing standardized protocols and definitions for different types of IF interventions, including fasting duration, frequency, and pattern, is necessary for better comparability across studies. Consensus among researchers, healthcare professionals, and relevant organizations would facilitate effective communication and collaboration, ultimately advancing our understanding of IF.
Furthermore, it is important to investigate the potential adverse effects and safety considerations of IF interventions, particularly in individuals with T2D. Systematic research in this area would identify any risks associated with IF and guide the development of appropriate monitoring and safety protocols. Behavioral support, contact with medical professionals, and educational interventions are key factors to consider alongside IF. Studying their impact on compliance, sustainability, and long-term outcomes would provide insights into effective strategies to support individuals in adhering to IF protocols, thus enhancing the success of the intervention.

By addressing these suggestions for future research, we can further enhance our knowledge and understanding of the effects, safety, and feasibility of IF in managing T2D. This, in turn, will influence clinical recommendations and improve patient care in the field of T2D management.

Conclusion

IF, especially TRF, has the potential to serve as an effective alternative dietary strategy for weight loss, enhancing glycaemic control, and improving psychological well-being in patients with T2D.

IF diet may be superior to other types of diets such as CER. IF diet is considered safe for individuals with T2D who control their diabetes through diet alone or take medications that do not increase the risk of hypoglycaemia. However, for individuals taking medications such as sulfonylureas and/or insulin, medication adjustments and regular monitoring, particularly during the initial stages, are necessary when following an IF diet, otherwise increased number of hypoglycaemic incidents may occur.

It is important to determine the most suitable and feasible time frame for energy consumption in order to promote healthy dietary habits and better metabolic health.

The heterogeneity and lack of standardized definitions and terminology associated with IF present significant challenges in drawing general conclusions and making comprehensive assessments of its effects on health to advance the field and facilitate meaningful research, it is essential to establish a consensus on the definition and terminology of IF. This will enable researchers to design more rigorous studies, improve comparability across studies, and enhance our understanding of the potential benefits and risks associated with different fasting protocols.

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