Less is more: effectiveness and feasibility of a fasting-mimicking diet programme in persons with type 2 diabetes in primary care

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PART I

BACKGROUND AND CONTEXT

Chapter 2

Metabolic impact of intermittent energy restriction and periodic fasting in patients with type 2 diabetes: a systematic review

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Nutrition Reviews. 2023;81(10):1329-1350

Abstract

Context

The effectiveness of intermittent energy restriction (IER) and periodic fasting (PF) in the management of type 2 diabetes (T2D) remains a subject of discussion.

Objective

The aim of this systematic review is to summarize current knowledge of the effects of IER and PF in patients with T2D on markers of metabolic control and the need for glucose-lowering medication.

Data Sources

PubMed, Embase, Emcare, Web of Science, Cochrane Library, CENTRAL, Academic Search Premier, Science Direct, Google Scholar, Wiley Online Library, and LWW Health Library were searched for eligible articles on March 20, 2018 (last update performed November 11, 2022). Studies that evaluated the effects of IER or PF diets in adult patients with T2D were included.

Data Extraction

This systematic review is reported according to PRISMA guidelines. Risk of bias was assessed through the Cochrane risk of bias tool. The search identified 692 unique records. Thirteen original studies were included.

Data Analysis

A qualitative synthesis of the results was constructed because the studies differed widely in terms of dietary interventions, study design, and study duration. Glycated hemoglobin (HbA_{1c}) declined in response to IER or PF in 5 of 10 studies, and fasting glucose declined in 5 of 7 studies. In 4 studies, the dosage of glucose-lowering medication could be reduced during IER or PF. Two studies evaluated long-term effects (≥1 year after ending the intervention). The benefits to HbA_{1c} or fasting glucose were generally not sustained over the long term. There are a limited number of studies on IER and PF interventions in patients with T2D. Most were judged to have at least some risk of bias.

Conclusion

The results of this systematic review suggest that IER and PF can improve glucose regulation in patients with T2D, at least in the short term. Moreover, these diets may allow for dosage reduction of glucose-lowering medication.

Systematic Review Registration

PROSPERO registration no. CRD42018104627.

Introduction

Reduced physical activity and adverse dietary habits have led to an increased prevalence of type 2 diabetes (T2D) in recent decades(1). The available pharmacological treatments for T2D do improve glucose metabolism, but they do not address the root cause of the disease, whereas appropriate lifestyle adaptation prevents cellular damage, ameliorates chronic inflammation, and potentially normalizes glucose tolerance(1-3). Remission of T2D, defined as normal plasma glucose levels without T2D medication, can be achieved by following a very low-energy diet for several weeks(4, 5). In various experiments, the amount of weight lost is related to the percentage of patients who achieve remission of their T2D(6, 7). However, not everyone can adhere to a very low-energy dietary regimen for several weeks, and weight maintenance after calorie restriction is difficult for many(8). The challenge is to find a diet that best suits the individual patient and can be adhered to over the long term(9, 10).

Intermittent energy restriction (IER) and periodic fasting (PF) have gained popularity as alternatives to continuous energy restriction (CER). Intermittent energy restriction refers to eating patterns in which individuals go through short time periods of restricted food intake, alternated with periods of unrestricted food intake. Periodic fasting refers to time periods of restricted food intake lasting 3 days or more(11). Since water-only fasting is difficult to sustain, diverse dietary regimens have been developed that mimic the effects of fasting while not requiring complete abstinence of eating for extended periods of time(11-14).

Beneficial effects of IER and PF on health parameters have been observed in animal models and in human studies. For example, IER can lower glucose and insulin levels in overweight animals, suggesting that it could be beneficial in the prevention of T2D(15-17). Furthermore, PF restores both insulin secretion and glucose homeostasis in mouse models of T2D(18, 19). In a qualitative study, women who followed an IER diet of 2 days per week for 4 months could better adhere to the IER diet than to previously attempted CER diets(20). Thus, IER and PF could be interesting alternative dietary options in the treatment of T2D.

Recent reviews showed that the effects of IER and CER on the reduction of body weight and fat mass were similar in humans(21, 22). Even though these reviews also included trials with patients with T2D, their primary outcome measure was weight loss. Specific outcomes for T2D, such as glycated hemoglobin (HbA_{1c}) levels and glucose-lowering medication use, were not systematically assessed. Currently, there is no overview of all reported IER and PF trials in patients with T2D that focuses on markers of metabolic control and the use of glucose-lowering medication. Therefore, a systematic review

of the effects of IER and PF in patients with T2D was conducted to evaluate whether IER and PF can improve markers of metabolic control, thereby allowing the use of glucose-lowering medication to be reduced. Parameters such as anthropometric measurements, quality of life, treatment satisfaction, and the feasibility of IER and PF interventions in clinical practice were also assessed as secondary endpoints.

Methods

The protocol for this systematic review was registered in the PROSPERO database on August 8, 2018, as CRD42018104627 (23). The review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (see **Appendix S1** in the Supporting Information online) (24, 25), and the PICO (Population, Intervention, Comparison, Outcomes) criteria were used for the search strategy (**Table 1**).

Parameter	Criterion
Population	Adult patients with type 2 diabetes
Intervention	Intermittent energy-restriction diets or periodic fasting diets
Comparison	Usual care, another dietary intervention, or no control group
Outcome	Primary outcome measures • Changes from baseline of HbA_{1c}, plasma glucose concentration, triglyceride concentration, HDL-C concentration, LDL-C concentration, total cholesterol concentration, glucose-lowering medication dosage Secondary outcome measures • Changes from baseline of body weight, BMI, waist circumference, body fat percentage, blood pressure, quality of life, and treatment satisfaction • Dropout rate

Table 1. PICO criteria for inclusion of studies.

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Eligibility criteria

Randomized controlled trials, nonrandomized trials, cohort studies, and observational studies were included when they evaluated the effects of IER or PF diets (as defined in **Table 2**) in adult patients with T2D recruited from any context. Studies that combined IER or PF with other interventions, studies comparing the intervention to usual care or another dietary intervention, and studies without a control group were eligible for inclusion.

Type of diet	Definition
Intermittent energy restriction	
Time-restricted eating	Restriction of energy intake during specific time periods of the day, typically between 12 and 16 hours each day
5:2 diet	Restriction of energy intake for 2 days per week
Alternate-day (modified) fasting	No food intake or restriction of energy intake on a fasting day, alternating with days of unrestricted food intake
Periodic fasting	
Periodic (modified) fasting	No food intake or restriction of energy intake during time periods of 3 days or more

Table 2. Different forms of intermittent energy restriction and periodic fasting.

Studies that analyzed the effects of IER or PF for reasons other than health improvement, eg, religious fasting, were excluded. Reviews and case reports were also excluded.

Literature search

The following electronic databases were searched for published articles on March 20, 2018: PubMed, Embase, Emcare, Web of Science, Cochrane Library, CENTRAL, Academic Search Premier, ScienceDirect, Google Scholar, Wiley Online Library, and LWW Health Library. The searches were re-run for additional eligible studies on November 7, 2019, July 14, 2021, and November 11, 2022.

Searches included the terms “diabetes mellitus, type 2” combined with “intermittent energy restriction,” “intermittent fasting,” “alternate day fasting,” “periodic fasting,” “time restricted feeding,” or variations of these terms (see **Appendix S2** in the Supporting Information online for the complete search strategy). No restrictions on language or publication date were applied. Reference lists and citations of included studies and relevant reviews were screened for additional relevant studies.

Study selection

After removal of duplicates, the search results were uploaded into Covidence software (26). Two reviewers (E.L.B. and D.E.H.; updates by E.L.B. and P.G.P.) independently screened titles and abstracts on the basis of inclusion and exclusion criteria. The full-text articles were then assessed independently by E.L.B. and D.E.H. (updates by E.L.B. and P.G.P.) to confirm eligibility. A third review member (H.P.) was available for discussion in case of inconsistencies.

Risk-of-bias assessment

Two review authors (E.L.B. and D.E.H.; updates by E.L.B. and P.G.P.) independently assessed the risk of bias in included studies. Disagreements were resolved by discussion with a third review author (H.P.), if necessary. The Cochrane Collaboration's tool for assessing risk of bias was used(27).

Data extraction

Study details and outcome data were extracted by two authors (E.L.B. and D.H.; updates by E.L.B. and M.P.S.) independently by using a standardized data form. Any discrepancies were solved by discussion. A third review member (H.P.) was available for discussion in case of continuing discrepancies.

The prespecified primary outcome measures were the changes from baseline of each of the following markers of metabolic control (in fasting condition, if applicable): HbA_{1c} level, plasma glucose concentration, triglyceride concentration, high-density lipoprotein-C (HDL-C) concentration, low-density lipoprotein cholesterol (LDL-C) concentration, and total cholesterol concentration. Another primary outcome measure was the change from baseline of the dosage of glucose-lowering medication.

The secondary outcome measures were changes from baseline in body weight, body mass index (BMI), waist circumference, body fat percentage, blood pressure, quality of life, and treatment satisfaction. The dropout rate was also a secondary outcome measure.

Results

Search results

The searches across the databases identified 885 records (**Figure 1**)(25). After the removal of duplicates, titles and abstracts of 692 unique records were examined, of which 661 were excluded. Two additional records were found by screening the reference lists of included studies. Of the 33 full-text articles assessed for eligibility, 19 were excluded (28-46). The most common reasons for exclusion were an intervention that was not a form of IER or PF and a study design that did not meet the inclusion criteria. In total, 14 articles met the selection criteria(47-60). One article (52) reported 2-year follow-up data of another included study(51). So, in total, 13 original studies were included in this review.

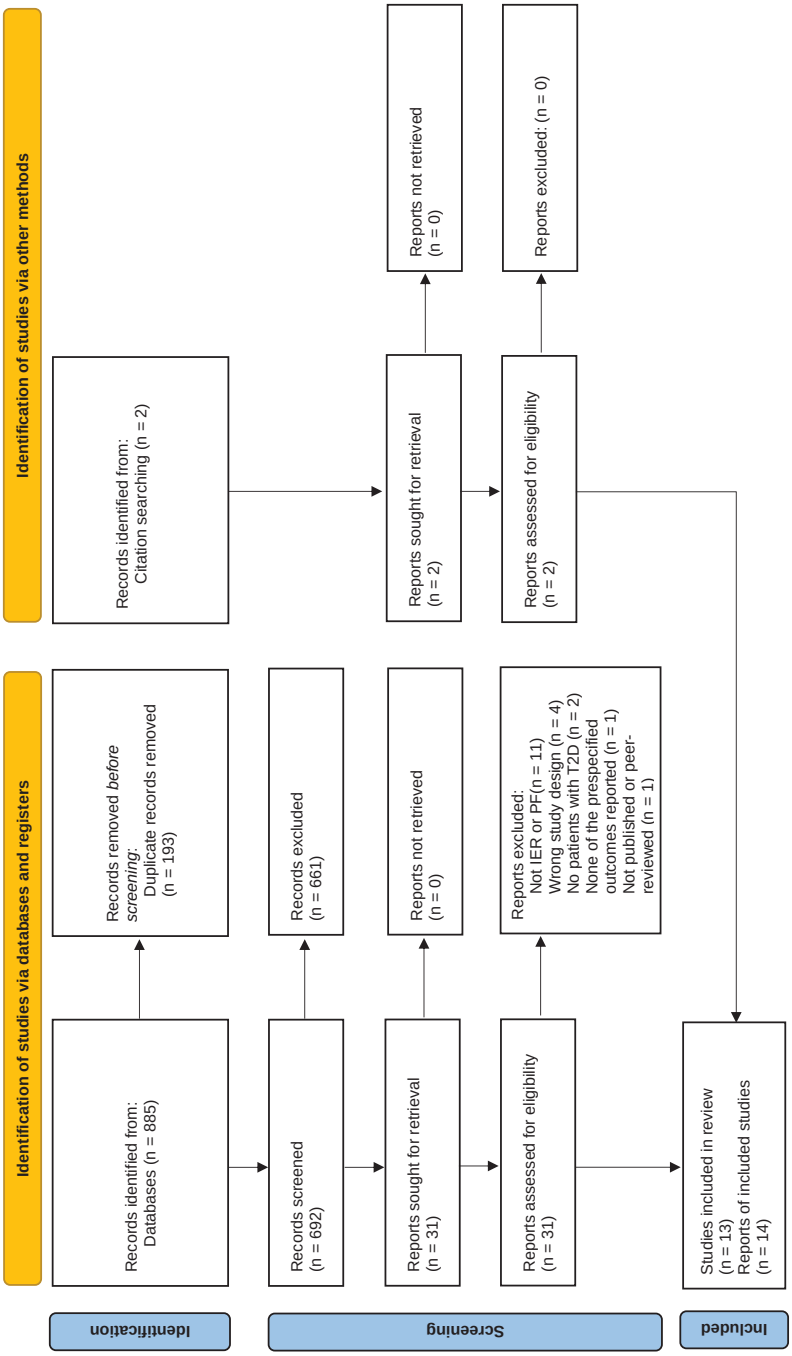

Figure 1. Flow diagram of the literature search process.

Abbreviations: IER, intermittent energy restriction; PF, periodic fasting; T2D, type 2 diabetes.

Study characteristics

The 13 studies evaluating the impact of IER and PF in T2D patients included in this systematic review (**Table 3**)(47-60) included a total of 817 patients. The size of patient populations ranged from 10 to 137 patients. Most studies had a rather small sample size, examining some 50 to 60 patients or fewer. Only 3 studies had a larger sample size, with 100 patients(59), 120 patients(53), or 137 patients(51, 52). Six of the included studies were feasibility studies and not powered to evaluate the primary outcome measures of this review(49, 50, 54, 56-58). The mean age of participants of all included studies was 55.6 years. At baseline, the mean BMI ranged from 26.3 to 37.9 kg/m^2 and the mean HbA_{1c} level from 7.2% to 8.5%. Seven of the included studies excluded patients who were treated with insulin(47-49, 55, 57, 59, 60).

Various forms of IER were studied. Five studies examined the effects of time-restricted eating (TRE)(47, 49, 53, 55, 57), of which one combined TRE with another specified diet(55). Four studies used a form of the 5:2 diet(50, 51, 54, 56), and one study examined the effects of alternate-day modified fasting (ADMF)(60). There were 3 studies of periodic modified fasting(48, 58, 59), of which 2 involved the use of a specific fasting-mimicking diet (FMD)(58, 59).

Different control interventions were compared with IER or PF. Eight studies were randomized controlled trials in which an IER method was compared with a non-IER method(48, 50, 51, 55, 56, 58-60). One study compared 2 similar IER interventions, which were scheduled either on 2 consecutive or on 2 non-consecutive days(54). One study was a randomized controlled trial in which TRE was compared with a control group that maintained their usual eating hours(53). Three studies were single-arm intervention studies(47, 49, 57).

Distinct additional interventions, like counselling by a dietitian(48, 51, 56, 60), exercise prescription(53, 56), and providing of some or all meals(48, 55, 58-60), also contributed to the wide heterogeneity among the studies. Seven trials used a specific protocol for diabetes medication alterations prior to start of the intervention in order to prevent hypoglycemia(50, 51, 54, 56, 58-60).

The intervention period varied from 2 weeks to 12 months. Only 3 studies had a duration of 6 months or more(51, 56, 58), and 2 studies reported additional long-term follow-up data collected 1 year or more after the intervention period (48, 52).

Four studies were performed in Australia(48, 50-52, 57), 2 in China(53, 59), 1 in the Czech Republic(55), 1 in Canada(47), 1 in New Zealand(54), 1 in Germany(58), 1 in India(49), 1 in Thailand(60), and 1 in the United Kingdom(56).

To summarize, 10 studies of IER interventions and 3 studies of PF interventions were included in this systematic review. Nine were randomized controlled trials that compared IER or PF with another dietary intervention or usual care, and 4 had other study designs. There was wide heterogeneity among the included studies, mainly in terms of dietary composition, other dietary interventions during nonfasting periods, additional interventions, different medication protocols, and study duration. Studies of IER interventions were categorized into 3 different subcategories, namely TRE (restriction of energy intake to delimited time periods of the day), the 5:2 diet (restriction of energy intake for 2 days a week), and ADMF (energy restriction on a fasting day, alternated with days of unrestricted food intake) (**Table 2**). Periodic fasting, which involves the restriction of energy intake over time periods that last 3 days or more, was considered a separate category.

Risk-of-bias assessment

Twelve of the included studies were judged to have a high risk of bias in at least one domain(47-50, 53-60), and the remaining study had an unclear risk of bias in two domains (**Figure 2** and **Appendix S3** in the Supporting Information online)(51, 52). "Incomplete outcome data" was one of the important domains in which studies scored a high risk of bias (n = 5) or an unclear risk of bias (n = 3). Often, it was unclear why data were missing. The domain "other bias" in the Cochrane risk of bias tool was often judged to have a high risk of bias (n = 8) due to additional interventions or study visits in the intervention groups(47, 55) or to a change in medication protocol during the trial(50, 54). Even though changes in medication protocols can be necessary for the safety of participants, they might influence the results, and not all studies clarified why and how changes were made. Furthermore, 2 of the included studies were single-arm studies(47, 57). Since all studies investigated a dietary intervention, blinding of participants and personnel was often not possible. Blinding of outcome assessment was not reported in most papers.

Outcomes

Quantitative synthesis

Because of the heterogeneity of study designs, dietary interventions, and study duration, it was not possible to perform a meta-analysis. Therefore, a qualitative synthesis of the results was performed.

Main results

This systematic review suggests that both primary and secondary outcome measures may improve in response to IER or PF (**Table 4**)(47-51, 53-60). However, the effects (for primary outcomes in particular) tend to be small and variable. The data will be discussed separately per method of energy restriction.

Reference; country	Study design	Inclusion criteria (I) and exclusion (E) criteria	No. and characteristics of participants (mean values)
Time-restricted eating studies			
Arnason et al (2017)(47); Canada	Observational intervention	**I:** T2D; age 18–65 y **E:** Ischemic heart disease or heart failure; chronic inflammatory diseases; chronic infections; moderate to severe renal disease (GFR < 45); uncontrolled hypertension and hypoglycemic unawareness; use of insulin or glyburide	N = 10 (1 man/9 women); age 53.8 y; duration of T2D NR; BMI 36.9 kg/m^2; HbA_{1c} NR
Bhandari et al (2022)(49); India	Observational intervention	**I:** T2D, not controlled with metformin alone **E:** Patients on insulin and sulfonylureas; ischemic heart disease; uncontrolled hypertension; diabetic complications	N = 12 (men/women NR); age NR; duration of T2D NR; BMI 37.9 kg/m^2; HbA_{1c} NR
Che et al (2021) (53); China	Randomized crossover trial	**I:** T2D; BMI ≥ 25 kg/m^2; age 18–70 y; stable weight for 3 mo prior to beginning of study (gain or loss < 2 kg); ability to complete study independently **E:** Previous weight loss surgery; pregnancy or intent to become pregnant; moderate or severe chronic hepatorenal disease or cardio-cerebrovascular disease; current acute complications of diabetes, such as diabetic ketosis, hyperglycemia, or hypertonicity; in past 3 mo, stress diseases such as surgery, trauma, and cardiovascular and cerebrovascular events; and mental disorders requiring antipsychotic drugs	N = 120 (65 men/55 women); age 48.5 y; duration of T2D 5.0 y; BMI 26.3 kg/m^2; HbA_{1c} 8.5%
Kahleova et al (2014)(55); Czech Republic	Randomized crossover trial	**I:** T2D (disease duration > 1y); use of oral hypoglycemic agents; age 30–70 y; BMI 27–50 kg/m^2; HbA_{1c} 6%–11.8% **E:** Alcohol or drug abuse; pregnancy or lactation; changes in medication or weight in last 3 mo; T1D; cardiostimulant use	N = 54 (29 men/25 women); age 59.4 y; duration of T2D 8.1 y; BMI 32.6 kg/m^2; HbA_{1c} 7.2%

Dietary intervention of interest	Length of intervention (L), follow-up (FU), dietary intervention (IG[a]), control group (CG[a]), change in medication (CM), additional interventions (AI)
TRE	**L:** 2-wk intervention phase **FU:** At 2 wk, additional visit after 2 wk **IG:** IER group with fasting goal of 18–20 h per day, with ad libitum zero-calorie coffee, tea, and water permitted during fasting hours. No caloric restriction. Macronutrients had to include at least 1/3 plate of protein **CG:** None **CM:** None upon start of intervention **AI:** None
TRE	**L:** 4-wk intervention phase **FU:** At 4 wk **IG:** IER group with fasting goal of 16 h per day, with ad libitum water, zero-calorie coffee, and tea permitted. No information on caloric restriction or composition of macronutrients **CG:** None **CM:** NR **AI:** NR
TRE	**L:** 12-wk intervention period **FU:** At 12 wk, no additional follow-up **IG:** IER group with fasting goal of 14 h per day. No caloric restriction or information on macronutrients. Water or tea without any calories allowed in fasting period **CG:** Asked to maintain their normal diet throughout the trial **CM:** None upon start of medication. Drug management protocol available during the trial **AI:** Participants were asked to maintain physical activity levels throughout the trial. Participants in IER group were asked to exercise outside of the fasting window. Steps were measured with a pedometer
TRE	**L:** 12-wk intervention period, followed by a 12-wk crossover period **FU:** At 12 wk and 24 wk **IG:** IER group (B2) contained 2 meals (breakfast & lunch), eaten between 6 am & 4 pm (14 h of fasting). Reduce energy by 2092 kJ/d (500 kcal/d), based on measurement of each individual's resting energy expenditure. Macronutrient distribution: 50%–55% carbohydrates, 20%–25% protein, < 30% from fat, with 30–40 g/d of fiber **CG:** Another dietary intervention group: Regimen of 3 main meals and 3 smaller snacks in between (A6). Reduce energy by 2092 kJ/d (500 kcal/d), based on measurement of each individual's resting energy expenditure. Macronutrient distribution: 50%–55% carbohydrates, 20%–25% protein, < 30% from fat, with 30–40 g/d of fiber **CM:** None upon start of intervention **AI:** All meals during entire study were provided for half of the participants, while the other half prepared their own meals

Reference; country	Study design	Inclusion criteria (I) and exclusion (E) criteria	No. and characteristics of participants (mean values)
Parr et al (2020) (57); Australia	Observational intervention	**I:** T2D; HbA_{1c} 6.5%–9%; diet controlled or taking no more than 2 oral hypoglycemic agents; currently consuming food (ie, dietary intake) over a period of 12 h or more habitually **E:** Use of sulfonyureas, insulin, GLP-1 agonists; not a regular breakfast consumer; unable to operate the camera function on a smart phone; strict diet (ie, vegan, celiac, gluten-free, ketogenic); had participated in regular fasting (defined as fasting ≤ 16 h/d or having completed 12 24-h fasts within past year); participating in shift work; not weight stable (> 5 kg change over last 3 mo); on prescribed medications required to be taken with food in early morning or late evening or taking other prescribed medications for < 3 mo; current smoker (tobacco, nicotine, or marijuana) or within 3 mo of quitting; pregnancy; breastfeeding; history of psychotic disorder, current diagnosis of other major psychiatric illness; psychopharmacological treatment that has not been stable for more than 3 mo; taking medications known to promote weight gain, weight loss, or interact with glucose metabolism (ie, corticosteroids); diagnosed GI conditions; surgery; impaired nutrient absorption; or antibiotic use in previous 3 mo	N = 19 (9 men/10 women); age 50.2 y; duration of T2D 3.4 y; BMI 34.4 kg/m^2; HbA_{1c} 7.6%
5:2 diet studies			
Carter et al (2016) (50); Australia	Randomized controlled trial (pilot trial)	**I:** T2D, age > 18; BMI ≥ 27. **E:** BP > 160/100 mmHg; previous weight loss surgery	N = 63 (30 men/33 women); age 61.5 y; duration of T2D 8.8 y; BMI 35.2 kg/m^2; HbA_{1c} 7.4%
Carter et al (2018 & 2019)(51, 52); Australia	Randomized noninferiority trial	**I:** T2D, age ≥ 18 y; BMI ≥ 27 kg/m^2 **E:** Pregnancy; breastfeeding; BP > 160/100 mmHg; no previous bariatric surgery	N = 137 (77 men/60 women); age 61.0 y; duration of T2D 8.0 y; BMI 36.0 kg/m^2; HbA_{1c} 7.3%
Corley et al (2018) (54); New Zealand	Randomized noncontrolled, parallel interventional trial	**I:** T2D; age > 18 y; any medication for T2D; HbA_{1c} 6.7%–10.0%; BMI 30–45 kg/m^2 **E:** T1D; weight change of > 5 kg in preceding 3 mo; eating disorder; pregnancy; BP > 180/100 mmHg; previous bariatric surgery; other significant medical conditions	N = 37 (22 men/15 women); age 59.9 y; duration of T2D 11.1 y; BMI 36.7 kg/m^2; HbA_{1c} 8.3%

Dietary intervention of interest	Length of intervention (L), follow-up (FU), dietary intervention (IG[a]), control group (CG[a]), change in medication (CM), additional interventions (AI)
TRE	**L:** 2-wk habitual period, followed by 4-wk intervention period **FU:** After 4-wk intervention period (compared with after 2-wk habitual period) **IG:** TRF group instructed to limit all eating occasions to between 10:00 am and 7:00 pm on as many days each week as possible. No instructions given about macronutrient distribution **CG:** None **CM:** None upon start of intervention **AI:** Participants were requested to take photos at every meal and complete daily food diaries
5:2 diet	**L:** 12-wk intervention period **FU:** At 12-wk, no additional follow-up **IG:** IER group with an energy restriction of 1670–2500 kJ/d (400–600 kcal/d) for 2 d each week, remaining 5 d habitual eating. No food or meal replacement was provided **CG:** Another dietary intervention group: CER diet of (1200–1500 kcal/d). Macronutrient distribution: 30% protein, 45% carbohydrates, 25% fat. No food or meal replacement provided **CM:** Medication management at start of intervention according to protocol; discontinuation/ reduction of sulfonylurea medication and/or insulin according to HbA_{1c}. Metformin unchanged **AI:** None
5:2 diet	**L:** 12-mo intervention period **FU:** At 12 mo, additional visit at 24 mo [Carter et al (2019)[52]] **IG:** IER group with energy restriction of 2090–2500 kJ/d (500–600 kcal/d) for 2 d each week, remaining 5 d habitual eating. Minimum of 50 g of protein per day. No food or meal replacement provided **CG:** Another dietary intervention group: CER diet of 5000–6280 kJ/d (1200–1500 kcal/d). Macronutrient distribution: 30% protein, 45% carbohydrates, 25% fat. No food or meal replacement provided **CM:** Medication management at start of intervention according to protocol; discontinuation/ reduction of sulfonylurea medication and/or insulin according to HbA_{1c} and intervention. Metformin unchanged **AI:** Meetings once every 2 wk, with a dietitian in the first 3 mo in both IG and CG
5:2 diet	**L:** 12-wk intervention period **FU:** At 12 wk, no additional follow-up **IG:** IER intervention (CF group) with an energy restriction of 2092–2510 kJ per day (500–600 kcal/d) for 2 consecutive days, remaining 5 d habitual eating. Composition of macronutrients not described **CG:** Also an IER intervention (NCF group) with energy restriction of 2092–2510 kJ per day (500–600 kcal/d) for 2 nonconsecutive days, remaining 5 d habitual eating. Composition of macronutrients not described **CM:** Medication management at start of intervention: reduction of sulfonylureas and insulin according to protocol. Metformin unchanged **AI:** None

Reference; country	Study design	Inclusion criteria (I) and exclusion (E) criteria	No. and characteristics of participants (mean values)
McDiarmid et al (2021)(56); United Kingdom	Randomized controlled trial	**I:** Overweight/obesity and T2D diagnosed during last 8 y, including those on insulin **E:** HbA_{1c} ≥ 108 mmol/mol; current diagnosed eating disorder; previous bariatric surgery; severe anxiety or depression	N = 79 (42 men/37 women); age 55.5 y; duration of T2D, n = 55 < 4 y and n = 34 4–8 y; BMI 36.4 kg/m^2; HbA_{1c} 7.8%
Alternate-day (modified) fasting studies			
Umphonsathien et al (2022)(60); Thailand	Randomized controlled trial	**I:** Age 30–60 y; T2D diagnosis within previous 10 y; BMI ≥ 23 kg/m^2; HbA_{1c} 6.5%–10% **E:** Fasting C-peptide level < 1 ng/mL; previous use of insulin; previous treatment with a thiazolidinedione or a GLP-1 receptor agonist in past 3 mo; serum creatinine > 1.5 mg/dL; serum ALT > 2.5-fold above upper limit	N = 40 (11 men/29 women); age 49.6 y; duration of T2D 4.6 y; BMI 30.0 kg/m^2; HbA_{1c} 7.4%
Periodic (modified) fasting studies			
Ash et al (2003) (48); Australia	Randomized controlled trial	**I:** T2D, treated with oral hypoglycemic agents or by diet alone; age < 70 y; BMI 25–40 kg/m^2 **E:** Active thyroid disease; active psychiatric disease; unstable angina; elevated urate levels; autonomic neuropathy; impaired renal function; medication such as lithium, anticonvulsants, or antipsychotic drugs	N = 51 (51 men/0 women); age 54 y; duration of T2D: 23.5% < 1 y, 51% 1–5 y, 25.5% > 5 y; BMI 31.7 kg/m^2; HbA_{1c} 7.9%

Dietary intervention of interest	Length of intervention (L), follow-up (FU), dietary intervention (IG[a]), control group (CG[a]), change in medication (CM), additional interventions (AI)
5:2 diet	**L:** 28-wk intervention period **FU:** At 28 wk and 52 wk **IG:** ILED group received Optifast low-energy diet for 2 consecutive days, 3430 kJ/d (820 kcal/d), followed by a 5 d Mediterranean diet (adjusted to participant's basal metabolic rate) **CG:** CLED group received low-energy diet for 8 wk, followed by stepped food reintroduction from 4184 kJ (1000 kcal) to 6276 kJ (1500 kcal) per day over 4 wk **CM:** Participants in CLED group discontinued all glucose-lowering medications except metformin and reduced or discontinued insulin, depending on baseline HbA_{1c}. ILED medication protocol depending on HbA_{1c} **AI:** Protocol available for weight maintenance/relapse management. ILED group and CLED group have a different protocol, which was designed conform their initial diet. Participants encouraged to aim for 30 min of moderate-intensity physical activity 5 d/wk and resistance exercise. Behavioral support from multidisciplinary team (dietitian, nurse, exercise specialist, and psychologist). Use of an app to monitor and self-report weight, blood glucose and BP
Alternate-day modified fasting	**L:** 2-wk run-in period and an 18-wk intervention period **FU:** At 20 wk **IG:** 2 different IER groups: VLCD-2: First a 2-week run-in period, participants were tried on VLCD (600 kcal/d) for 10 d to assess compliance. In the 18-wk IER period, participants received 2 nonconsecutive days per week of intermittent VLCD. Ad libitum food consumption on nonrestricted days VLCD-4: First a 2-week run-in period, participants were tried on VLCD (600 kcal/d) for 10 d to assess compliance. In the 18-wk IER period, participants received 4 nonconsecutive days per week of intermittent VLCD. Ad libitum food consumption on nonrestricted days Macronutrient composition: 55% carbohydrates, 15% protein, 30% fat **CG:** Participants received normal diet of 1500–2000 kcal/d throughout study period and continued to receive usual diabetes care **CM:** At start of VLCD, dosage of glucose-lowering medications was reduced by 50%. In run-in period, glucose-lowering medications were either decreased or discontinued by an endocrinologist, based on glycemic control. An extensive medication protocol is available **AI:** In some cases, 200 mL of Once Pro (Thai Otsuka, Thailand) was provided to replace 1 meal. Neither which participants received the meal replacement products nor the reason was reported All participants received additional appointments with an endocrinologist and a dietitian every 2 wk for 20 wk All participants were required to self-monitor their blood glucose levels by a fingerstick at least 2×/wk and, when necessary, to prevent hypoglycemia or hyperglycemia
Periodic modified fasting	**L:** 12-wk intervention period **FU:** At 12 wk, additional visit at 18 mo **IG:** IER group with liquid meal replacement formula of 4180 kJ/d (1000 kcal/d) for 4 consecutive days each week. Remaining 3 d of the week, normal meals containing 6000–7000 kJ/d (1400–1700 kcal/d) **CG:** 2 other dietary intervention groups: PPM group: Had all meals provided to them. 6900 kJ/d (1650 kcal/d). 51% of energy from carbohydrates, 20% from protein, 29% from fat SSM group: Dietary recommendations, 6000–7000 kJ/d (1400–1700 kcal/d) diet, with 50% of energy from carbohydrates and 30% from fat **CM:** None upon start of intervention **AI:** Prior to randomization, participants underwent 2 wk of dietary stabilization, which involved individualized dietary counseling. Every 2 wk, counseling by dietitian

Reference; country	Study design	Inclusion criteria (I) and exclusion (E) criteria	No. and characteristics of participants (mean values)
Sulaj et al (2022) (58); Germany	Randomized controlled trial	**I:** T2D with good glycemic and BP control; optimized treatment according to guidelines; increased ACR for 2 consecutive early-morning sport urine samples; age 50–75 y; eGFR > 30 mL/min/173 cm^2; BMI 23–40 kg/m^2 **E:** Legally incapacitated persons; other form of diabetes; acute infection/fever; severe heart, kidney, hematological, or liver disease; heart failure; nondiabetic liver disease; severe peripheral artery disease; nondiabetic glomerulopathy; immunosuppressive therapy; alcohol or drug abuse; history of cancer disease in last 5 y prior to study; infectious hepatitis; HIV infection; autoimmune disease or immunosuppressive therapy; participation in other interventional studies; anemia or hematological disease; other causes of polyneuropathy; pacemaker; food allergy	N = 40 (29 men/11 women); age 65.8 y; duration of T2D 14.2 y; BMI 30.6 kg/m^2; HbA_{1c} 7.9%
Tang & Lin (2020)(59); China	Randomized controlled trial	**I:** T2D; age 18–65 y; BMI ≥ 28 kg/m^2; HbA_{1c} 7.0%–10.0%; stable weight (weight change ≤ 10% for at least 3 mo before study inclusion); willingness to use a glucometer **E:** Participation in other clinical trials within 3 mo preceding study enrollment; SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg; regular use of insulin, oral steroids, or anti-inflammatory drugs; diagnosis of CVD; stroke, GI disease, chronic nephritis, hepatobiliary disease, or renovascular disease; pregnant and lactating women; relatives of investigators of the trial, employees of the hospital, or others who were related to trial personnel; major illness or physical weakness; investigators' judgment that participant may be unable to complete the study	N = 100 (46 men/54 women); age 49.9 y; duration of T2D NR; BMI 30.1 kg/m^2; HbA_{1c} 7.9%

Table 3. Characteristics of the included studies.

Abbreviations: A6, 6 meals/day; ACR, albumin-to-creatinine ratio; ALT, alanine aminotransferase; B2, 2 meals/day; BMI, body mass index; BP, blood pressure; CER, continuous energy restriction; CF, consecutive fasting; CLED, continuous low-energy diet; CVD, cardiovascular disease; DPB, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMD, fasting-mimicking diet; FPG, fasting plasma glucose; GFR, glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; HbA_{1c}, glycated hemoglobin; IER, intermittent energy restriction; ILED, intermittent low-energy diet; NCF, nonconsecutive fasting; NR, not reported; PPM, preportioned meals; SPB, systolic blood pressure; SSM, self-selected meals; T1D, type 1 diabetes; T2D, type 2 diabetes; TRE, time-restricted eating; VLCD, very low-calorie diet.
[a]Includes number of calories and composition of macronutrients.

Dietary intervention of interest	Length of intervention (L), follow-up (FU), dietary intervention (IG[a]), control group (CG[a]), change in medication (CM), additional interventions (AI)
Periodic modified fasting (FMD)	**L:** 6-mo intervention period **FU:** At 6 mo and 9 mo **IG:** FMD meal replacement diet for 5 consecutive days each month, containing 4600 kJ (1100 kcal) on day 1 and 3000 kJ (717 kcal) on days 2–5 **CG:** Mediterranean diet without a change in caloric intake compared to participant's diet for 5 days each month **CM:** Patients on insulin therapy were instructed to discontinue short-acting insulin and to reduce the long-acting insulin by 50% when taking FMD. Oral antidiabetic therapy was also discontinued during FMD. Glucose-lowering medication was reduced in case of a reduction in FPG during follow-up by > 20% compared to the previous measurement **AI:** Glycemic levels were self-monitored with a capillary blood glucose-monitoring system. All participants were instructed to avoid excessive physical activity during FMD or Mediterranean diet and to return to normal physical activity afterward
Periodic modified fasting (FMD)	**L:** 3-mo intervention period **FU:** At 4 mo **IG:** FMD meal replacement powder from Monday to Friday in second week of a month (energy provision on day 1 and days 2–5 was 5004 kJ/1196 kcal and 3368 kJ/805 kcal) and normal meals for rest of month. Composition of macronutrients NR **CG:** Meal replacement powder from Monday to Friday in second week of a month (calories met recommended daily requirement for normal adults:7531–7950 kJ (1800–1900 kcal) for women and 8284–9790 kJ (1980–2340 kcal) for men). Composition of macronutrients NR **CM:** All patients received metformin 0.5 g once daily as treatment for diabetes. Metformin was adjusted for patients in test group who had hypoglycemia or other discomforts on FMD meal replacement days **AI:** None

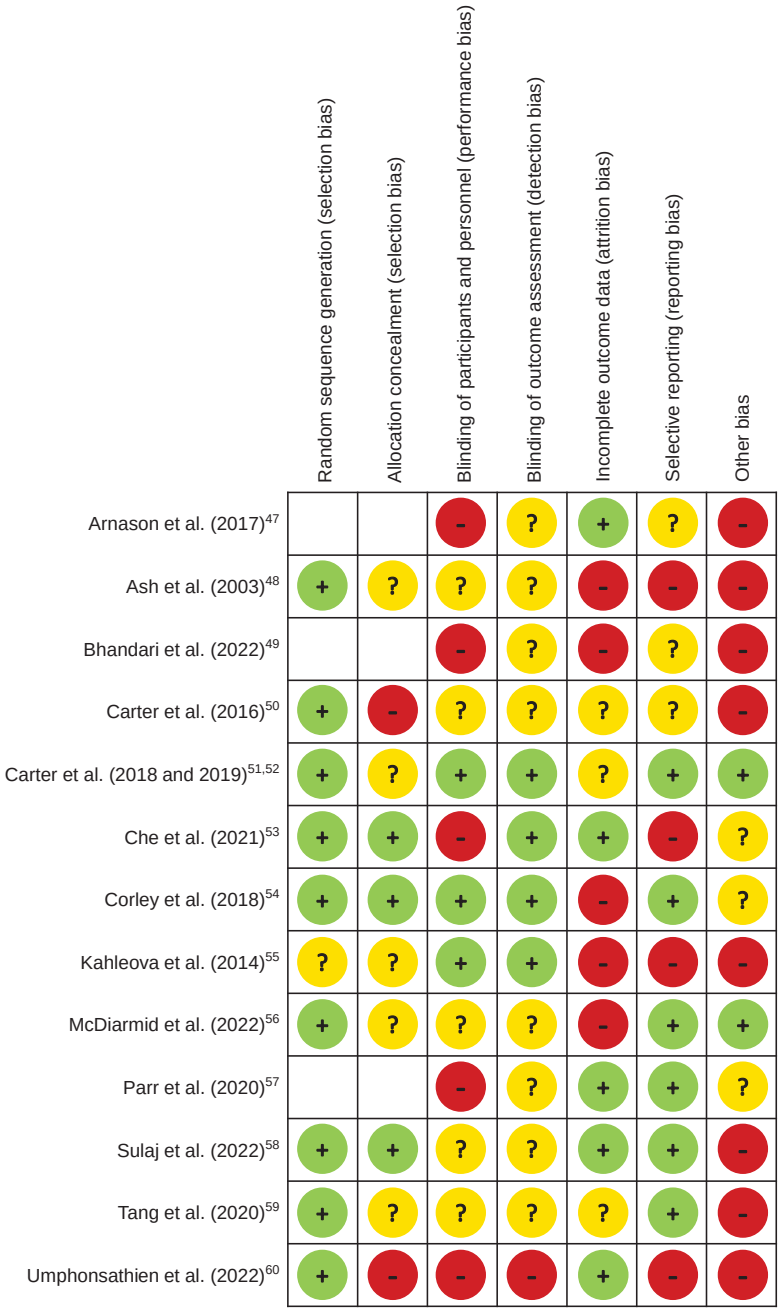

Figure 2. Risk-of-bias summary.

Time-restricted eating

Primary outcome measures (Table 4)

Time-restricted eating entails restriction of energy intake to delimited time periods of the day, typically between 12 and 16 hours. Five studies of TRE were included in this review(47, 49, 53, 55, 57). Data on HbA_{1c} were reported in 3 studies(53, 55, 57). Che et al(53) observed a decline in HbA_{1c} in response to 12 weeks of 10-hour restricted eating (8:00 am to 6:00 pm) as compared with ad libitum eating. In contrast, HbA_{1c} declined to a similar extent in response to 12 weeks of eating 2 meals per day (6:00 am to 4:00 pm) as compared with 6 meals ad libitum in the study by Kahleova et al(55). Furthermore, HbA_{1c} did not decline to a significant extent as compared with baseline levels in response to 4 weeks of TRE (10:00 am to 7:00 pm) in the study by Parr et al(57), but the study duration may have been too short to exert a measurable effect on HbA_{1c}.

Fasting glucose levels were reported in all 5 of the TRE studies. They declined significantly more (than in controls) in response to TRE in the studies by Che et al(53) and Kahleova et al(55). Bhandari et al(49) reported a highly significant reduction in fasting glucose after 4 weeks of TRE (fasting goal of 16 hours per day) in a single-arm intervention study. In contrast, fasting glucose levels did not significantly decline in the single-arm intervention studies by Arnason et al(47) (2 weeks of TRE) and Parr et al(57) (4 weeks of TRE).

Three studies reported data on lipid levels(53, 55, 57). Plasma triglycerides as well as total cholesterol and LDL-C declined significantly more in response to 12 weeks of (8:00 am to 6:00 pm) TRE as compared with ad libitum eating in the study by Che et al(53). Plasma lipid levels did not change in the study by Parr et al(57) and declined to a similar extent in the intervention (2 meals between 6:00 am to 4:00 pm) and control (6 meals/ad libitum) groups in the study by Kahleova et al(55).

Only Che et al(53) reported data on glucose-lowering medication use(53), which declined in the TRE group as compared with the ad libitum eating group.

Reference	Duration of follow-up	Change from baseline to end of intervention phase			
		Markers of metabolic control (fasting condition)			Change in use of glucose-lowering medication
		HbA_{1c} (%)	Glucose (mmol/L)	TG, HDL-C, LDL-C, TC (mmol/L)	
Time-restricted eating					
Arnason et al (2017)(47)	2 wk	–	−0.5	–	–
Bhandari et al (2022)(49)	4 wk	–	−1.1*	–	–
Che et al. (2021) (53)	12 wk	IER: −1.54 ± 0.19;*** CG: −0.66 ± 0.16	IER: −1.47 ± 0.25*** CG: −0.78 ± 0.21	IER: −0.23 ± 0.08***; −0.16 ± 0.04***; −0.42 ± 0.13***; −0.32 ± 0.07*** CG: −0.13 ± 0.06; −0.15 ± 0.05; −0.21 ± 0.13; −0.15 ± 0.06	IER: MES −0.66 ± 0.17*** CG: MES −0.21 ± 0.04
Kahleova et al (2014)(55)	24 wk	IER: −0.25 CG: −0.23	IER: −0.78*** CG: −0.47	IER: −0.17; +0.003; −0.06; −0.07 CG: −0.28; +0.016; −0.08; −0.05	–
Parr et al (2020) (57)	4 wk	−0.17	−0.18	0.00; +0.01; -0.17; −0.13	NR
5:2 diet					
Carter et al (2016)(50)	12 wk	IER: −0.5 ± 0.8 CER: −0.6 ± 1.0	–	–	IER: MES −0.4 ± 0.5 CER: MES −0.4 ± 0.6
Carter et al (2018)(51)	12 mo	IER: −0.3 ± 0.1** CER: −0.5 ± 0.2 Between-group difference within equivalence margin	NR	NR	IER: MES −0.6 ± 0.1** CER: MES −0.3 ± 0.1
Corley et al (2018)(54)	12 wk	NCF: −0.7 CF: −0.6	NCF: −1.1 CF: −1.3	NCF: −0.1; 0.0; −0.1; −0.4 CF: −0.1; 0.0; +0.1; +0.1	NR

Anthropometric values				Blood pressure		Patient-perceived quality of life[a]	Dropout rate and compliance
Body weight (kg)	BMI (kg/m^2)	WC (cm)	Body fat (%)	SBP (mmHg)	DBP (mmHg)		
–1.4*	–0.52*	–1.75	–	–3	–0.72	–	No dropouts Goal of 18–20 h of fasting was not reached (average, 16.8 h)
–1.24*	–0.44*	–1.6*	–	–	–	–	–
IER: –2.98 ± 0.43*** CG: –0.83 ± 0.32	IER: –1.64 ± 0.38*** CG: –0.42 ± 0.24	–	–	–	–	IER: SF-12 5.92 ± 1.38*** CG: 1.71 ± 1.41	–
IER: –3.7*** CG: –2.3	IER: –1.23*** CG: –0.82	IER: –5.14*** CG: –1.37	–	–	–	–	Dropouts: 3 in IER, 4 in CG Self-reported energy intake comparable
–0.07	NR	–	–0.07 kg	–0.51	–0.54	AQoL-8D: IL +0.16; H –0.07; MH 0.00; C 0.00; R 0.00; SW –0.22; P 0.00; S 0.00	No dropouts Compliance, defined as adherence to TRF time window, was 20 ± 7 of the 28 d (≈5 d/wk)
IER: –8 CER: –8	–	–	IER: –1.7 ± 2.4 CER: –2.1 ± 2.1	–	–	–	Dropouts: 5 in IER group, 7 in CER group Compliance to diet not reported
IER: –6.8 ± 0.8** CER: –5.0 ± 0.8 Between-group difference outside equivalence margin	IER: –2.3 ± 0.3** CER: –1.9 ± 0.3	–	IER: –2.3 ± 0.6 CER: –1.6 ± 0.3 Between-group difference outside equivalence margin	–	–	–	Dropouts similar in both groups: 21 in CER group and 19 in IER group Compliance at 12 mo: 49% in CER group and 44% in IER group
NCF: –3.6 CF: –3.1	NCF: –0.8 CF: –0.5	NCF: –3.4 CF: –1.6	NCF: –0.9 CF: –1.1	NCF: –4 CF: –3	NCF: –3 CF: –2	ADDQoL + 0.66 on a scale of 6**	Dropouts: 3 in NCF, 1 in CF Self-reported adherence rate (12 wk) to calorie target: 24.2%

Reference	Duration of follow-up	Change from baseline to end of intervention phase			
		Markers of metabolic control (fasting condition)			Change in use of glucose-lowering medication
		HbA_{1c} (%)	Glucose (mmol/L)	TG, HDL-C, LDL-C, TC (mmol/L)	
McDiarmid et al (2022)(56)	28 wk	ILED: −0.9 CLED: −1.1	–	–	ILED: MES -0.2 CLED: MES -0.8
Alternate-day (modified) fasting					
Umphonsathien et al (2022)(60)	20 wk	CG: −0.1 ± 0.3 VLCD-2: −0.7 ± 0.3 VLCD-4: −1.2 ± 0.3**	CG: −0.20 ± 0.35 VLCD-2: −0.65 ± 0.32 VLCD-4: −1.03 ± 0.32**	CG: −0.40 ± −0.40; +0.04 ± 006; +0.23 ± 0.33; +0.29 ± 0.35 VLCD-2: −1.12 ± 0.37**; −0.02 ± 0.05; +0.40 ± 0.30; +0.26 ± 0.32 VLCD-4: −1.07 ± 0.37**; +0.06 ± 0.05; +0.22 ± 0.30; +0.09 ± 0.32	Discontinuation of glucose-lowering medication CG: 58% VLCD-2: 64% VLCD-4: 86%
Periodic (modified) fasting					
Ash et al (2003) (48)	12 wk	NR	–	NR	–
Sulaj et al (2022)(58)	6 mo	FMD: −1.4*** CG: 0.0	FMD: −1.4 CG: −0.4	FMD: −1.76; +0.06; −0.02; +0.63 CG: −0.01; +0.10; +0.07; +0.24	Medication reduced in 67% of those in FMD group; 21% of CG had to increase medication use
Tang & Lin (2020)(59)	4 mo	IG: −1.36*** CG: −0.43	IG: −2.31*** CG: −1.30	IG: −1.75***; +1.05***; −1.86***; −2.78*** CG: −0.42; +0.21; −0.58; −0.58	NR

Table 4. Primary and secondary outcomes in the studies included in the systematic review.

Abbreviations and symbols: –, data not measured; ADDQoL, Audit of Diabetes-Dependent Quality of Life 19 questionnaire; AQoL-8D, Assessment of Quality of Life (including the following domains: IL, independent living; H, happiness; MH, mental health; C, coping; R, relationship value; SW, self-worth; P, pain value; S, senses); BMI, body mass index; CER, continuous energy restriction; CF, consecutive fasting; CG, control group; CLED, continuous low-energy diet; DPB, diastolic blood pressure; FMD, fasting-mimicking diet; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IER, intermittent energy restriction; IG, intervention group; ILED, intermittent low-energy diet; LDL-C, low-density lipoprotein cholesterol; MES, medication effect score ([actual drug dose/maximum drug dose] x drug mean adjustment factor); NCF, nonconsecutive fasting; NR, data not reported (by group); PPM, preportioned meals; SBP, systolic blood pressure; SF-12, 12-Item Short-Form Health Survey; SF-36, 36-Item Short-Form Health Survey; SSM, self-selected meals; TC, total cholesterol; TG, triglycerides; TRF, time-restricted feeding; VLCD-1, very low-calorie diet intermittently for 1 day/week; VLCD-5, very low-calorie diet intermittently for 5 consecutive days; WC, waist circumference.
[a] No study reported data on patient satisfaction with treatment.
*Statistically significant difference by time, from baseline to end of intervention phase.
**Statistically significant difference by time, from baseline to end of intervention phase. No significant difference between groups.
***Statistically significant difference by time, from baseline to end of intervention phase and between groups.

Anthropometric values				Blood pressure		Patient-perceived quality of life[a]	Dropout rate and compliance
Body weight (kg)	BMI (kg/m^2)	WC (cm)	Body fat (%)	SBP (mmHg)	DBP (mmHg)		
ILED: −6.9 CLED: −7.7	–	–	–	–	–	–	Retention of trial participants: ILED: 69% CLED: 75%
CG: −4.9 ± 1.4** VLCD-2: −5.5 ± 1.3** VLCD-4: −8.6 ± 1.3**	CG: −2.0 ± 0.6** VLCD-2: −2.1 ± 0.5** VLCD-4: −3.6 ± 0.5**	–	CG: −3.8 kg ± 1.1 kg** VLCD-2: −2.1 kg ± 0.5 kg** VLCD-4: −3.6 kg ± 0.5 kg**	CG: −14.9 ± 5.0** VLCD-2: −1.2 ± 4.6 VLCD-4: −9.7 ± 4.6**	CG: −6.5 ± 4.6 VLCD-2: −0.1 ± 4.2 VLCD-4: −3.8 ± 4.2	SF-36 CG: 120 ± 171 VLCD-2: 313 ± 158 VLCD-4: 615 ± 158**	No dropouts
NR	–	NR	IER: −2.0 ± 1.1 PPM: −2.6 ± 1.6 SSM: +0.9 ± 1.4	–	–	–	No dropouts at 12 wk Compliance to diet not reported
FMD: −9.9*** CG: −0.2	FMD: −3.3*** CG: −0.2	–	FMD: −2.3 CG: +0.3	FMD: −1.6 CG: +0.5	FMD: −2.1 CG: 0.0	–	Not reported per group. 78% of participants were seen at follow-up
NR	IG: −5.11*** CG: −1.13	IG: −14.28*** CG: −5.94	–	IG: −14.18*** CG: −6.14	IG: −10.98*** CG: −5.42	–	No dropouts

Secondary outcome measures (Table 4)

In 4 of the 5 studies, a decline in body weight and BMI was observed in people on TRE either over time(47, 49) or in comparison with a control group(53, 55). Waist circumference declined in response to TRE in 2 of the 5 studies(49, 55). Che et al(53) also reported that the quality of life improved in patients using TRE as compared with those who ate ad libitum. Two studies examined compliance with the prescribed dietary regimen. Arnason et al(47) reported acceptable compliance in their study, in which the goal of TRE for 18 to 20 hours per day was not completely reached, but participants did fast for an average of 16.8 hours per day. Parr et al(57) reported that patients complied with the recommended TRE time window for only 5 days per week. Other secondary outcomes were either not reported or did not yield significant results.

Summary

The TRE studies included in this review reported a decline in HbA_{1c} (2 out of 3 studies), fasting glucose (3 out of 5 studies), and body weight (4 out of 5 studies) in response to TRE. Plasma lipid levels improved in response to TRE in only one(53) of 3 studies that reported these data(53, 55, 57). The study by Che et al(53) was the only one to report data on medication use and quality of life. Both outcome measures improved in response to TRE.

The 5:2 diet

Primary outcome measures (Table 4)

The 5:2 diet restricts energy intake for 2 days per week. All 4 of the 5:2 diet studies included in this review reported data on HbA_{1c}(50, 51, 54, 56). In the noninferiority trial by Carter et al(51), 2 days of caloric restriction (500–600 kcal/d) per week was compared with CER of 1200 to 1500 kcal/d for 12 months. Levels of HbA_{1c} declined in both groups to a similar, modest extent that was within the equivalence margin. In the feasibility study by McDiarmid et al(56), HbA_{1c} declined over time to a similar extent in the IER group (caloric restriction of 820 kcal/d for 2 days per week during 28 weeks) and the CER group (caloric restriction of 820 kcal/d for 8 weeks, yielding an equal number of days of caloric restriction in the intervention and control groups). In the pilot study by Carter et al(50), who compared the effects of a severely calorie-restricted diet (1670–2500 kJ/d) on 2 days per week with modest CER (5000–6500 kJ/d) for 12 weeks, HbA_{1c} declined to a similar extent in both groups. Corley et al(54) reported a similar decline in HbA_{1c} and fasting glucose levels in 2 groups of participants who restricted calories (to 500–600 kcal/d) on either 2 consecutive or 2 nonconsecutive days per week for 12 weeks.

Total cholesterol, LDL-C, or HDL-C concentrations were not affected by either intervention in the study by Corley et al(54), which was the only study that evaluated the impact of the 5:2 diet on lipid levels.

Changes in glucose-lowering medication were evaluated in 3 studies(50, 51, 56), of which 2 were pilot/feasibility studies(50, 56). In the study by Carter et al(51), the use of medication declined similarly in both groups. A tendency toward a similar decline in medication use in both groups was also observed in the pilot studies by Carter et al(50) and McDiarmid et al(56).

Secondary outcome measures (Table 4)
Weight loss was reported by all 4 included studies(50, 51, 54, 56). In the noninferiority study by Carter et al(51), participants in both groups lost weight after 12 months. The between-group difference was outside the equivalence margin, indicating that IER may be superior to CER for weight reduction. In the 3 other studies(50, 54, 56), body weight declined over time to a similar extent in the intervention and the control groups.

Quality of life significantly increased in both arms (500–600 kcal/d for 2 consecutive days or 2 nonconsecutive days) combined in the study by Corley et al(54). The other studies did not report data on quality of life.

Compliance was very good in the noninferiority study by Carter et al(51) in the first 3 months (97% in IER group vs 90% in CER group), but dropped significantly by the end of the 12-month intervention period (44% in IER group vs 49% in CER group). In the study by Corley et al(54), self-reported adherence to the calorie target was only 24.2%. Dropout rates were generally similar between the IER groups and the control groups. Other secondary outcomes were either not measured or did not yield significant results.

Summary
Three of the 4 studies evaluating the impact of the 5:2 diet on metabolic control in patients with T2D compared the effects with CER(50, 51, 56), while the other compared 2 different IER interventions(54). Two were feasibility studies(50, 56). In concert, the studies suggest that intermittent 5:2 calorie restriction is as effective as CER in terms of glycemic control and weight loss in patients with T2D. A lack of available data precludes conclusions with regard to other measures of metabolic control.

Alternate-day (modified) fasting

Primary outcome measures (Table 4)

Alternate-day (modified) fasting entails no food intake or restriction of energy intake on a fasting day, alternated by days of unrestricted food intake. Only one study that evaluated the effects of ADMF on metabolic parameters in T2D could be included. Umphonsathien et al(60) compared two ADMF groups (600 kcal, 2 days per week or 4 days per week, for 18 weeks) and a control group that received a normal diet containing 1500 to 2000 kcal/d throughout the study period. Both 2 days and 4 days of fasting per week, alternated by ad libitum food intake, induced a significant decline in HbA_{1c} and fasting glucose concentrations at 18 weeks. Notably, there were no significant differences between the 3 groups, since both measures of glycemic control improved in the control group receiving CER as well, albeit to a lesser, not statistically significant extent.

Furthermore, plasma triglyceride levels were significantly reduced in both ADMF groups at 18 weeks but were not different from baseline in the control group. Total cholesterol, HDL-C, and LDL-C levels were not significantly affected by either intervention.

Interestingly, glucose-lowering medication could be reduced in 86% of the ADMF 4 days per week group and in 64% of the ADMF 2 days per week group, while 58% of control participants could discontinue medication as well. Medication was adjusted by an endocrinologist in accordance with a (de-)medication protocol based on blood glucose levels by fingerstick tests at least twice per week. No statistical tests were performed.

Secondary outcome measures (Table 4)

Body weight, BMI, and body fat declined significantly in both of the ADMF intervention groups as well as in the control group over time, with no significant differences between groups. The decline in systolic blood pressure and the increase in quality of life at 18 weeks was significant only in patients fasting for 4 days per week, but both outcome measures changed in similar directions in the other study arms, and differences between groups were not statistically significant. Other secondary outcomes were either not measured or did not yield significant results.

Summary

Only one study evaluating the effects of ADMF could be included in this review. The data suggest that 2 or 4 days of severe restriction of calories per week, alternated with ad libitum food intake, over a period of 18 weeks improves glycemic control and reduces body fat to a broadly similar extent, although the effects of 4 days of calorie restriction were slightly more favorable. Continuous, more modest energy restriction also improves metabolic measures, albeit to a lesser (but not significantly different) extent.

Periodic (modified) fasting

Primary outcome measures (Table 4)

Periodic (modified) fasting was defined as no intake or a restricted intake of food over time periods that last 3 consecutive days or more, used intermittently with ad libitum intake. Three studies evaluating the impact of PF in T2D could be included(48, 58, 59). In the study by Ash et al(48), participants were randomized to receive one of 3 isocaloric restricted (average, 1400–1700 kcal/d) dietary regimens: IER for 4 days per week alternated with 3 days of ad libitum eating; preportioned meals every day; or self-selected meals for 12 weeks. Data on primary outcomes of this study were not available. The studies by Sulaj et al(58) and Tang et al(59) examined the effects of an FMD for 5 consecutive days per month over half a year(58) or 4 months(59). Periodic FMD programs lasting 4 to 7 days are designed to mimic the physiological effects of water-only fasting while minimizing the burden by allowing patients to consume food and confining the fasting period to a limited number of days. These low-calorie (800–1100 kcal/d) plant-based formula diets typically are low in sugar and protein, primarily comprising complex carbohydrates and healthy fats(61). The study by Sulaj et al(58) compared the FMD group with a control group receiving a Mediterranean diet containing as many calories as usual for each individual participant for 5 consecutive days per month, while the control group in the study by Tang and Lin(59) received meal replacement products containing the recommended daily requirements for healthy adults for 5 consecutive days every month. Levels of HbA_{1c} declined more in people using FMD as compared with controls in both studies. Tang and Lin(59) also observed a reduction in fasting glucose concentrations as well as improved plasma lipid levels. In the study by Sulaj et al(58), glucose-lowering medication could be reduced in 67% of participants using FMD, while it had to be increased in 21% of the participants using the Mediterranean control diet.

Secondary outcome measures (Table 4)

In both studies evaluating the effects of FMD, BMI declined significantly more in participants using FMD(58, 59). The study by Tang and Lin(59) also revealed a larger reduction in waist circumference and in systolic as well as diastolic blood pressure in the FMD group as compared with the control group. In the study by Ash et al(48), people on preportioned meals lost slightly more body fat compared with those who consumed self-selected meals, but not compared with the IER group. Other secondary outcomes were either not measured or did not yield significant results.

Summary

Just one study evaluated the effects of periodic "general" energy restriction on metabolic markers in patients with T2D, while 2 studies examined the effects of periodic FMD programs. The results of these studies show that periodic use of an FMD appears to improve body weight and glycemic control more significantly as compared with similarly timed "healthy diet" interventions containing more calories.

Long-term follow-up

Two studies provided data from long-term follow-up (≥ 1 year after the intervention)(48, 52). In the study by Ash et al(48), participants were invited for an additional follow-up visit after 18 months. Fifty-two percent of the participants responded. Of those, 15% had a stable body weight and 85% had regained weight. There was no difference in body weight (regain) between study groups. No individuals continued to lose weight, and none of the improvements in clinical parameters were maintained.

In the study by Carter et al(52), follow-up data from 61% of the participants were collected after 24 months. In the 5:2 diet group as well as in the CER group (1200–1500 kcal/d), HbA_{1c} and fasting plasma glucose had increased since the end of the intervention: HbA_{1c} increased even above baseline levels and fasting plasma glucose returned to baseline levels. Weight loss and the reduction in total medication dosage were maintained over time. None of the participants were still following the diet on a regular basis, but most participants reported following the diets to some extent, for example by occasionally using IER or by limiting portion size in the CER group to help maintain body weight.

In summary, limited long-term follow-up (≥ 1 year) data indicate that the effects of (intermittent) energy restriction are not maintained in the long run.

Discussion

Principal findings

This systematic review is the first to summarize current knowledge of the effects of IER (TRE, 5:2 diet, ADMF) and PF on markers of metabolic control and glucose-lowering medication dosage in patients with T2D. Most studies compare the impact of IER with the effects of CER or a distinct IER dietary regimen. In aggregate, the available evidence suggests that IER and PF ameliorate anthropometric and metabolic anomalies to a similar extent as CER. This finding is consistent with the conclusion of other reviews, which mainly included studies of patients without T2D. These reviews,

like this one, documented similar effects of IER and CER in terms of weight loss(21, 22), loss of fat mass or fat-free mass, or glucose homeostasis(21). Only 2 studies compared the effects of IER or PF with those of dietary interventions containing normally recommended amounts of energy, and both revealed clear benefits of calorie restriction. Time-restricted eating had favorable effects on anthropometric values in 4 of the 5 available studies and had favorable effects on metabolic control 3 of the 5 available studies. There is insufficient evidence to draw definitive conclusions about the impact of IER or PF on blood pressure or lipid levels.

There are some indications that IER and PF can reduce the need for glucose-lowering medication, but only 6 studies reported glucose-lowering medication as an outcome measure(50, 51, 53, 56, 58, 60). The available descriptive data suggest that the dosage of glucose-lowering medication can possibly be lowered. However, the majority of the results are not statistically tested and definitive conclusions about the impact of IER and PF on the need for glucose-lowering medication in people with T2D cannot be drawn.

Data on compliance were not reported in most of the available papers. The compliance rate in the study by Carter et al (51), who examined a 5:2 diet, was excellent in the first 3 months but dropped significantly in the following 9 months. Notably, compliance was similar in the control group using CER. All studies reported dropout rates, which were generally similar between the intervention and control groups. The relatively low dropout rate in most of the included studies might be explained by the short duration of follow-up, since only 3 studies examined an intervention that lasted 6 months or more(51, 56, 58). Based on the available data on compliance, it is not possible to conclude that the adherence to IER or PF is better than that to any other (energy-restricted) diet. In a substudy, Parr et al(57) interviewed participants. Hunger, daily stressors, and emotions were the main barriers to adherence. Other known factors, such as the duration of the intervention, face-to-face contact, multiple intervention strategies, and follow-up prompts might play a role in maintaining dietary behavioral change(62).

This review uncovers a lack of studies that consider patient perceptions like quality of life and treatment satisfaction. Since adhering to any diet is difficult(63), patient perceptions should be an important consideration(10, 64). In 3 of the 4 studies that did measure quality of life, improvement at the end of the intervention phase was observed to a similar extent in both the intervention and the control groups(53, 54, 60). Treatment satisfaction was not measured in any of the included studies.

Strengths and limitations

One of the strengths of this review is that a very broad search was conducted to identify all possible studies of IER or PF interventions in patients with T2D. This review focused on markers of metabolic control and the need for glucose-lowering medication, while previous reviews, often including studies with both healthy participants and T2D patients, focused primarily on weight loss. Another strength of this review is that it documents patient perceptions and adherence to the diet. Notably, both issues, although critically important for clinical practice, are often overlooked or not reported.

One of the limitations of the review is that a meta-analysis of outcome measures could not be conducted. Several categories of IER and PF diets were defined (**Table 2**), but even within a category, the dietary interventions, study designs, and study duration were too heterogeneous to allow clustering of the studies.

The short duration of some of the interventions in the included studies is a limitation in itself, since considerable time is required for a dietary intervention to become ingrained into an individual's routine(1, 10). Indeed, the few trials that performed long-term follow-up suggest that improvements in markers of metabolic control and weight loss are often not sustained in the long run, which obviously limits the impact of clinical application of the intervention.

The risk of bias in the majority of available studies is high, which hampers proper interpretation of the data and creates uncertainty about the applicability of IER and PF in clinical practice.

Clinical implications

The evidence for benefits of IER and PF in patients with T2D remains limited to date. There is some evidence to support benefits in terms of glucose regulation and use of glucose-lowering drugs. Indeed, as the available evidence suggests that the effects of IER on HbA_{1c} and weight loss are similar to those of CER(51), patients appear to have diverse options to choose the dietary intervention that suits them best. At this time, there is insufficient data comparing different forms of IER and PF diets to each other to recommend one above the others. Interestingly, most of the available evidence documents favorable effects of TRE on body weight, HbA_{1c}, and fasting glucose in patients with T2D.

Safety remains one of the main concerns when considering IER or PF in the treatment of T2D. Notably, 7 of the included studies excluded patients who were treated with insulin(47-49, 55, 57, 59, 60), as these patients are at high risk of hypoglycemia during

calorie/carbohydrate restriction. Only one of the included trials was specifically designed to assess hypoglycemic events during 5:2 regimens in patients with T2D using sulfonylurea derivatives or insulin(54). The risk of hypoglycemia was increased on fasting days to a similar extent in patients using either medication, despite (apparently insufficient) dosage reduction. No difference was found between fasting on consecutive days or nonconsecutive days. Therefore, it is important to assess the risk of hypoglycemia before following an IER or PF diet. In this context, flash glucose monitoring may contribute to better management(65). At the moment, there are no evidence-based guidelines on the management of glucose-lowering medication during IER or PF regimens. Grajower et al(66) propose a medication adjustment protocol based on knowledge of the mechanism of action of glucose-lowering medication. In addition, they recommend frequent glucose monitoring for patients who use sulfonylureas or insulin.

Overall, there is some evidence to support the benefits of IER and PF diets for patients with T2D as an alternative or adjunct to other dietary interventions. On the basis of current knowledge, it is not possible to recommend one specific type of IER or PF diet over the others. Notably, most of the available trials evaluate effects in patients with T2D who do not use sulfonylurea derivatives or insulin. In these patients, careful monitoring of blood glucose concentrations and proper adaptation of the drug dose obviously are a prerequisite for safe application of IER or PF.

Future research

Many of the studies in this review were small and focused mainly on feasibility. Future studies, therefore, should be sufficiently powered to evaluate markers of metabolic control. In addition, they should include the dosage of glucose-lowering medication as one of the outcome measures. A reduction in glucose-lowering medication without deterioration of glucose metabolism is a favorable outcome for T2D patients. Moreover, since a study period of at least 1 year is necessary to achieve a lasting change in behavior(1, 22), future studies should have a long intervention period and additional long-term follow-up. Lastly, it will be important to compare the effects of distinct types of IER and PF diets as an adjunct to usual care and to identify personal characteristics that predict the response to these diverse interventions. Since a growing body of evidence compellingly indicates that the metabolic response to nutritional interventions is highly personal (largely dependent on factors such as gut microbiome and genetic variants) and is affected by behavioral and environmental conditions, the impact of these cues should be tested in future trials(67). Ultimately, big data analytical techniques will probably be required to create personalized dietary regimens to optimize metabolic control in people with T2D.

Conclusion

Limited evidence at a high risk of bias suggests that IER and PF ameliorate various anthropometric and metabolic anomalies in patients with T2D, at least in the short term, as long as the intervention lasts. Moreover, IER and PF may allow for a reduction in the dosage of glucose-lowering medication. The benefits of IER and PF appear to be similar to those of CER.

Declarations

Acknowledgments

The authors thank Mr J.W. Schoones from the Walaeus Library of the Leiden University Medical Center for his support to perform the electronic search strategies.

Author contributions

E.B., P.P., M.N., and H.P. designed the study. E.B., P.P., and D.H. performed the literature search and selected the studies. E.B., M.S. and D.H. collected the data. All authors interpreted the data and contributed to the discussion. E.B. wrote the manuscript. P.P., M.S., D.H., M.N., and H.P. critically reviewed and edited the manuscript. All authors critically evaluated and approved the last version of the manuscript.

Funding

There was no specific funding for this review, but salaries of E.B. and M.S. (PhD students) were funded in the context of the FIT (Fasting in diabetes Treatment) trial. The FIT trial was cofunded by the PPP (public-private partnership) Allowance made available by Health~Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships as well as by a contribution from the Dutch Diabetes Foundation and L-Nutra (Los Angeles, CA). The funding sources had no role in the design of the systematic review or the collection, analysis and interpretation of the data, the manuscript preparation or revision, or the publication decisions.

Declaration of interest

The authors have no relevant interests to declare.

QR-code to article and supplementary information

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