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SUMMARY WITH CRITICAL APPRAISAL

Intermittent Fasting for Adults with Type 2 Diabetes: A Review of the Clinical Effectiveness and Guidelines

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Abbreviations

BMI	body mass index
BMJ	British Medical Journal
CRD	Centre for Reviews and Dissemination
HbA1C	hemoglobin A1C
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
MeSH	Medical Subject Headings
NMA	network meta-analysis
NS	non-significant
OGTT	oral glucose tolerance test
PICO	Population Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RFPM	Remote Food Photography Method
RoBANS	Risk of Bias for Nonrandomized Studies
SD	standard deviation
SMBG	self-monitoring of blood glucose
SR	systematic review
T2D	type 2 diabetes
YPAS	Yale Physical Activity Survey

Context and Policy Issues

Diabetes is a global health issue that is estimated to affect 463 million individuals worldwide.[1] In Canada, 11 million individuals are living with diabetes or prediabetes.[2] The high prevalence of diabetes globally is especially concerning given its association with a variety of health conditions including hypertension, heart disease, stroke, cataracts, and glaucoma.[3,4]

Type 2 diabetes (T2D) is the most prevalent type accounting for approximately 90 percent of individuals living with diabetes.[2,5] T2D is a metabolic disorder characterized by a lack of insulin production by the pancreas or an inability for the body to adequately use the produced insulin.[6] T2D is believed to have both genetic (e.g., insulin release and responsiveness) and environmental (e.g., obesity) components to its pathogenesis.[6,7] Lifestyle modifications, including weight loss and diet changes, are frequently used as the initial management strategy for adults with T2D as it may improve aspects of the condition, such as glycemic control and hypertension.[6,7] Despite this, there is still controversy as to what is the best dietary approach for the management of adults with T2D.[8]

A complementary 2019 CADTH Summary of Critical Appraisal examined the clinical effectiveness and guidelines regarding the use of low carbohydrate diet in adults with T2D.[9] This report found 10 systematic reviews (SRs) regarding dietary approaches for individuals with T2D, albeit no direct comparisons between low-carbohydrate and standard diets in the primary studies in the SRs, and four evidence-based guidelines to answer the research questions.[9] Indirect comparisons between low-carbohydrate and standard diets were available in three SRs with network meta-analyses (NMAs) and the results were mixed. Some indirect comparisons suggested a low carbohydrate diet is more effective in reducing triglyceride and fasting glucose levels, but insignificant for reducing cholesterol and body mass index (BMI). Two NMAs conducted indirect comparisons of low-carbohydrate and standard diets for the outcome glycated hemoglobin (HbA1c); one NMA found low-carbohydrate diets significantly more effective in reducing HbA1c whereas the other NMA

found low-carbohydrate diets were not significantly effective at reducing HbA1c. Recommendations from the included guidelines also varied, with one guideline highlighting that various diets are acceptable for the management of T2D.[9]

Another potential dietary intervention for individuals with T2D is intermittent fasting.[10] Intermittent fasting is a dietary, and recently popularized, approach that cycles between controlled and voluntary brief periods of fasting, with either no food or significant calorie reduction, and periods of unrestricted eating.[10-12] Generally, the most common options of intermittent fasting are the twice-a-week method (5:2), alternate day fasting, time-restricted eating (e.g., 16/8 or 14/10 method), and the 24 hour fast (eat: stop: eat method).[13] The twice-a-week method involves two 'fasting days' (with < 600 calories consumed for men, < 500 for women) per week and the other five days of the week involve following a standard diet.[13,14] Alternate day fasting involves modified fasting every other day (e.g., < 500 calories on fasting days and standard diet on alternate, non-fasting days).[13] Time-restricted eating method limits eating to a segment of time (usually eight hours or less per day; e.g., 11:00 am to 7:00 pm); outside of that window, the individual maintains in a fasted state (usually 16 hours or more per day; e.g., 7:00 pm to 11:00 am). The 24 hour fast method involves fasting completely for 24 hours, usually once or twice per week, and then following a standard diet for the non-fasting days.[13] Intermittent fasting may be a desired approach for adults with T2D by reducing hemoglobin A1C (HbA1C) levels and the need for insulin therapy as suggested by a recent case series published in British Medical Journal (BMJ) Case Reports.[10] Before considering intermittent fasting as a management strategy for adults with T2D, a summary of comparative studies with consideration of study quality and effectiveness relative to other dietary approaches would be valuable.

Thus, the aim of this report is to summarize the evidence regarding both the clinical effectiveness of and evidence-based guidelines regarding the use of intermittent fasting for adults with T2D.

Research Questions

1. What is the clinical effectiveness regarding the use of intermittent fasting for adults with type 2 diabetes?
2. What are the evidence-based guidelines regarding the use of intermittent fasting for adults with type 2 diabetes?

Key Findings

One before-after study was identified regarding the clinical effectiveness of intermittent fasting for adults with type 2 diabetes. Evidence of limited quality from this study suggested that two weeks of intermittent fasting significantly reduced body weight and body-mass index compared to a standard diet, but these differences were not retained after a two-week follow-up. No significant differences were reported for waist circumference, blood pressure or markers for inflammation (C-reactive protein) and insulin resistance (Homeostasis Model Assessment of Insulin Resistance). A positive relationship was found between the number of hours fasted and morning self-monitored glucose levels reaching target values, but this relationship was not found for afternoon or evening self-monitored glucose levels. Descriptively, the included study found reduced caloric, carbohydrate and fat intake, and higher physical activity levels during the intermittent fasting phase (intervention) when compared to standard diet at both baseline and follow-up phases. No evidence-based

guidelines for the use of intermittent fasting for adults with type 2 diabetes were identified. The limited evidence on this topic suggests further research comparing intermittent fasting to standard or low carbohydrate diets is needed in order to determine its place as an intervention for adults with type 2 diabetes.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were intermittent fasting and type 2 diabetes. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and October 17, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant publications were retrieved and assessed for inclusion. The final selection of full-text publications was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1&2: Adults (18 years or older) with type 2 diabetes
Intervention	Q1&2: Intermittent Fasting in all of its forms (i.e.,16 hour fast/8 hour eating window; weekly 24 hour fast; 24 hour fasting twice a week on different days [also known as 5:2 method]; alternate day fasting; one meal per day fast)
Comparator	Q1: Standard diet (e.g., regular eating habits with no restriction by food group); Low-carbohydrate diet Q2: Not applicable
Outcomes	Q1: Clinical effectiveness: glucose control (e.g., HbA1c levels, fasting plasma glucose), insulin sensitivity, reduction in drug/medication use, weight loss, weight gain, mortality, and morbidity, Safety (harms/risks/adverse events) Q2: Evidence-based guidelines
Study Designs	Q1: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled trials Q2: Guidelines

Exclusion Criteria

Publications were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2014. Case reports, case series, and guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included non-randomized study was critically appraised using the Risk of Bias for Nonrandomized Studies (RoBANS).[15] Summary scores were not calculated for the included

studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 235 citations were identified in the literature search. Following screening of titles and abstracts, 210 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 29 potentially relevant publications, 28 were excluded for various reasons, and one primary study met the inclusion criteria and was included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The non-randomized study included in this report used a prospective before-after pilot study design.[17] The study was designed as three two-week phases: baseline (phase 1), intervention (phase 2), and follow-up (phase 3).

Country of Origin

The included study was conducted in Canada.[17]

Population

The primary study included community-dwelling adults (aged 44 to 62 years) with a diagnosis of T2D.[17] All participants were taking metformin as a part of their daily diabetic management. To be eligible for the study, participants (i) must not have certain medical conditions including ischemic heart disease or heart failure, chronic inflammatory diseases, chronic infections, moderate to severe renal disease, uncontrolled hypertension and hypoglycemic unawareness; or (ii) must not have managed their T2D with insulin or glyburide due to their increased risk of hypoglycemia.[17]

Interventions and Comparators

Due to the nature of the included study's before-after design, the comparator of interest was normal dietary patterns (i.e., standard diet; breakfast, lunch and dinner) for the two-week period prior to the intervention (i.e., baseline, phase 1).[17] The intervention of interest was intermittent fasting using the time-restricted eating method for a two-week period with a fasting goal of 18 to 20 hours per day with zero-calorie coffee, tea, and water intake during fasting hours permitted (phase 2). During the feeding time, participants had no restrictions on what they ate, but were encouraged to include one third of their plate with protein to promote satiety. To explore retention effects, the study included a two-week follow-up period after the intervention phase where participants reverted back to their normal dietary patterns (phase 3).[17]

Outcomes

The included study investigated the following anthropometric, biochemical, and behavioural outcomes and measured after the end of each of the three time periods (baseline, intervention, follow-up): body weight, BMI, waist circumference, blood pressure, c-reactive protein (an inflammatory marker), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), self-monitoring of blood glucose (SMBG), daily hours fasted, caloric intake, and physical activity levels.[17] Biochemical (via fasted blood draws) and anthropometric measurements were measured and/or obtained by the same individual. SMBG was self-reported by participants using a logbook where SMBG levels were recorded and reported three times daily (fasting morning, random afternoon, and postprandial evening) using a glucometer. Total hours consecutively fasted per day was self-reported by the participants using a logbook. Caloric intake was also self-reported using the Remote Food Photography Method (RFPM), including a random three-day food diary within each phase. This method was used in this study to capture estimates of energy intake. Physical activity was recorded using the Yale Physical Activity Survey (YPAS). For all outcomes, a decrease in the measured values represented a clinical improvement in the respective outcome except for daily hours fasted and physical activity levels.[17]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Non-randomized study

The quality of evidence from the included non-randomized study[17] was assessed using the RoBANS checklist.[15] Overall, the quality of the included study was low.[17] Strengths of the study included prospectively collected data, outcomes measured using standard approaches (e.g., weight, BMI, blood tests) or with validated scales (RFPM) which reduces risk of confirmation bias due to inappropriate outcome assessment methods, and the study population was the same for both before and after the intervention reducing selection bias due to inappropriate comparison target group. Despite these strengths, there was no information provided to suggest that the study had a pre-specified protocol presenting uncertainty about selective outcome reporting bias. Participants were recruited by displaying posters in general practitioners' offices and hospitals along with advertisements in local newspapers and online increasing the chances of the study population being representative of the source population. Despite this, the small sample size of ten participants prevents the practicality of the participants being truly representative of the source population. There was also uncertainty about whether the outcome assessors were blinded to the study hypothesis or exposure to the intervention. Thus, the risk of confirmation bias due to inappropriate blinding of assessors was unclear. For most outcomes, all study participants had before and after data but there was missing data from participants for specific assessments, including comparison data for daily hours fasted and full SMBG log for ordinal logistic regression calculations (missing data for two participants) and follow-up data for food intake via the RFPM (missing data for six participants). Moreover, the number of hours fasted per day could have varied from participant-to-participant and day-to-day with participants having the goal of fasting for a period of 18 to 20 hours per day and was not a mandatory requirement. This scenario increases uncertainty about the risk of performance bias. In addition, certain outcomes relied on self-reported data, including hours fasted, SMBG, and caloric intake which increases the risk for recall and measurement error bias.[17] Because the included study used a before-after

design the researchers could not control for elements that are also changing at the same time as the intervention is implemented (e.g., physical activity), which generally limits the applicability of these results. Taken together, these limitations substantially decrease confidence in the results of this study.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Intermittent Fasting

One non-randomized study examined the clinical effectiveness of intermittent fasting for adults with T2D.[17] This study reported on several anthropometric, biochemical and behavioural outcomes at three time points: baseline (i.e., phase 1, two weeks after following standard diet), intervention (phase 2, two weeks after following intermittent fasting), and follow-up (phase 3, standard diet for two weeks after phase 2).[17]

Anthropometric outcomes

Body weight, BMI, waist circumference, and blood pressure were assessed in the included study.[17] Relative to following a standard diet, there was a significant reduction in body weight ($P = 0.009$) and BMI ($P = 0.01$) after two weeks of intermittent fasting compared to baseline values, but these changes were not retained at follow-up. There were also no significant differences between baseline and after follow-up, further suggesting no overall change from pre- to post-intervention. Moreover, there were no significant differences in waist circumferences or blood pressure (diastolic and systolic) for any comparison.[17]

Biochemical outcomes

C-reactive protein, HOMA-IR, and SMBG were measured in the included study.[17] Study authors found no significant differences in C-reactive protein and HOMA-IR for any comparison.[17] However, an increased fasting duration improved at-goal (< 7.0 mmol/L) morning SMBG levels 2.5-fold, from 13.8% at baseline (standard diet) to 34.1% as reported post-intervention (intermittent fasting) but was not maintained at follow-up (15.1%). There was a positive relationship between number of hours fasted and morning fasting glucose reaching target values ($P = 0.004$) but not for afternoon or evening SMBG (all $P > 0.1$). Postprandial SMBGs improved during intermittent fasting, with 60.5% readings below 9.05 mmol/L, compared to 52.6% at baseline and with less glucose variation but was not maintained at follow-up (54.1%).[17]

Behavioural outcomes

The included study explored daily hours fasted, caloric intake and exercise as behavioural outcomes.[17] Expectedly, the study found a significant increase in the number of hours fasted during the intermittent fasting phase versus baseline (standard diet, $P > 0.005$) and during intermittent fasting versus follow-up (standard diet, $P < 0.005$) but not between baseline and follow-up ($P = 0.09$). The authors descriptively reported that participants tended to have a lower caloric, carbohydrate, and fat intake during the intermittent fasting phase versus baseline (standard diet). Four of the 10 participants recorded their food intake at follow-up so these data could not be objectively compared. In addition, study authors described participants as having more physical activity during the intervention phase (intermittent fasting) compared to baseline (standard diet) or follow-up (standard diet), though no statistical testing was provided.[17]

Guidelines

No relevant evidence regarding intermittent fasting for adults with T2D was identified; therefore, no summary can be provided.

Limitations

Certain limitations are noteworthy when reviewing the report.

Limited evidence from one low quality clinical study[17] was identified regarding the clinical effectiveness of intermittent fasting compared to standard diet for adults with T2D. This was a pilot study with ten participants and not all outcomes of interest had complete follow up data for all participants. The incomplete data set compounded with a low initial sample size may suggest that the study is not sufficiently powered to detect significant differences in the explored outcomes. Moreover, the intervention was for two-weeks which may not be sufficiently long enough to observe a meaningful effect in the clinical outcomes explored. In the included study, some key outcomes were not explored, such as HbA1c levels (a measure of glucose control), reduction in medication use, mortality, and morbidity. All participants were taking metformin, most participants were taking other medications throughout the study, and physical activity was not controlled for, reflective of real-life conditions. However, the true effects of the intervention may be confounded by this for certain outcomes, including SMBG levels and weight-related outcomes (weight loss, BMI, waist circumference). This type of intermittent fasting method tested was a timed fasting approach with participants having the goal of fasting 18 to 20 hours. Future studies may want to consider having participants follow a more stringent regiment where participants must sustain a minimum number of hours in fasting state or comparing other methods of intermittent fasting, such as the twice-a-week method (5:2), alternate day fasting, and the 24 hour fast. In addition, this study compared intermittent fasting with a standard diet. Additional studies comparing intermittent fasting to a low carbohydrate diet are also needed. No relevant guidelines were identified further suggesting it is unclear if or how intermittent fasting should be incorporated as a dietary intervention for adults with T2D. These limitations warrant the use of caution when interpreting the findings of this report.

Conclusions and Implications for Decision or Policy Making

This report identified limited, low quality evidence about the clinical effectiveness of intermittent fasting for adults with T2D. No eligible guidelines were identified on this topic. This report, therefore, found less and lower quality evidence than the previous 2019 CADTH Rapid Response report[9] that summarized the clinical effectiveness and evidence-based guidelines regarding the use of a low carbohydrate diet for adults with T2D (10 SRs and four guidelines). This may be due to intermittent fasting being a more novel intervention for adults with T2D versus a low carbohydrate diet.

Regarding clinical effectiveness of intermittent fasting, one non-randomized pilot study[17] conducted in Canada was identified from the search. The study examined the effects of a short-term intermittent fasting regimen (i.e., two weeks) via several anthropometric, biochemical, and behavioural outcomes and the clinical findings varied. Compared to a standard diet, two-weeks of intermittent fasting significantly reduced body weight and BMI for study participants with T2D, but these differences were not maintained after a two-week follow-up. No significant differences were reported for waist circumference, blood pressure, C-reactive protein or HOMA-IR levels. The authors uncovered a positive relationship between the number of hours fasted and morning SMBG reaching target values, but this

relationship was not found for afternoon or evening SMBG levels. The study described participants having reduced caloric, carbohydrate and fat intake and higher physical activity levels during the intermittent fasting phase when compared to the standard diet phases (baseline and follow-up). As mentioned in the study's conclusions, findings are exploratory and larger, longer study is necessary to verify these findings. Thus, it is premature to draw conclusions about the comparative effectiveness of intermittent fasting versus a standard diet given the paucity of clinical evidence and inherent methodological flaws noted within the included study.

No eligible evidence-based guidelines were identified for intermittent fasting for adults with T2D; therefore, no conclusions regarding the recommended use of intermittent fasting can be provided. The 2018 Diabetes Canada Guidelines on nutrition therapy[18] considered intermittent fasting in its review of the evidence and states that there is a paucity of evidence regarding this dietary approach in patients with T2D. No recommendations specific to intermittent fasting for patients with T2D were provided; therefore, this guideline was not included in this Rapid Response report. However, the limited quantity of evidence identified for the guideline is consistent with the findings of this report.

Given the limited availability and low quality of evidence, the effectiveness and use of intermittent fasting for adults with T2D remains uncertain. Further comparative and high-quality research studies addressing intermittent fasting versus standard or low carbohydrate diets may help to reduce uncertainty.

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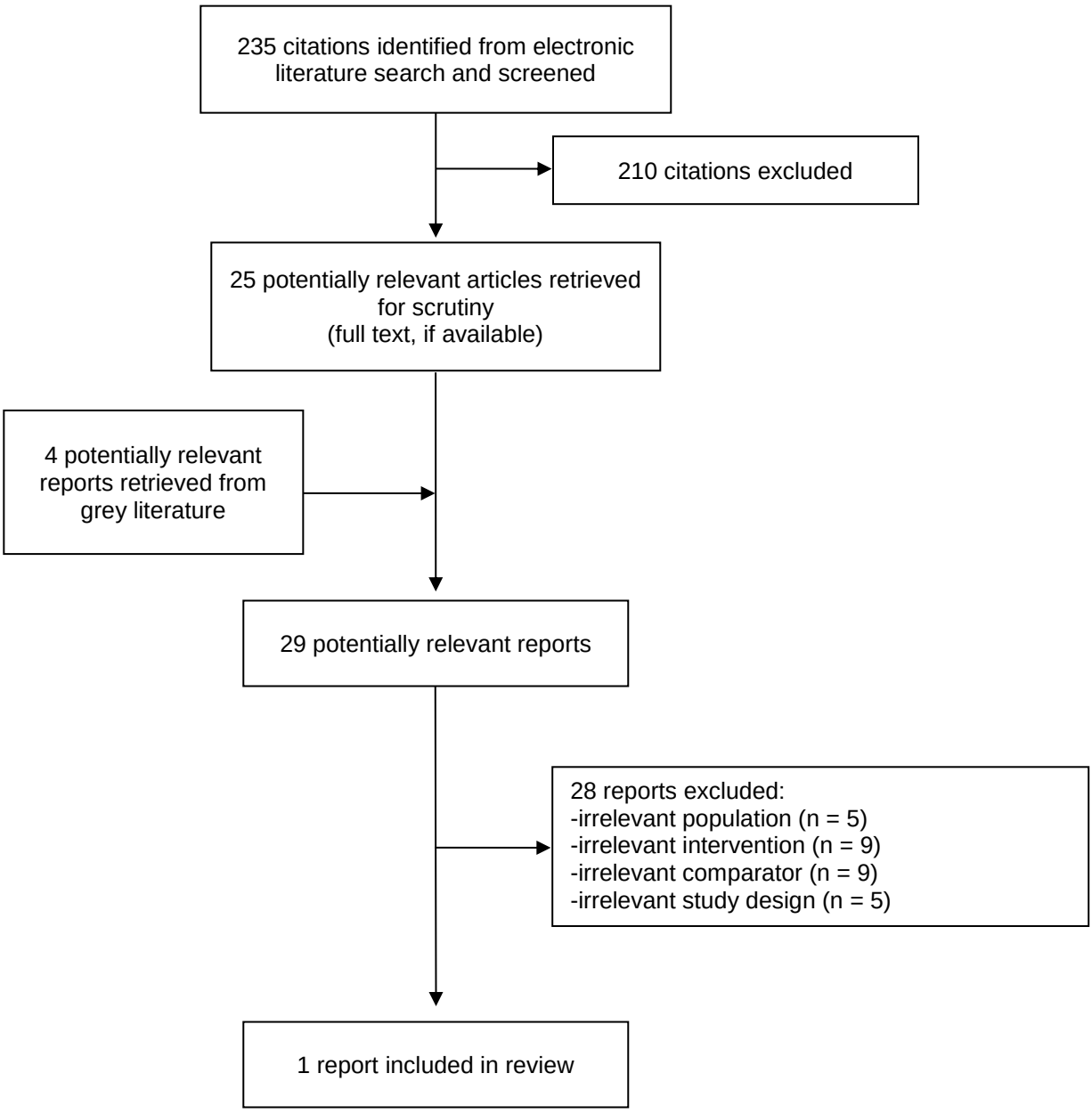
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publication

Table 2: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator	Clinical Outcomes, Length of Follow-Up
Arnason 2017[17] Canada	Prospective before-after pilot study	10 adults (44 to 62 years old) with a diagnosis of T2D, confirmed by fasting glucose > 7.0 mmol, HbA1c > 6.5%, or OGTT > 11.0 mmol (90.0% women; mean age ± SD = 53.8 ± 9.1 years; mean BMI ± SD = 36.9 ± 8.3 kg/m^2) Exclusion criteria: adults with certain medical conditions including ischemic heart disease or heart failure, chronic inflammatory diseases, chronic infections, moderate to severe renal disease, uncontrolled hypertension and hypoglycemic unawareness; adults who managed their T2D with insulin or glyburide due to their increased risk of hypoglycemia	Comparator: normal dietary patterns (breakfast, lunch and dinner; baseline or phase 1; 2 weeks) Intervention: intermittent fasting using the time-restricted method with a fasting goal of 18-20 hours per day with ad libitum zero-calorie coffee, tea, and water intake during fasting hours permitted (phase 2; 2 weeks)	<u>Anthropometric outcomes:</u> • Body weight (kg) • BMI (kg/m^2) • Waist circumference (cm) • Blood pressure (systolic, diastolic, mmHg) <u>Biochemical outcomes:</u> • C-reactive protein (mg/L) • HOMA-IR • SMBG (14-day average; SMBG pooled for morning or fasting, afternoon, and postprandial) <u>Behaviour outcomes</u>: • Daily hours fasted • Caloric intake (via food photography using Remote Food Photography Method) • Physical activity (via Yale Physical Activity Survey) Follow-up: 2 weeks (normal dietary patterns after completing intervention phase or phase 3)

BMI = body mass index; HbA1c = hemoglobin A1C; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; OGTT = oral glucose tolerance test; SMBG = self-monitoring of blood glucose; SD = standard deviation; T2D = type 2 diabetes.

Appendix 3: Critical Appraisal of Included Publication

Table 3: Strengths and Limitations of Primary Clinical Study using Risk of Bias for Nonrandomized Studies (RoBANS)[15]

Strengths	Limitations
Arnason (2017)[17]	
- This before-and-after study collected data prospectively, thereby reducing risk of bias. - Outcomes were measured using standard approaches (e.g., weight, BMI, blood tests) or with validated scales (RFPM), which reduces risk of confirmation bias due to inappropriate outcome assessment methods - The study population was the same for both before and after the intervention. Therefore, selection bias due to inappropriate comparison target group was low.	- It was unclear whether the study authors had a pre-specified protocol for the study presenting uncertainty about selective outcome reporting bias - Participants were recruited via posting posters in general practitioners' offices and hospitals as well as advertisements in local newspapers and online. However, no details were provided regarding where the 10 included participants were recruited from, which reduces the ability to understand if the study population is truly representative of the source population - For most outcomes, all study participants had before and after data. However, there was missing data from participants for specific comparisons (regression calculation comparing daily hours fasted and full SMBG log, food intake via RFPM), which increases the risk of attrition bias due to incomplete or missing data - The number of hours fasted per day could vary from person to person and day to day with the parameter being that participants had the goal of fasting for a period of 18-20 hour per day. Thus, there was uncertainty about the level of risk of performance bias. - It is unknown if the outcome assessors were blinded to the study hypothesis or exposure to the intervention. Thus, the risk of confirmation bias due to inappropriate blinding of assessors was unclear. - Certain outcomes relied on self-reported data (SMBG and behavioural outcomes) which increases the risk for recall and measurement error bias.

BMI = body mass index; SMBG = self-monitoring of blood glucose; RFPM = remote food photography method

Appendix 4: Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Arnason 2017[17]	
<u>Anthropometric outcomes</u> Body weight - Significant reduction after intervention[a] (mean ± SD = 99.2 ± 21.3 kg) compared to baseline[a] (100.6 ± 21.7 kg), mean difference = -1.4 kg, *P* = 0.009 - NS difference between intervention (99.2 ± 21.3 kg) and follow-up[a] (99.5 ± 21.5 kg), *P* = 1.0 - NS difference between baseline (100.6 ± 21.7 kg) and follow-up (99.5 ± 21.5 kg), *P* = 0.08 BMI - Significant reduction after intervention (36.4 ± 8.1 kg/m^2) compared to baseline (36.9 ± 8.3 kg/m^2), mean difference = -0.52 kg/m^2, *P* = 0.01 - NS difference between intervention (36.4 ± 8.1 kg/m^2) and follow-up (36.5 ± 8.1 kg/m^2), *P* = 1.0 - NS difference between baseline (36.9 ± 8.3 kg/m^2) and follow-up (36.5 ± 8.1 kg/m^2), *P* = 0.09 Waist circumference - NS difference between baseline (109.6 ± 11.1 cm) and intervention (107.8 ± 11.1 cm), *P* = 0.09 - NS difference between intervention (107.8 ± 11.1 cm) and follow-up (107.5 ± 10.9 cm), *P* = 1.0 - NS difference between baseline (109.6 ± 11.1 cm) and follow-up (107.5 ± 10.9 cm), *P* = 0.24 Systolic blood pressure - NS difference between baseline (130.0 ± 17.8 mmHg) and intervention (127.0 ± 21.4 mmHg) for systolic (*P* = 0.83) blood pressure - NS difference between intervention (127.0 ± 21.4 mmHg) and follow-up (128.5 ± 14.3 mmHg) for systolic blood pressure (*P* = 1.0) - NS difference between baseline (130.0 ± 17.8 mmHg) and follow-up (128.5 ± 14.3 mmHg) for systolic blood pressure (*P* = 1.0) Diastolic blood pressure - NS difference between baseline (80.5 ± 13.2 mmHg) and intervention (79.8 ± 15.7 mmHg) for diastolic blood pressure (*P* = 1.0) - NS difference between intervention (79.8 ± 15.7 mmHg) and follow-up (81.7 ± 12.2 mmHg) for diastolic blood pressure (*P* = 0.76) - NS difference between baseline (80.5 ± 13.2 mmHg) and follow-up (81.7 ± 12.2 mmHg) for diastolic blood pressure (*P* = 1.0) <u>Biochemical outcomes</u> C-reactive protein - NS difference between baseline (4.3 ± 3.8 mg/L) and intervention (4.0 ± 3.7mg/L), *P* = 0.9 - NS difference between intervention (4.0 ± 3.7 mg/L) and follow-up (4.1 ± 3.5 mg/L), *P* = 1.0	"The results from this pilot study indicate that short-term daily IF may be a safe, tolerable, dietary intervention in T2D patients that may improve key outcomes including body weight, fasting glucose and postprandial variability. These findings should be viewed as exploratory, and a larger, longer study is necessary to corroborate these findings." (p. 155)

Main Study Findings	Authors' Conclusion
- NS difference between baseline (4.3 ± 3.8 mg/L) and follow-up (4.1 ± 3.5 mg/L), *P* = 1.0 HOMA-IR - NS difference between baseline (6.9 ± 3.0) to intervention (6.5 ± 2.4), *P* = 1.0 - NS difference between intervention (6.5 ± 2.4) and follow-up (6.6 ± 3.0), *P* = 1.0 - NS difference between baseline (6.9 ± 3.0) and follow-up (6.6 ± 3.0), *P* = 1.0 SMBG - Positive relationship between number of hours fasted and (morning) fasting glucose reaching target values (χ^2 likelihood ratio 8.36, *P* = 0.004) but not for afternoon or evening SMBG (all *P* > 0.1) - The increased fasting duration improved at-goal (< 7.0 mmol/L) morning SMBG to 34.1%, from a baseline of 13.8% (2.5-fold difference) but was not maintained at follow-up (15.1%). - Postprandial SMBGs improved during intervention, with 60.5% readings below 9.05 mmol/L, compared to 52.6% at baseline, and with less glucose variation, but was not maintained at follow-up (54.1%) <u>Behavioural outcomes</u> Daily hours fasted - Significant increase in hours fasted when comparing baseline (11.6 ± 1.9 hours) and intervention (16.8 ± 1.2 hours), mean difference = +5.2 hours, *P* < 0.005 - Significant decrease in hours fasted when comparing intervention (16.8 ± 1.2 hours) and follow-up (11.5 ± 2.0 hours), -5.3 hours, *P* < 0.005 - NS difference between baseline (11.6 ± 1.9 hours) and follow-up (11.5 ± 2.0 hours), *P* = 0.09 Diet - Lower caloric intake during intervention (1605.7 ± 375.5 kcal/day) compared to baseline (1904.3 ± 404.1 kcal/day, significance testing not provided) - Lower carbohydrate intake during intervention (142.7 ± 62.1 g/day) compared to baseline (190.6 ± 58.5 g/day, significance testing not provided) - Lower fat intake during intervention (63.6 ± 25.2 g/day) compared to baseline (86.9 ± 16.6 g/day, significance testing not provided) - No difference in protein intake during intervention (93.2 ± 26.1 g/day) compared to baseline (94.2 ± 26.6 g/day, significance testing not provided) Exercise - Physical activity increased in intervention (6778.56 ± 4329.5 kcal/week), compared to baseline (4922.3 ± 3774.4 kcal/week, significance testing not provided) - Physical activity decreased at follow-up (4329.0 ± 3440.8 kcal/week) compared to intervention ((6778.56 ± 4329.5 kcal/week), significance testing not provided)	

BMI = body mass index; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; IF = intermittent fasting; NS = non-significant; SMBG = self-monitoring of blood glucose; SD = standard deviation; T2D = type 2 diabetes.

[a] baseline = phase 1 (standard diet; 2-weeks); intervention = phase 2 (IF, 2 weeks); follow-up = phase 3 (standard diet, 2 weeks)

Appendix 5: Additional References of Potential Interest

Unclear Intervention

Fasting until noon triggers increased postprandial hyperglycemia and impaired insulin response after lunch and dinner in individuals with type 2 diabetes: a randomized clinical trial. Diabetes Care. 2015 Oct;38(10):1820-6. https://www.ncbi.nlm.nih.gov/pubmed/26220945

King A, Clark D. Omitting late-night eating may cause hypoglycemia in "well controlled" basal insulin-treated type 2 diabetes. Endocrine Practice. 2014 Nov 4;21(3):280-5. https://www.ncbi.nlm.nih.gov/pubmed/25370327/

Consensus Reports and Guidelines with Unclear Recommendations

Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019 May;42(5):731-754. (American Diabetes Association). https://www.ncbi.nlm.nih.gov/pubmed/31000505 Ongoing Trials

Seth Leavitt. Biweekly Interval Intermittent Fasting for Type 2 Diabetes, a Safety Study. 2019 May 6. [last updated 2019 Jul 3]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT03938441 ClinicalTrials.gov Identifier: NCT03938441. Accessed 2019 Nov 13.

Conference Abstract

Fasting, Intermittent Fasting or Caloric Restriction as Nutritional Management of Adults With Type 2 Diabetes. A Systematic Review (Preliminary Results). IUNS 21st International Congress of Nutrition Buenos Aires, Argentina, October 15–20, 2017. https://www.karger.com/Article/PDF/480486 Accessed 2019 Nov 13.