Clinical Question

A.D. is a 45 yo M w/ a PMHx of HTN, HLD, GERD, and prediabetes presenting for an annual well visit. Pt reports a 15-lb weight gain over the past year and a BMI of 35. HbA1c is 6.3. Pt recently immigrated from India. He is seeking nutritional guidance to better control his A1c. States he has tried elimination diets, but does not enjoy American food and wants to continue eating his cultural food.

Pico Question:

In adults with prediabetes or type 2 diabetes, does intermittent fasting compared to continuous calorie restriction improve glycemic control as measured by HbA1c and fasting glucose?

PICO search terms:

Population	**Intervention**	**Comparison**	**Outcome**
Prediabetes	Intermittent fasting	Continuous caloric restriction	Hemoglobin A1C
Diabetes Mellitus Type 2	Time-restricted feeding	Daily caloric restriction	HbA1c
Adults	Alternate-day fasting	Standard diet	Fasting glucose
Insulin resistance	Fasting protocols	Caloric restriction	Glycemic control
			Insulin sensitivity

Search tools and strategy used:

Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

PubMed
Search Terms - ("Diabetes Mellitus, Type 2 OR "Insulin resistance" OR prediabetes OR "type 2 diabetes") AND ("Intermittent Fasting" OR "time-restricted feeding" OR "alternate day fasting" OR "fasting protocols") AND ("Caloric Restriction" OR "standard diet" OR "continuous calorie restriction" OR "daily caloric restriction")
AND ("Hemoglobin A1C" OR HbA1c OR "fasting glucose" OR "glycemic control" OR “insulin sensitivity”)
Results - 35
Filters- 2016-2026, meta-analysis

Science Direct
Search Terms - Intermittent fasting, glycemic control, diabetes
Results - 187
Filters- 2016-2026, meta-analysis

Google Scholar
Search Terms - "intermittent fasting" "glycemic control" "diabetes" "continuous caloric restriction" "meta analysis"
Results - 46
Filters - 2016-2026, meta-analysis

Cochrane Library
Search Terms - Diabetes, intermittent fasting, glycemic control
Results - 94
Filters- 2016-2026

Selection Criteria

My PICO question was my primary filter in my selection criteria. I only focused on studies that compared IF to CER and their effects on glycemic control. While I used 4 different search databases, ScienceDirect had a paywall, so I could not view full articles on that database. Therefore, I chose 2 papers from PubMed, 1 from Google Scholar, and 1 from Cochrane Library. The selections from Google Scholar and PubMed were straightforward because they met my filtering criteria, and they were meta-analyses or systematic reviews with large populations. The rationale for selecting the article from Cochrane Library was more nuanced, but I chose it because it is a single RCT. One of the shortcomings of meta-analysis and systematic reviews on dietary interventions is poor reliability due to heterogeneous interventions, controls, and poor reporting standardization. With a single RCT, you may have poor reporting, but your intervention and control are homogenous.

Articles Chosen

Citation	Semnani-Azad, Z., Khan, T. A., Chiavaroli, L., Chen, V., Bhatt, H. A., Chen, A., Chiang, N., Oguntala, J., Kabisch, S., Lau, D. C. W., Wharton, S., Sharma, A. M., Harris, L., Leiter, L. A., Hill, J. O., Hu, F. B., Lean, M. E. J., Kahleová, H., Rahelic, D., Salas-Salvadó, J., Kendall, C. W. C., & Sievenpiper, J. L. (2025). Intermittent fasting strategies and their effects on body weight and other cardiometabolic risk factors: Systematic review and network meta-analysis of randomised clinical trials. *BMJ, 389*, e082007.
Abstract	Objective To assess the effect of intermittent fasting diets, with continuous energy restriction or unrestricted (ad-libitum) diets on intermediate cardiometabolic outcomes from randomised clinical trials. Design Systematic review and network meta-analysis. Data sources Medline, Embase, and central databases from inception to 14 November 2024. Eligibility criteria for selecting studies Randomised clinical trials comparing the association of intermittent fasting diets (alternate day fasting, time restricted eating, and whole day fasting), continuous energy restriction, and ad-libitum diets were included. Main outcomes Outcomes included body weight (primary) and measures of anthropometry, glucose metabolism, lipid profiles, blood pressure, C-reactive protein, and markers of liver disease. Data synthesis A network meta-analysis based on a frequentist framework was performed with data expressed as mean difference with 95% confidence intervals (CIs). The certainty of the evidence was assessed using grading of recommendations assessment, development, and evaluation (GRADE). Results 99 randomised clinical trials involving 6582 adults of varying health conditions (720 healthy, 5862 existing health conditions) were identified. All intermittent fasting and continuous energy restriction diet strategies reduced body weight when compared

	with ad-libitum diet. Compared with continuous energy restriction, alternate day fasting was the only form of intermittent fasting diet strategy to show benefit in body weight reduction (mean difference −1.29 kg (95% CI −1.99 to −0.59), moderate certainty of evidence). Additionally, alternate day fasting showed a trivial reduction in body weight compared with both time restricted eating and whole day fasting (mean difference −1.69 kg (−2.49 to −0.88) and −1.05 kg (−1.90 to −0.19), respectively, both with moderate certainty of evidence). Estimates were similar among trials with less than 24 weeks follow-up (n=76); however, moderate-to-long-term trials (≥24 weeks, n=17) only showed benefits in weight reduction in diet strategies compared with ad-libitum. Furthermore, in comparisons between intermittent fasting strategies, alternate day fasting lowered total cholesterol, triglycerides, and non-high density lipoprotein compared with time restricted eating. Compared with whole day fasting, however, time restricted eating resulted in a small increase in total cholesterol, low density lipoprotein cholesterol, and non-high density lipoprotein cholesterol. No differences were noted between intermittent fasting, continuous energy restriction, and ad-libitum diets for HbA_{1c} and high density lipoprotein. **Conclusions** Minor differences were noted between some intermittent fasting diets and continuous energy restriction, with some benefit of weight loss with alternate day fasting in shorter duration trials. The current evidence provides some indication that intermittent fasting diets have similar benefits to continuous energy restriction for weight loss and cardiometabolic risk factors. Longer duration trials are needed to further substantiate these findings.
Link/PDF	https://pmc.ncbi.nlm.nih.gov/articles/PMC12175170/ - PDF on brightspace

Citation	Liu, F., Zhang, Z., Sun, W., & Li, T. (2025). The metabolic effects of intermittent fasting in patients with type 2 diabetes exist in the short term but disappear after its discontinuation: A systematic review and meta-analysis of randomized controlled trials. *Nutrition Research, 138*, 135–150.
Abstract	This meta-analysis aimed to determine the short- (< 3 months) and long-term (≥ 3 months) metabolic effects of IF in patients with type 2 diabetes. We hypothesized that IF is non-inferior to other dietary control methods (including continuous energy restriction, standard diet, Mediterranean diet and ad libitum diet) in terms of both short-term and long-term metabolic impacts in patients with type 2 diabetes. We searched for studies in the MEDLINE, EMBASE, and Cochrane Library until August 20, 2023. Studies with non-type 2 diabetes patients, interventions other than IF, no control group, or non-randomized clinical trial designs were excluded. A meta-analysis was then conducted with a random effects model. The Risk of Bias was assessed using the Cochrane risk-of-bias tool (ROB 2). 12 articles with a total of 966 participants were included. IF significantly decreased glycated hemoglobin A1c (HbA1c) (standardized mean difference [SMD]: –0.93; 95% confidence interval [CI]: –1.64, –0.22; P = 0.01), fasting plasma glucose (FPG) (SMD: –0.73; 95% CI: –0.92, –0.54; P < 0.00001) and body weight (SMD: –1.11; 95% CI: –1.92, –0.31; P

	= 0.007) in the short term compared to control interventions, but showed a similar effect to control interventions in the long term. Substantial heterogeneity existed among our studies. Over the intervention period, long-term IF may safely and feasibly help patients with type 2 diabetes effectively manage blood sugar and reduce body weight, but the metabolic benefits of IF don't endure after its discontinuation. Therefore, continual long-term IF may provide more lasting metabolic benefits.
Link/PDF	https://www.sciencedirect.com/science/article/pii/S0271531725000600?via%3Dihub - PDF on brightspace

Citation	Sharma, S. K., Mudgal, S. K., Kalra, S., Gaur, R., Thakur, K., & Agarwal, R. (2023). Effect of intermittent fasting on glycaemic control in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *touchREVIEWS in Endocrinology, 19*(1), 25–32.
Abstract	**Background:** Type 2 diabetes mellitus (T2DM) is a severe public health issue notably impacting human life and health expenditure. It has been observed in literature that intermittent fasting (IF) addresses diabetes and its underlying cause, which benefits people with diabetes. Therefore, this study aimed to evaluate the effectiveness of IF treatment on glycaemic control in people with T2DM compared with control group. **Methods:** Systematic review and meta-analysis of interventional studies among patients with T2DM with glycated haemoglobin (HbA1c) as an outcome was performed. A comprehensive search of electronic databases, including PubMed, Embase and Google Scholar, for articles published before 24 April 2022, was done. Studies reporting 24 hours of complete fasting or intermittent restricted energy intake (feeding permitted for only 4–8 hours daily, with 16–20 hours of fasting) and reporting changes in HbA1c and fasting glucose levels were eligible. Meta-analysis was performed using Cochrane's Q statistic and the I_2 statistical approach. **Results:** Eleven studies (13 arms) measuring the effect of IF on patients' HbA1c level were analysed. There was no statistically significant difference between IF and control groups (Standardized mean difference [SMD] -0.08, 95% confidence interval [CI] -0.20 to 0.04;p=0.19, I_2=22%). Overall, seven studies on patients' fasting blood glucose were analysed, and the meta-analysis revealed no significant difference between the two groups i.e. IF and control groups (SMD 0.06, 95% CI -0.25 to 0.38;p=0.69, I_2=76%). **Conclusion:** IF and usual diet pattern have no difference in terms of glycaemic control. Although, IF may be used as a preventative diet pattern in the pre-diabetic population, as it works well in the long-term to achieve controlled sugar levels. Study registration: The protocol of this study was registered in The International Prospective Register of Systematic Reviews (PROSPERO) with a registration number CRD42022328528.
Link/PDF	https://pmc.ncbi.nlm.nih.gov/articles/PMC10258621/ - PDF on Brightspace

Citation	Carter, S., Clifton, P. M., & Keogh, J. B. (2018). Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: A randomized noninferiority trial. *JAMA Network Open, 1*(3), e180756.
Abstract	**Importance** Intermittent energy restriction is an alternative weight loss method that is becoming popular; however, to date, there are no long-term clinical trials of intermittent energy restriction in patients with type 2 diabetes. **Objective** To compare the effects of intermittent energy restriction (2 days per week) with those of continuous energy restriction on glycemic control and weight loss in patients with type 2 diabetes during a 12-month period. **Design, Setting, and Participants** Adult participants (N = 137) with type 2 diabetes were randomized 1:1 to

	parallel diet groups (intermittent energy restriction [n = 70] or continuous energy restriction [n = 67]) between April 7, 2015, and September 7, 2017, at the University of South Australia. Medications likely to cause hypoglycemia were reduced at baseline according to the medication management protocol. **Interventions** An intermittent energy restriction diet (500-600 kcal/d) followed for 2 nonconsecutive days per week (participants followed their usual diet for the other 5 days) or a continuous energy restriction diet (1200-1500 kcal/d) followed for 7 days per week for 12 months. **Main Outcomes and Measures** The primary outcome was change in hemoglobin A_{1c} (HbA_{1c}) level, with equivalence prespecified by a 90% CI margin of ±0.5%. The secondary outcome was weight loss with equivalence set at ±2.5 kg (±1.75 kg for fat mass loss and ±0.75 kg for fat-free mass loss). All other outcomes were tested for superiority. **Results** Of the 137 randomized participants (77 women and 60 men; mean [SD] age, 61.0 [9.1] years; mean [SD] body mass index, 36.0 [5.8] [calculated as weight in kilograms divided by height in meters squared]; and mean [SD] HbA_{1c} level, 7.3% [1.3%]), 97 completed the trial. Intention-to-treat analysis showed similar reductions in mean (SEM) HbA_{1c} level between the continuous and intermittent energy restriction groups (–0.5% [0.2%] vs –0.3% [0.1%]; *P* = .65), with a between-group difference of 0.2% (90% CI, –0.2% to 0.5%) meeting the criteria for equivalence. Mean (SEM) weight change was similar between the continuous and intermittent energy restriction groups (–5.0 [0.8] kg vs –6.8 [0.8] kg; *P* = .25), but the between-group difference did not meet the criteria for equivalence (–1.8 kg; 90% CI, –3.7 to 0.07 kg), nor did the between-group difference in fat mass (–1.3 kg; 90% CI, –2.8 to 0.2 kg) or fat-free mass (–0.5 kg; 90% CI, –1.4 to 0.4 kg). There were no significant differences between groups in final step count, fasting glucose levels, lipid levels, or total medication effect score at 12 months. Effects did not differ using completers analysis. Hypoglycemic or hyperglycemic events in the first 2 weeks of treatment were similar between the continuous and intermittent energy restriction groups (mean number [SEM] of events, 3.2 [0.7] vs 4.9 [1.4]; *P* = .28), affecting 35% of participants (16 of 46) using sulfonylureas and/or insulin. **Conclusions and Relevance** Intermittent energy restriction is an effective alternative diet strategy for the reduction of HbA_{1c} and is comparable with continuous energy restriction in patients with type 2 diabetes.
Link/PDF	https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2688344 - PDF on brightspace

Summary of the Evidence

Author (Date)	**Level of Evidence**	**Sample/Setting**	**Outcome(s) Studied**	**Key Findings**	**Limitations and Biases**
Semnani-Azad et al. (2025)	Level 1: Systematic review + network meta-analysis	**99 RCTs** **N=** 6,582 **Populations:** DM2, DM1, Obesity, metabolic syndrome, NAFLD **Median age:** 45 **Median BMI:** 31.3 **Median follow-up**: 12 weeks (3-52) **Setting:** mixed, primarily outpt and community-based clinical trial settings	**Primary:** Body weight **Secondary:** HbA1c Fasting glucose, Fasting insulin, HOMA-IR (insulin resistance), Lipid profile, Blood pressure, Inflammatory markers (CRP), Liver enzymes (ALT)	**Diabetic subgroup:** ***Weight loss -*** Alternate day fasting (ADF) showed the greatest weight loss (−4.42 kg vs ad-libitum) ADF showed ~1.29 kg more weight loss than CER ***Glycemic markers -*** IF showed reductions in fasting glucose over CRE. IF showed no clear HbA1c advantage over CER. **HbA1c:** no significant difference IF vs continuous energy restriction (CER) **Fasting glucose:** IF showed reductions in fasting glucose over ad-libitum (at will) eating. IF showed no difference in fasting glucose vs CER **HOMA-IR (Insulin resistance):** IF showed a small improvement over ad-libitum eating. IF showed no difference vs CER **ADF-specific benefits:** greater benefits to lipid profiles and reductions in blood pressure across all interventions	**1. Heterogeneity:** - different fasting protocols - IF, ADF - different calorie goals for CRE diets - different dietary composition of diets **2. Short durations** - median f/u of 12 weeks - only 5 trials >52 weeks - only 17 trials had >24 week f/u - HbA1c reflects 3-month glucose control, which may not be captured in a 12 week f/u - Short durations limit sustained benefits and control of DM progression **3. Adherence** - dropped significantly in long-term studies (one study had 74% at 6 weeks drop to 22% at 52 weeks) - adherence is always an issue w/ dietary trials **4. Indirect population** - Only 11 studies specifically looked at DM2
Liu, Zhang, Sun, & Li (2025)	Level 1: Systematic review + meta-analysis	**12 RCTs** **N=** 966 **Population:** adults w/ DM2 **Setting:** primarily an outpatient clinic **Median age:** n/a **Median BMI:** n/a **Median follow-up**: n/a	**Glycemic control:** HbA1c, fasting plasma glucose (FPG), fasting insulin **Anthropometrics:** body weight, BMI, fat mass, and fat-free mass **Lipids:** HDL, LDL, TG, total cholesterol **Blood pressure:** SBP and DBP	**Short-term effects(<3 months) of IF compared to Control** ***HbA1c:*** significant decreases (standardized mean difference (SMD) –0.93, 95% CI –1.64 to –0.22) ***FPG:*** significant decreases (SMD –0.73, 95% CI –0.92 to –0.54) ***Weight:*** significant decreases (SMD –1.11, 95% CI –1.92 to –0.31) **Long-term effects(≥3 months) of IF compared to Control** ***HbA1c:*** not statistically significant (SMD –0.35, 95% CI –0.85 to 0.15) ***FPG:*** not statistically significant (SMD –0.15, 95% CI –0.35 to 0.04) ***Weight:*** not statistically significant (SMD –0.23, 95% CI –0.59 to 0.13) **Duration Interpretation:** IF interventions found modest A1C reductions, but those	**1. Heterogeneity** - There are various "controls" that IF was compared to. Controls include: CER, ad libitum diets, and the Mediterranean diet - Different study durations (7 days to 52 weeks) **2. Sample Sizes** - Several studies w/ small sample sizes - increased risk of random error - Small studies tend to show larger treatment effects and can skew the pooled data **3. Short follow-ups** - Many f/u periods ≤12 weeks, not adequately capturing A1C **4. Biases** - Cannot be blinded due to dietary intervention -> slight performance bias possible - Publication bias may be present. The authors found an asymmetric funnel plot (smaller contrary studies

				benefits fade after IF discontinuation.	may be excluded, and large studies showing benefit included)
Sharma, S. K. (2023)	Level I: Systematic review + meta-analysis	**11 RCTs** **N=** 879 adults w/ DM2 **Age:** 45-65 yo **Duration:** 8 weeks to 12 months **Setting:** primarily outpt clinic	**Primary:** Glycemic control via A1C and FBG **Secondary:** weight, lipid profile, and HOMA-IR	**Glycemic Control:** ***A1C:*** IF vs. control showed a reduction of SMD −0.08, (95% CI: −0.20 to 0.04), which is not statistically significant. I^2 = 22%, indicating low heterogeneity and more reliability. ***FBG:*** IF vs. control showed a reduction of SMD 0.06 (95% CI: −0.25 to 0.38), which is not statistically significant. I^2 = 76%, indicating high heterogeneity and lower reliability **Age differences*:*** IF vs control in participants ≤60 years was statistically significant as seen by SMD −0.20, 95% CI: −0.39 to −0.01. I^2 = 24%, representing low heterogeneity and higher reliability. This indicates IF may have additional benefits for younger patients.	**1. Heterogeneity** - Different IF protocols including TRF, ADF, Intermittent energy restriction (2-day/week severe restriction), and Very low-calorie diets (400–600 kcal/day) - This makes glycemic control outcomes inconsistent **2. Small sample size** - 879 participants across 11 studies, with a range of 33 - 137 participants per study - Smaller study sizes can lead to overrated intervention effects in meta-analyses **3. Variable intervention duration** - Range from 8 weeks to 12 months - Shorter studies may not capture changes in A1C **4. Gaps in clinical application** - most studies did not include insulin-dependent patients - We can't derive if IF is safe for pts on insulin from this data. We can assume a higher risk of hypoglycemia w/ IF
Carter, S (2018)	Level 1, Randomized, non-inferiority clinical trial	**N=**137 adults w/ DM2 **Mean age:** 61 yo **Mean BMI:** 36 **Setting:** Outpt research clinic **f/u period:** 12 months	**Primary:** Glycemic control via HbA1c and Fasting plasma glucose (FPG) **Secondary:** Weight loss, Fat mass / fat-free mass, Lipid profile, Medication effect score (MES), Hypoglycemic/hyperglycemic events, and physical activity via step count	**Glycemic control:** ***A1C:*** CER had a greater reduction -0.5% than IF -0.3%. But the IF reduction is non-inferior bc it falls w/in +-0.5% margins ***FPG:*** similar between groups **Secondary outcomes** ***Weight loss:*** IM group had greater loss (-6.8kg) compared to CER (-5.0 kg) ~36% more weight loss. Not statistically significant, though, just a trend ***Medication effect score (MES):*** Both groups reduced medication needs, but the IF group had a greater reduction in insulin use. Despite a reduction in insulin use, A1C reduction was non-inferior. ***Safety:*** similar hypoglycemia and hyperglycemia rates between groups. Common concern w/ IF is hypoglycemic episodes, but with proper medication adjustments, the rates were similar between groups.	**1. Free-living design** - Diet adherence was self-reported, a major point of potential error - Caloric intake could easily be misreported **2. Medication confounding:** - insulin-dependent participants in the IF group had insulin reductions -> this adds a confounding variable which potentially influences A1C independent of diet **3. High dropout rate** - 40/137 participants did not complete the study, increasing the risk of attrition bias **4. Population/Selection bias** - Baseline glycemic control was good w/ a mean A1C of 7.3% - Study does not reflect pts w/ poorly controlled DM2

<u>Conclusions:</u> Briefly summarize the conclusions of each article, then provide an overarching conclusion.

<u>Semnani-Azad et al. (2025)</u>: This is one of the largest studies analyzing the effects of fasting on cardiometabolic health, including subgroups w/ DM pts. IF showed some improvements over CER in glycemic control, but not a clear benefit in the A1C. An interesting secondary finding was that ADF produces the greatest weight loss out of the interventions tested.

<u>Zhang, Sun, & Li (2025):</u> This study focused on the effect that IF duration had on glycemic control and outcomes. The authors found that IF has a statistically significant benefit over other control w/in a 3-month period. When the IF practice is discontinued, the additional benefit fades. If IF is continued past 3 months, the additional benefit may continue.

<u>Sharma, S. K. (2023):</u> This study found no statistically significant benefit of IF over standard interventions. It also highlights the high heterogeneity of IF protocols included in studies, decreasing the strength of conclusions. These findings do suggest a statistically significant benefit w/ IF for patients <60 yo.

Carter, S. (2018): This non-inferiority RCT found that IF is non-inferior to CER, while CER saw a .2% greater reduction in A1C overall. Secondary outcomes found greater weight loss and reduction in medication needs (especially insulin) w/ IF. Reduction in insulin use may be a major clinical net benefit. Concerns still remain over hypoglycemic episodes. The certainty is limited due to a free-living setting and a moderate attrition rate.

<u>PICO Question:</u> In adults with prediabetes or type 2 diabetes, does intermittent fasting compared to continuous calorie restriction improve glycemic control as measured by HbA1c and fasting glucose?

<u>Clinical Bottom Line:</u> In adults w/ DM2, IF is a viable alternative strategy for achieving glycemic control, but it is not superior to CRE in reducing A1C long term. Some studies suggest superior glycemic control w/ IF during short-term bursts of 3 months or less, but the effect diminishes when IF protocols are stopped. IF protocols may have additional glycemic control in pts <60. Insulin-dependent pts may see additional benefits w/ IF due to reduced long-term insulin exposure.

<u>Weight of the evidence –</u> summarize the weaknesses/strengths of the articles and explain how they factored into your clinical bottom line (this may recap what you discussed in the criteria for choosing the articles)

1. Semnani-Azad et al. (2025)
This network meta-analysis of 99 RCTs and 6,582 participants is one of the largest studies of its kind ever performed, making its conclusions a significant contribution to the literature. Most IF studies suffer from small sample sizes, leading to population outcome bias, but the large size of this study overcomes that. These factors greatly contribute to the clinical bottom line, showing that IF and fasting protocols are well-studied interventions w/ non-inferior clinical outcomes. The weakness of the study and its application to my PICO topic is the heterogeneity of the population, including pts w/ DM2, DM1, metabolic syndrome, and obesity.

2. Zhang, Sun, & Li (2025)
This meta-analysis of 12 RCTs and 966 participants is more specific to my PICO question, synthesizing a vast amount of information specific to DM2 patients. I ranked it second because while it is more specific than the Semnani study, it is a smaller body of work. The contributions to the clinical bottom line provide a more nuanced perspective on the intervention, showing that IF provides non-inferior and potentially superior benefits in the first 3 months, but those benefits fade when the intervention is discontinued. This additional information may aid a pt in selecting which intervention best fits their long-term goals. The weakness of this study includes heterogeneity of control interventions and small sample sizes, potentially skewing positive findings.

3. Carter, S. (2018):

This is a single RCT including 137 patients in a free-living design. Free-living designs have pros and cons, but the major pro here is that it simulates "regular patient lifestyle." This provides real-life population insight compared to a tightly controlled ward design. While RCTs are high-level evidence, this study ranks third because it is not as high-level as a systematic review or meta-analysis. While this study also shows IF non-inferiority, it provides additional benefit to the clinical bottom line; IF can allow medication deprescribing (especially insulin), providing additional options for clinicians and patients in their medical decision-making.A significant drawback of this study is the high dropout rate (40/137) and self-reporting bias.

4. Sharma, S. K. (2023)
Including 11 RCTs and 879 participants w/ DM2, these are high-level data that directly answer my PICO question. It is ranked last due to its high heterogeneity (I = 76%), which decreases its reliability. The data show the non-inferiority of IF for glycemic control. Its unique contribution to the clinical bottom line is IF's potential additional control for pts <60yo. Again, its heterogeneity and overall lack of statistical significance diminish an IF recommendation as a 1st line intervention over CRE.

<u>Magnitude of any effects</u>

1. Semani-Azad et al. (2025): No significant difference in A1C control between IF and CER. ADF shows significant benefit in weight control over CER (-1.29kg 95% CI −1.99 to −0.59), but does not show a clear advantage in glycemic control.

2. Zhang, Sun, & Li (2025): Shows a statistically significant reduction in A1C w/ IF (SMD -0.93) compared to CER. This benefit is typically short-term and fades when IF interventions are stopped.

3. Carter, S. (2018): A1C reduction of -0.5% w/ CER vs. -0.3% w IF. While CER shows a greater reduction, IF is statistically non-inferior.

4. Sharma, S. K. (2023): No statistical difference between A1C outcomes between IF and CRE groups (SMD -0.08, 95% CI −0.20 to 0.04). Potential benefit for pts <60 with IF.

<u>Clinical significance (not just statistical significance)</u>

The data show that IF is a non-inferior intervention for glycemic control compared to traditional CER. Providers can feel comfortable in recommending IF as one possible tool for DM patients who are struggling to achieve their clinical outcomes. It's important to recognize the pros, cons, and needed adjustments that come w/ an IF protocol, as the intervention may not fit everyone's lifestyle. Personalized clinical design making is important when recommending IF. The data show there may be additional glycemic control for pts <60 yo. The data also show that insulin-dependent pts may benefit from improved weight loss due to reduced insulin exposure. Alternatively, there is an increased risk of hypoglycemia with IF, a very important consideration for our DM pts. For pts who view IF as a miracle cure, it is also important to note that the protocol is not superior to CRE.

Perhaps the greatest barrier to glycemic control and metabolic health present across all interventions is long-term adherence. The intervention that a patient can adhere to long-term provides more benefit than something they can only maintain in short-term bursts. Good clinical care is not just about finding an intervention that provides the greatest clinical benefit, but an intervention that fits easily into the patient’s lifestyle. Pts will have different experiences with IF, but for those who prefer it, providers can recommend it as a sound intervention.

Any other considerations important in weighing this evidence to guide practice - Dietary studies are some of the most difficult to perform in medicine. That is because the gold standard for a dietary RCT would require pts to live in a metabolic ward long term; their BMR, caloric expenditure, and every calorie consumed would be tightly regulated and monitored by researchers. Performing a long-term metabolic ward study of that type is too costly and unethical. While the body of data on IF is expanding, the current data all share similar shortcomings: heterogeneity of IF protocols, heterogeneity of controls, inconsistent reporting, and small sample sizes. It is difficult to recruit large numbers of patients for fasting studies. Dietary studies are typically plagued by high dropout rates, such as the 40/137 seen in the Carter analysis. Despite these shortcomings, the current evidence clearly shows that IF is non-inferior to CRE.

While studies such as the Semani-azad et al study represent the forefront of research on this topic, more studies are needed to draw definitive conclusions. Moving forward, a large-scale meta-analysis with true homogeneity would allow for more definitive conclusions to be drawn. New tools such as CGMs would aid in tightly monitoring glycemic outcomes in future studies.