Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 DiabetesA Randomized Noninferiority Trial

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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.

Follow Up: At 12 months Intention-to-treat analysis showed an increase in mean [SEM] HbA1c level at 24 months in both the continuous and intermittent groups (0.4% [0.3%] vs 0.1% [0.2%] respectively; P=0.32) (4.4 [3.3mmol/mol] vs 1.1 [2.2mmol/mol]; P=0.32), with a between-group difference of 0.3% (90% CI, -0.31 to 0.83%) (3.3mmol/mol [90% CI, -3.2 to 9.1mmol/mol]) outside the prespecified boundary of ±0.5% (5.5mmol/mol), so statistical equivalence was not shown. Weight loss was maintained (P<0.001) at -3.9kg [1.1kg] in both groups at 24 months, with a between-group difference of 0.07kg (90% CI, -2.5 to 2.6kg) outside the prespecified boundary of ±2.5kg. There were no significant differences between groups in body composition, fasting glucose levels, lipid levels, or total medication effect score at 24 months, which remained less than baseline.

Trial Registration anzctr.org.au Identifier: ACTRN12615000383561