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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

The effect of intermittent compared with continuous energy restriction on glycaemic control in patients with type 2 diabetes: 24-month follow-up of a randomised noninferiority trial

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ARTICLE INFO

Article history:
Received 12 December 2018
Received in revised form
11 February 2019
Accepted 14 March 2019
Available online 19 March 2019

Keywords:
Type 2 diabetes mellitus
Intermittent energy restriction
Intermittent fasting
Obesity
Weight loss

ABSTRACT

Aims: We investigated the effects of intermittent compared to continuous energy restriction on glycaemic control in patients with type 2 diabetes mellitus.

Methods: Adults (N = 137) with type 2 diabetes (mean [SD] HbA1c level, 7.3% (56 mmol/mol) [1.3%] [14.2 mmol/mol]) were randomised to one of two diets for 12 months. The intermittent group (n = 70) followed a 2100–2500 kJ (500–600 kcal) diet 2 non-consecutive days/week and their usual diet for 5 days/week. The continuous group (n = 67) followed a 5000–6300 kJ (1200–1500 kcal) diet for 7 days/week. Follow-up occurred at 24 months, 12 months after the completed intervention. The primary outcome was change in HbA1c and the secondary outcome was weight loss.

Results: 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 [3.3 mmol/mol] vs 1.1 [2.2 mmol/mol]; $P = 0.32$), with a between-group difference of 0.3% (90% CI, −0.31 to 0.83%) (3.3 mmol/mol [90% CI, −3.2 to 9.1 mmol/mol]) outside the prespecified boundary of ± 0.5% (5.5 mmol/mol), so statistical equivalence was not shown. Weight loss was maintained ($P < 0.001$) at −3.9 kg [1.1 kg] in both groups at 24 months, with a between-group difference of 0.07 kg (90% CI, −2.5 to 2.6 kg) outside the prespecified boundary of ±2.5 kg. 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.

Conclusions: In this prospective analysis weight loss was maintained but despite this HbA1c increased to above baseline levels in both groups.

1. Introduction

Diabetes is a major public health problem affecting 422 million adults worldwide and imposes a significant economic burden on the global healthcare system (US$ 827 billion annually) [1–2]. Type 2 diabetes is the most common form of diabetes contributing to 90% of the cases and is strongly related to weight gain in adult life. The vast majority of

Abbreviations: HbA1c, glycated haemoglobin A1c

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https://doi.org/10.1016/j.diabres.2019.03.022
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patients with type 2 diabetes are overweight or obese; therefore achieving long-term weight management is essential to diabetes treatment.

Intermittent energy restriction is an alternative weight loss method defined as short periods of severe energy restriction interspersed with normal energy intake. It has been suggested that because this method offers a reduced burden of dietary restriction and shows promise in achieving weight loss goals, it may be a useful alternative to standard continuous weight loss diets [3–5]. Reviews of the literature comparing continuous with intermittent energy restriction have demonstrated similar weight loss in both groups, often attributed to the similar weekly energy restriction [3–9]. However, there have been few studies to date investigating the effects of intermittent compared to continuous energy restriction in people with type 2 diabetes [10–14] and the available long-term maintenance data is limited [14].

The aim of these analyses was to determine the effects of a 2-day intermittent energy restriction diet compared with continuous energy restriction in people with type 2 diabetes at 24-month follow-up, 12 months after the completed intervention. Specifically, the primary outcome was change in HbA1c level and the secondary outcome was weight loss and body composition changes.

2. Subjects, materials & methods

2.1. *Study methods*

As previously reported, a 12-month randomised controlled trial was conducted to determine the effect of a 2-day intermittent energy restriction diet compared with continuous energy restriction in a cohort of people with type 2 diabetes [11]. Briefly, participants were randomised 1:1 to treatment groups, stratified by sex and body mass index (as obese or non-obese). Participants randomised to the intermittent energy restriction group followed a diet of 2100 to 2500 kJ/day (500–600 kcal/day) for 2 days of the week and followed their usual diet for the other 5 days. Participants in the continuous energy restriction group followed a diet of 5000 to 6300 kJ/day (1200–1500 kcal/day) (45% carbohydrate, 30% protein and 25% fat) [15]. Both groups received written dietary information booklets with portion advice and sample menus; no food or meal replacements were provided. Dietary counselling was provided by a dietitian (S.C.) and occurred every 2 weeks for the first 3 months and every 2 to 3 months for the final 9 months. Written informed consent was obtained from each subject included in the study. The study protocol was approved by the University of South Australian Human Research Ethics Committee and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000383561).

After the end of this 12-month trial, participants were followed-up again 12 months later (24 months after baseline) for measurement of HbA1c, body composition and a fasting blood sample.

2.2. *Participants*

Participants were >18 years of age with diagnosed type 2 diabetes of any duration managed with diet, oral hypoglycaemic agents (OHA) and/or insulin and who were overweight or obese (body mass index $\geq$27). Participants reported being otherwise healthy with blood pressure of <160/100 mm Hg, not pregnant or breastfeeding with no previous weight loss surgery. Participants were recruited from April 2015 until September 2017 using flyers posted in public places and via advertisements in print and broadcast media.

2.3. *Measurements*

The primary outcome was change in HbA1c level measured using a point-of-care immunoassay analyser (DCA Vantage Analyser, Siemens Healthcare Diagnostics). The secondary outcome was change in body weight measured (barefoot while wearing light clothing) on calibrated digital scales in the fasted state (minimum, 8 h). Body composition was measured by dual-energy x-ray absorptiometry (Lunar iDXA, Getz Healthcare) by a licensed radiation technician. Exploratory outcomes included daily step count; participants were contacted one week before their follow-up appointment and ask to monitor steps using a waistband pedometer (G-sensor, Pocket Pedometer, Walking With Attitude). Medication effect score (MES) was used to quantify medication changes. The MES is calculated as (actual drug dose/maximum drug dose) $\times$ drug mean adjustment factor [16]. Blood samples were obtained to measure fasting glucose and lipid levels using Konelab analysis (Konelab 20XTi, Thermo Electron Corporation) at the University of South Australia.

2.4. *Sample size*

The original randomised controlled trial was powered to demonstrate equivalence in HbA1c levels between groups with a sample size of 104 participants: $P < 0.05$ with 80% power and a 90% CI boundary of ±0.5% (5.5 mmol/mol). For weight, a very similar number was required, using a boundary limit of ±2.5 kg (±1.75 kg for fat mass and ±0.75 kg for fat-free mass). All other measures were exploratory, and we had no hypothesis with regard to equivalence, so only superiority tests were performed.

2.5. *Statistical analysis*

Data are presented as mean ± standard error of the mean with a 2-sided 90% CI, including the equivalence margin, unless otherwise stated. Independent samples t-tests and Pearson chi-squared tests were used to analyse differences between groups at baseline. Change over time, differences between treatments, and time by treatment interactions were assessed on an intention-to-treat basis, including data from all 137 participants who underwent randomisation under a missing-at-random assumption tested using a linear mixed model and from 84 completers using repeated-measures analysis of variance. Pearson correlation was used to determine independent factors associated with major outcome measures at 24 months. Analyses were performed using SPSS, version 25 (IBM SPSS Statistical Software) and graphs were generated using Microsoft Excel 2016 for Windows (Microsoft Inc). A 2-tailed $P < 0.05$ was considered statistically significant.

3. Results

A total of 137 participants were recruited, 97 participants completed the 12-month intervention phase (71%) and 84 were followed up at 24 months (61%) (Fig. 1). Loss to follow-up was not different between the diet groups ($P = 0.86$). Table 1 shows the baseline characteristics of all participants randomised as well as the participants that attended and did not attend the follow-up. There were no differences in baseline characteristics by randomisation. The participants that were followed up at 24 months were on average older at baseline compared with those who did not attend (62 ± 9 years vs. 59 ± 10 years; $P = 0.03$) and had lower HbA1c (7.1 ± 1.1% vs. 7.7 ± 1.4%; $P = 0.006$) (54 ± 12 mmol/mol vs. 61 ± 15.3 mmol/mol), BMI (35 ± 4.8 kg/m^2 vs. 39 ± 6.7 kg/m^2; $P = 0.005$), body fat percentage (42 ± 7.1% vs. 45 ± 6.4%; $P = 0.02$), body fat in kilograms (39 ± 8.6 kg vs. 44 ± 9.8 kg; $P = 0.02$) and android fat in kilograms (4.4 ± 1.0 kg vs. 4.9 ± 1.3 kg; $P = 0.01$). It is important to note that none of the participants were following the diets at 24 months. Most participants reported following parts or principles from the diets, e.g. occasionally using intermittent energy restriction or watching portion sizes in the continuous energy restriction group to help maintain weight.

3.1. *Glycaemic control*

Measures of change in glycaemic control from baseline to 24-month follow-up are presented in Table 2 and Fig. 2. HbA1c and fasting plasma glucose were similar to baseline levels ($P = 0.14$ and $P = 0.46$ respectively) with HbA1c increasing above baseline levels in both groups. Total medication dose reduction was maintained over time ($P = 0.004$) and was not correlated to HbA1c ($r = -0.2$; $P = 0.16$). MES for insulin change was significantly different between groups at 24 months (-0.2 [0.1] in the continuous group vs −0.6 [0.2] in the intermittent group; $P = 0.002$) but this did not account for any difference in HbA1c ($r = −0.1$; $P = 0.6$). HbA1c results did not differ using completers analysis (Table 3). Of the 84 participants at follow-up, HbA1c level remained stable for 4 participants (0.05%) increased for 57 (68%) participants, and decreased for 22 (26%) participants.

3.2. *Weight maintenance*

Measures of change in weight maintenance from baseline to 24-month follow-up are presented in Table 2 and Fig. 2. At 24-months, weight loss was maintained ($P < 0.001$) as was

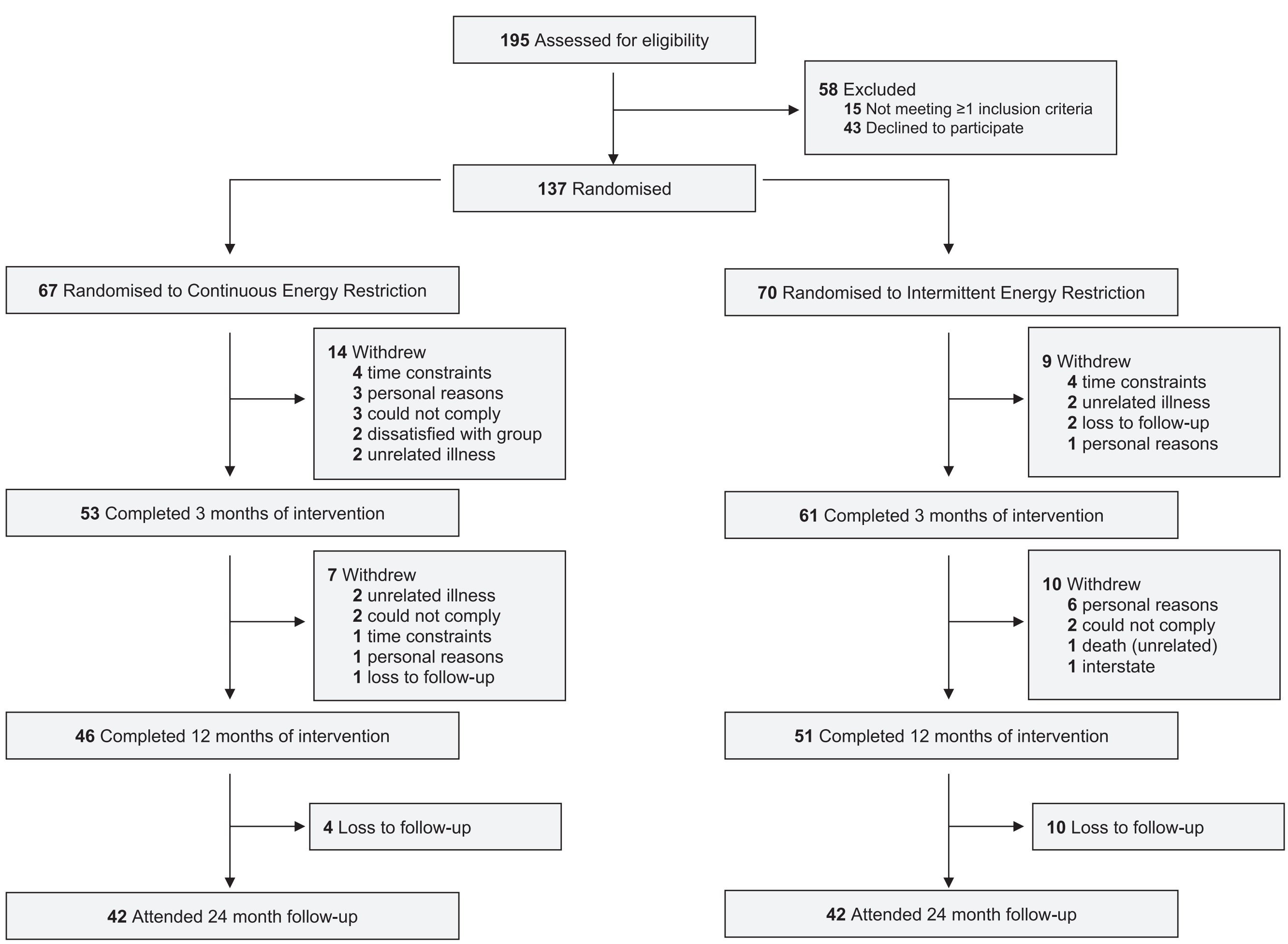


Fig. 1 – Flow Diagram.

Table 1 – Baseline Characteristics[a].

Characteristics	Mean (SD) Value				
	Continuous (n = 67)	Intermittent (n = 70)	All Participant (N = 137)	Attended at 24-months (n = 84)	Did Not Attend at 24-months (n = 53)
Age, y	61 (9.2)	61 (9.0)	61 (9.1)	62 (8.5)	59 (9.6)
Gender, n (%)					
Female	38 (57)	39 (56)	77 (56)	42 (50)	35 (47)
Male	29 (43)	31 (44)	60 (44)	42 (50)	18 (34)
Glycaemic Control					
HbA_{1c}, %	7.5 (1.4)	7.2 (1.2)	7.3 (1.3)	7.1 (1.1)	7.7 (1.4)
HbA_{1c}, mmol/mol	58 (15.3)	55 (13.1)	56 (14.2)	54 (12)	61 (15.3)
FPG, mmol/L	8.8 (2.5)	8.3 (2.6)	8.5 (2.3)	8.4 (2.1)	8.9 (2.8)
Duration of diabetes, y	8.1 (6.5)	7.9 (5.9)	8 (6.2)	7.8 (6.0)	8.4 (6.6)
Diabetes Medications, n (%)					
Diet	20 (30)	18 (26)	38 (28)	25 (30)	13 (25)
OHA	39 (68)	43 (61)	82 (60)	41 (49)	30 (57)
Insulin	14 (21)	14 (20)	28 (20)	11 (13)	6 (11)
Medication Effect Score					
OHA	1.4 (0.8)	1.3 (0.8)	1.4 (0.8)	1.3 (0.8)	1.5 (0.7)
Insulin	1.5 (1.1)	1.8 (1.1)	1.6 (1.1)	1.5 (1.0)	1.9 (1.4)
Total	1.8 (1.1)	1.7 (1.3)	1.8 (1.2)	1.7 (1.3)	1.9 (1.0)
CVD risk markers					
Lipid-lowering medication, n (%)	41 (61)	46 (66)	87 (64)	55 (65)	32 (60)
Total cholesterol, mmol/L	5.0 (1.7)	4.6 (1.3)	4.8 (1.5)	4.9 (1.6)	4.7 (0.7)
HDL cholesterol, mmol/L	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)
LDL cholesterol, mmol/L	3.0 (1.3)	2.8 (1.1)	2.9 (1.2)	2.9 (1.3)	2.7 (0.7)
Triglycerides, mmol/L	1.9 (1.4)	1.5 (0.7)	1.7 (1.1)	1.7 (1.2)	1.6 (0.8)
Body weight and composition					
Weight, kg	102 (17)	100 (19)	101 (18)	98 (14)	106 (21)
BMI, kg/m^2	37 (5.7)	35 (5.8)	36 (5.8)	35 (4.8)	38 (6.7)
Total Body Fat, %	44 (6.6)	42 (7.3)	43 (7.0)	42 (7.1)	45 (6.4)
Total Fat Mass, kg	42 (9.1)	40 (9.4)	41 (9.3)	39 (8.6)	44 (9.8)
Total FF Mass, kg	54 (9.5)	54 (9.8)	54 (9.6)	54 (9.6)	53 (9.6)
Android Fat, %[b]	52 (5.6)	51 (6.1)	52 (5.9)	51 (6.1)	53 (5.3)
Android Fat Mass, kg	4.8 (1.2)	4.4 (1.1)	4.6 (1.2)	4.3 (1.0)	4.9 (1.3)
Android FF Mass, kg	4.3 (0.9)	4.2 (0.8)	4.2 (0.8)	4.2 (0.8)	4.3 (1.0)
VAT, kg	2.5 (0.9)	2.2 (0.9)	2.3 (0.9)	2.3 (0.9)	2.5 (0.9)
Physical activity					
Activity count, steps/day	5889 (2893)	6800 (3187)	6363 (3071)	6320 (3036)	6463 (3191)

Abbreviations: HbA_{1c}, glycated haemoglobin A1c (to convert NGSP to IFCC; IFCC = (10.93 * NGSP) – 23.50); FPG, fasting plasma glucose; MES, medication effects score (MES = (actual drug dose/maximum drug dose)*drug mean adjustment factor); OHA, oral hypoglycaemic agents; HDL, high-density lipoprotein; LDL, low density lipoprotein; BMI, body mass index; FF, fat-free; VAT, visceral adipose tissue.

[a] Data were analysed using independent samples *t*-test (for continuous variables) and chi-squared test (for categorical variables) and given as mean (SD).

[b] Android fat % is the percent fat of tissue in the android region.

Table 2 – Primary, Secondary and Exploratory Outcomes by Time Point and Change from Baseline to 24-months for Intermittent vs. Continuous Groups (Intention-to-Treat Analysis)[a].

	Mean (SEM)				P Value for Time	Mean (SEM) [95% CI]		P Value for Diet by Time
Variables	Baseline	3 Months	12 Months	24 Months		Continuous	Intermittent	
HbA_{1c}, %	7.3 (0.1)	6.7 (0.1)	6.9 (0.1)	7.6 (0.2)	<0.001	0.4 (0.3) [−0.2 to 0.9]	0.1 (0.2) [−0.3 to 0.5]	0.32
HbA_{1c}, mmol/mol	56 (1.1)	50 (1.1)	52 (1.1)	60 (2.2)	<0.001	4.4 () −2.2 to 9.8]	1.1 (2.2) [−3.3 to 5.5]	0.32
FPG, mmol/L[b]	8.5 (0.2)	7.5 (0.2)	7.5 (0.2)	8.2 (0.3)	<0.001	−0.3 (0.6) [−1.6 to 1.0]	−0.2 (0.5) [−1.2 to 0.8]	0.45
MES OHA[c]	1.4 (0.1)	1.2 (0.1)	1.1 (0.1)	1.1 (0.1)	<0.001	−0.2 (0.1) [−0.4 to 0.03]	−0.2 (0.1) [−0.5 to −0.01]	0.49
MES Insulin[d]	1.7 (0.2)	1.1 (0.2)	0.9 (0.2)	1.2 (0.2)	<0.001	−0.2 (0.1) [−0.5 to 0.02]	−0.6 (0.2) [−1.2 to −0.1]	0.002
MES Total[e]	1.8 (0.2)	1.4 (0.1)	1.3 (0.1)	1.4 (0.1)	<0.001	−0.2 (0.1) [−0.5 to 0.1]	−0.4 (0.2) [−0.7 to −0.1]	0.15
Total Cholesterol, mmol/L[f]	4.8 (0.1)	4.3 (0.1)	4.4 (0.1)	4.6 (0.1)	<0.001	−0.3 (0.2) [−0.9 to 0.2]	0.03 (0.2) [−0.3 to 0.4]	0.12
HDL−C, mmol/L[f]	1.2 (0.04)	1.1 (0.03)	1.2 (0.04)	1.1 (0.04)	0.001	−0.08 (0.06) [−0.2 to 0.04]	−0.1 (0.06) [−0.2 to 0.02]	0.15
LDL−C, mmol/L[f]	2.9 (0.1)	2.5 (0.1)	2.6 (0.1)	2.9 (0.1)	<0.001	−0.2 (0.2) [−0.6 to 0.3]	0.2 (0.2) [−0.2 to 0.5]	0.13
Triglycerides, mmol/L[f]	1.7 (0.1)	1.3 (0.06)	1.4 (0.08)	1.6 (0.1)	<0.001	−0.2 (0.3) [−0.7 to 0.3]	−0.02 (0.2) [−0.3 to 0.3]	0.49
Weight, kg	101 (1.5)	95 (1.5)	95 (1.5)	97 (1.5)	<0.001	−3.9 (1.1) [−6.0 to −1.7]	−3.9 (1.1) [−6.1 to −1.7]	0.19
BMI, kg/m^2	36 (0.5)	34 (0.5)	34 (0.5)	35 (0.5)	<0.001	−1.4 (0.4) [−2.2 to −0.7]	−1.3 (0.4) [−2.1 to −0.6]	0.26
Total Body Fat, %[g]	43 (0.6)	41 (0.8)	40 (0.9)	41 (1.0)	0.01	−2.6 (1.4) [−5.4 to 0.3]	−2.3 (1.8) [−6.0 to 1.3]	0.83
Total Fat Mass, kg[g]	41 (0.8)	36 (0.9)	36 (1.1)	37 (1.1)	<0.001	−3.7 (1.9) [−7.4 to 0.1]	−5.1 (2.1) [−9.3 to −1.0]	0.71
Total FF Mass, kg[g]	54 (0.9)	53 (0.9)	53 (1.0)	53 (1.1)	0.78	0.6 (2.0) [−3.3 to 4.5]	−2.8 (2.0) [−6.7 to 1.1]	0.69
Android Fat, %[g], [h]	52 (0.5)	48 (0.8)	48 (0.9)	49 (1.0)	<0.001	−2.6 (1.4) [−5.4 to 0.1]	−3.0 (1.8) [−6.7 to 0.7]	0.48
Android Fat Mass, kg[g]	4.6 (0.1)	3.8 (0.1)	3.8 (0.1)	3.9 (0.1)	<0.001	−0.6 (0.2) [−1.1 to −0.1]	−0.8 (0.2) [−1.3 to −0.4]	0.69
Android FF Mass, kg[g]	4.2 (0.1)	4.0 (0.1)	4.0 (0.1)	3.9 (0.1)	0.05	−0.1 (0.2) [−0.5 to 0.2]	−0.4 (0.2) [−0.8 to −0.1]	0.49
VAT, kg[g]	2.3 (0.1)	1.9 (0.1)	2.1 (0.1)	2.3 (0.1)	0.003	−0.01 (0.2) [−0.4 to 0.4]	−0.1 (0.2) [−0.5 to 0.3]	0.90
Step count[i]	6344 (276)	7812 (366)	7192 (364)	6505 (360)	<0.001	575 (549) [−513 to 1663]	−204 (551) [−1298 to 891]	0.05

Abbreviations: HbA_{1c}, glycated haemoglobin A1c; FPG, fasting plasma glucose; MES, medication effects score (MES = (actual drug dose/maximum drug dose) * drug mean adjustment factor); OHA, oral hypoglycaemic agents; HDL, high-density lipoprotein; LDL, low density lipoprotein; BMI, body mass index; FF, fat-free; VAT, visceral adipose tissue.

[a] Data were included for 137 participants (67 in the continuous energy restriction group and 70 in the intermittent energy restriction group) unless otherwise stated: mean (SEM) and 95% CI were estimated using an intention-to-treat analysis with a linear mixed model.

[b] For a total of 110 participants (51 in the continuous energy restriction group and 59 in the intermittent energy restriction group). Missing declined venepuncture or missing blood sample at baseline.

[c] For a total of 96 participants (46 in the continuous energy restriction group and 50 in the intermittent energy restriction group) using OHA.

[d] For a total of 28 participants (14 in the continuous energy restriction group and 14 in the intermittent energy restriction group) using insulin.

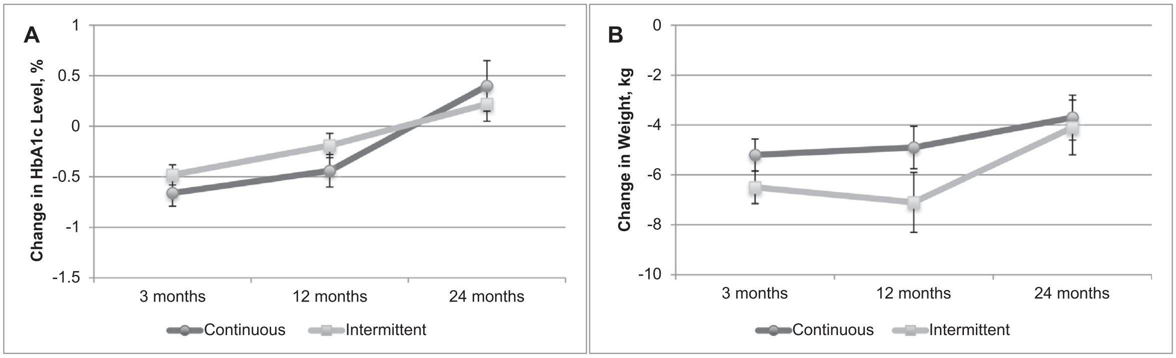
[e] For a total of 99 participants (47 in the continuous energy restriction group and 52 in the intermittent energy restriction group) using OHA and insulin.

[f] For a total of 101 participants (46 in the continuous energy restriction group and 55 in the intermittent energy restriction group). Missing declined venepuncture or missing blood sample at baseline or changed lipid medication during trial.

[g] For a total of 128 participants (64 in the continuous energy restriction group and 64 in the intermittent energy restriction group). Missing with weight >130 kg or who declined dual-energy x-ray absorptiometry scan.

[h] Percentage fat of tissue in the android region.

[i] For a total of 119 participants (57 in the continuous energy restriction group and 62 in the intermittent energy restriction group) using a pedometer.



A. Change in HbA1c Level; **B**. Change in Weight

Fig. 2 – Change in HbA1c Level and Weight from Baseline to 24-months for the Intermittent vs Continuous Groups (Completers Analysis).

total body fat loss ($P = 0.002$) with total lean mass remaining stable ($P = 0.78$). Weight at 24 months was directly correlated to HbA1c change between 12 and 24 months ($r = 0.3$, $P < 0.001$) but HbA1c increased above baseline between 12 and 24 months regardless of weight loss at 24 months (0.6% [0.2%] weight loss vs. 0.8% weight gain; $P = 0.53$). In the completers analysis, of the 84 participants at follow-up, 18 (21%) were weight stable (≤1 kg weight loss or gain) and 44 (52%) regained weight (>1 kg weight gain) 31 (37%) continued to lose weight; weight maintenance did not differ between groups using completers analysis (Table 3). There was however a difference in change between groups for total fat-free mass at 24 months (Table 3), which was highly correlated to weight change at 24 months for the intermittent group only ($r = 0.6$; $P < 0.001$). More participants in the intermittent group lost > 10% body weight (n = 8 vs n = 2) and these participants had a greater total fat-free mass loss compared to the continuous group (−4.9 kg [0.6 kg] intermittent vs −2.1 kg [0.3 kg] continuous; $P = 0.06$). Comparing this to participants who lost >5% but <10% body weight, total fat-free mass loss was similar in both groups (−2.0 kg [0.8 kg] intermittent and −2.1 kg [0.6 kg] continuous; $P = 0.9$). fat-free mass did not differ between groups when expressed as a mean (SEM) percentage of weight lost (38% [38%] in the continuous energy restriction group and 55% [32%] in the intermittent energy restriction group; P = 0.7).

3.3. *Serum lipids*

Measures of total cholesterol, LDL-C and triglycerides at 24-months were not significantly different from baseline (P = 0.40, P = 0.8, P = 0.7 respectively) but HDL was reduced ($P = 0.02$) (Table 2).

3.4. *Activity*

Step count remained above baseline levels at 24-months in the continuous group but was below baseline in the intermittent group (Table 2). Despite this, total step count was still similar in both groups at 24 months (6464 [5 1 6] steps in the continuous group vs 6596 [3 6 0] steps in the intermittent group; $P = 0.69$). Weight change between 12 and 24 months was significantly correlated with step change (r = -0.3; P = 0.02).

3.5. *Equivalence testing*

For the primary outcome, the mean between-group difference in the change in HbA1c level from baseline to 24 months was 0.3% (90% CI, −0.31 to 0.83%) (3.3 mmol/mol [90% CI, −3.2 to 9.1 mmol/mol]), which is outside the prespecified boundary of ± 0.5% (5.5 mmol/mol), so statistical equivalence has not been shown. Analysis of the secondary outcome did not demonstrate equivalence. The mean between-group difference in weight change was 0.07 kg (90% CI, −2.5 to 2.6 kg), which is close to but outside the prespecified boundary of ± 2.5 kg. The mean between-group difference in change was 1.5 kg (90% CI, −3.2 to 6.1 kg) for fat mass and 3.4 kg (90% CI, −1.2 to 8.0 kg) for fat-free mass, both outside the prespecified boundary of ± 1.75 kg for fat mass and ± 0.75 kg for fat-free mass, so statistical equivalence has not been shown.

4. Discussion

In this follow-up study, HbA1c had increased by 0.3% (3.3 mmol/mol) from baseline at 24 months. Similarly, a 10-year retrospective study found patients with stable HbA1c (<7%, 53 mmol/mol) experience increases to their HbA1c every year by 0.3% (3.3 mmol/mol) [17]. In the United Kingdom Prospective Diabetes Study, regardless of the type of treatment, conventional diet treatment vs intensive medication therapy, HbA1c reduced initially but then gradually increased even with continued treatment [18]. Beta cell function declines linearly with time, which is a well-known contributing factor to reduced treatment efficacy [19]. Similar results were found in this study, with HbA1c level increasing in participants who continued to lose weight and at a similar rate to those who gained weight ($P = 0.53$). Wing et al tested an intermittent very-low-calorie diet within a continuous energy restriction compared to continuous restriction on its own and showed that even when weight loss was maintained over 2 years, improvements in HbA1c levels were not maintained [20]. Although change in medication was not related to

Table 3 – Primary and Secondary Outcomes From Baseline to 24-months for Intermittent vs. Continuous Groups (Completers Analysis)[a].

Variables	Mean (SEM) [95% CI]	*P* Value for Time	Mean (SEM) [95% CI]		*P* Value for Diet by Time
			Continuous	Intermittent	
HbA$_{1c}$, %	0.3 (0.2) [-0.01 to 0.6]	<0.001	0.4 (0.3) [−0.1 to 0.9]	0.2 (0.2) [−0.1 to 0.6]	0.28
HbA$_{1c}$, mmol/mol	3.3 (2.2) [−0.1 to 6.6]	<0.001	4.4 (3.3) [−1.1 to 9.8]	2.2 (2.2) [−1.1 to 6.6]	0.28
Weight, kg	−3.9 (0.7) [−5.3 to −2.5]	<0.001	−3.7 (0.9) [−5.6 to −1.9]	−4.1 (1.1) [−6.3 to −1.9]	0.26
Weight, kg[b]	−4.0 (0.8) [−5.6 to −2.4]	<0.001	−3.6 (1.0) [−2.4 to 4.0]	−4.4 (1.3) [−4.9 to 0.4]	0.14
Total Body Fat, %[c]	−1.1 (0.5) [−2.1 to −0.07]	<0.001	−1.3 (0.7) [−2.6 to 0.05]	−0.9 (0.8) [−2.6 to 0.7]	0.16
Total Fat Mass, kg[c]	−2.5 (0.7) [−3.9 to −1.1]	<0.001	−2.6 (1.0) [−4.6 to −0.7]	−2.3 (1.0) [−4.4 to −0.3]	0.15
Total FF Mass, kg[c]	−1.5 (0.3) [−2.0 to −1.0]	<0.001	−0.8 (0.3) [−1.4 to 0.1]	−2.2 (0.4) [−3.1 to −1.4]	0.02
Android Fat, %[c], [d]	−2.0 (0.8) [−3.7 to −0.4]	<0.001	−2.2 (1.0) [−4.3 to −0.06]	−1.9 (1.3) [−4.5 to 0.7]	0.08
Android Fat Mass, kg[c]	−0.5 (0.1) [−0.7 to −0.3]	<0.001	−0.5 (0.1) [−0.8 to −0.2]	−0.5 (0.1) [−0.8 to −0.2]	0.22
Android FF Mass, kg[c]	−0.2 (0.05) [−0.3 to −0.1]	<0.001	−0.1 (0.08) [−0.2 to 0.08]	−0.3 (0.04) [−0.4 to −0.2]	0.06
VAT, kg[c]	0.01 (0.07) [−0.1 to 0.1]	<0.001	−0.01 (0.1) [−0.2 to 0.2]	0.04 (0.1) [−0.2 to 0.3]	0.32

Abbreviations: HbA$_{1c}$, glycated haemoglobin A1c; BMI, body mass index; FF, fat-free; VAT, visceral adipose tissue.

[a] Data were included for 84 participants (42 in the continuous energy restriction group and 42 in the intermittent energy restriction group) unless otherwise stated: mean (SEM) and 95% CI were estimated with repeated-measures ANOVA.

[b] Weight change for the 67 participants with DEXA data.

[c] For a total of 67 participants (34 in the continuous energy restriction group and 33 in the intermittent energy restriction group). Missing with weight>130 kg or who declined dual-energy x-ray absorptiometry scan.

[d] Percentage fat of tissue in the android region.

change in HbA1c the use of medication at 24 months was still less than at baseline, so this is a factor in the difference in HbA1c from baseline. Between 12 and 24 months participants were under the care of their personal general practitioners or endocrinologists for medication management.

In this study, participants regained 33% of their weight lost between 12 and 24-month, a result that is not uncommon. Participants in the Look Ahead Study regained approximately 25% of their weight lost between years 1 and 2 [21]. Similar results have been found in other intermittent vs continuous restriction follow-up studies. Ash et al. found that both intermittent and continuous restriction groups regained weight and HbA1c increased as a result to levels slightly above baseline at 18-month follow up [14]. Our results confirm this and indicate that without ongoing intervention and dietetic support a regression of glycaemic control and weight gain is likely irrespective of type of treatment, results that are supported by the literature [22,23]. We speculate that those participants who maintained weight loss adjusted to the overall reduced energy requirement. In addition to this, participants reported occasionally implementing diet principles to assist with weight maintenance.

There was some discrepancy in total fat-free mass change between groups using ITT compared to completers analysis. Using completers analysis, the intermittent group lost significantly more fat-free mass at 24 months compared to the continuous group ($P = 0.02$). This result is in direct contradiction to previous findings supporting better fat-free mass preservation using intermittent compared to continuous energy restriction [5]. In this study, loss of fat-free mass was highly correlated to weight change at 24 months ($r = 0.6$; $P < 0.001$) and the difference likely due to the greater fat-free mass loss for participants in the intermittent group who lost >10% body weight. In addition to this, when expressed as a percentage of weight lost, fat-free mass percentage change did not differ between groups. It is important to note that step change was not correlated to fat-free mass loss.

Although changes to HbA1c and weight were statistically similar between groups, due to the large within-group variability equivalence could not be demonstrated. Intermittent energy restriction may be superior to continuous energy restriction for HbA1c and weight maintenance, although a sample population of >300 participants would be required to demonstrate superiority with 80% power. Attrition over the duration of the study means the estimates at 24 months are less reliable. It is important to note that participants in this study represent a highly motivated population sample that may not represent the wider population. Subjects were asked to monitor steps one week prior to their 24-month follow-up appointment. Although participants were asked to maintain their usual activity, it is possible that some participants may have altered their activity in view of their re-evaluation and this may have had an affect on both glycaemic control and body composition.

The results of this study demonstrate that the use of intermittent energy restriction as a treatment method for patients with type 2 diabetes is as effective as using a continuous energy restriction. We speculate that ongoing dietetic support is likely more important than the type of dietary intervention and that this should not be overlooked in the long-term treatment of chronic lifestyle conditions.

Conflict of interest

None.

Sources of support

SC was supported by a University of South Australia Postgraduate award. PMC was supported by a National Health and Medical Research Council principal research fellowship.

Authors' contributions

SC, PMC and JBK designed research and analysed data. SC conducted research and wrote paper. PMC and JBK (guarantor) had primary responsibility for final content and critically reviewed the manuscript.

Acknowledgments

We would like to thank all participants and the staff of the Sansom Institute for Health Research.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.022.

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