Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation

Flash glucose monitoring for the safe use of a 2-day intermittent energy restriction in patients with type 2 diabetes at risk of hypoglycaemia: An exploratory study

S. Carter, P.M. Clifton *, *J.P. Keogh*

School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia
Alliance for Research in Exercise, Nutrition and Activity, University of South Australia, Adelaide, South Australia, Australia

ARTICLE INFO

Article history:
Received 20 December 2018
Received in revised form
28 March 2019
Accepted 2 April 2019
Available online 5 April 2019

Keywords:
Type 2 diabetes mellitus
Intermittent energy restriction
Medication management
Insulin
Sulphonylureas

ABSTRACT

Aims: Two medication change protocols were tested, both based on haemoglobin A1c (HbA1c), with one protocol also accounting for hypoglycaemic events. The aim was to compare the two protocols during intermittent energy restriction (5:2 diet).

Methods: Forty-two adults with type 2 diabetes (HbA1c ≥ 7% [53 mmol/mol], BMI of ≥27 kg/m^2) treated with sulphonylureas and/or insulin were recruited and randomised 1:1 to fixed or adjusted medication protocols. Participants experiencing hypoglycaemia during a 2-week usual diet period then followed the 5:2 diet for 2 weeks (2 non-consecutive very-low-calorie days [500–600 kcal] and 5 habitual eating days/week), following the allocated medication protocol. The primary outcome was to determine if the adjusted protocol was superior to the fixed protocol at reducing hypoglycaemic events during the 5:2 diet. Flash glucose monitoring was used throughout to detect hypoglycaemia.

Results: There was a significant difference in change in the number of hypoglycaemic events between fixed and adjusted protocols (−1.0 vs. −3.5; $P = 0.04$). Over 60% of participants on the adjusted protocol had no hypoglycaemic events.

Conclusions: This pilot study demonstrates the importance of assessing the risk of hypoglycaemia before starting a 5:2 diet and that the adjusted medication protocol is likely the best option for patients at risk.

Clinical trial registry: This study has been registered with the Australia New Zealand Clinical Trial Registry (ANZCTR) www.anzctr.org.au and given the registration number ACTRN12617000512325.

Abbreviation: HbA1c, glycated haemoglobin A1c

* Corresponding author at: GPO Box 2471, Adelaide, SA 5000, Australia.
E-mail address: peter.clifton@unisa.edu.au (P.M. Clifton).

https://doi.org/10.1016/j.diabres.2019.04.013
0168-8227/

1. Introduction

Type 2 diabetes is a progressive condition closely linked to the epidemic of obesity and requires long-term medication management to limit the development of a wide range of complications [1]. To combat the rising rates of type 2 diabetes worldwide and the significant economic burden [2] there is a need for new treatment methods that are safe and effective.

Conventional daily calorie restriction regimes are still the most common diet strategies used for weight loss [3] and although effective, some individuals find daily calorie restriction difficult to adhere to long term [4,5]. Interest has been focused on intermittent energy restriction as an alternative weight loss method as it offers a reduced burden of dietary restriction [6] and shows promise in achieving weight loss goals [7,8]. Intermittent energy restriction uses very-low-calorie restriction on some days of the week with ad libitum energy intake on others with the schedule varying from several hours of restriction per day to several days per week [9]. There have been few studies to date investigating the effects intermittent energy restriction in people with type 2 diabetes [10–14] and fewer again using medication likely to cause hypoglycaemia (sulphonylurea and/or insulin) [10–12]. A type of intermittent energy restriction, known as the 5:2 diet, has been shown to be an effective alternative treatment method comparable to moderate continuous energy restriction for both weight loss and blood glucose control in people with type 2 diabetes [10,11]. The method involves 2 days of very-low-calorie intake (500–600 kcal) [2100–2500 kJ/day] and 5 days of ad libitum eating per week but the best approach for medication management while using this method in people using medications likely to cause hypoglycaemia is yet to be fully explored. In our 12-month trial a medication management plan was developed based on baseline haemoglobin A1c (HbA1c) to limit hypoglycaemic events [11,15], but events still occurred, albeit only in participants who reported events before starting treatment [11]. Therefore, the aim of this study was to compare two medication protocols; a protocol that accounted for hypoglycaemic events prior to treatment and adjusts for these events by a greater reduction in medication than the previous protocol based on HbA1c only in a small sample of participants using medication likely to cause hypoglycaemia (sulphonylurea medications and/or insulin). We hypothesised that the adjusted protocol would be more effective at reducing hypoglycaemic events during treatment.

2. Materials and methods

2.1. Study design, participants and randomisation

This was a parallel randomised pilot trial, conducted at the Sansom Institute of Health Research, University of South Australia (19th of May 2017 until the 1st of August 2018). The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000512325). Ethics approval was obtained from the University of South Australia Human Research Ethics Committee (Application No. 0000036405). Procedures were in accordance with ethical standards, including obtaining written informed consent.

Participants were recruited via advertisements in print and broadcast media as well as letters sent to 250 eligible participants via the National Diabetes Services Scheme database. Inclusion criteria were adults (≥18 years of age) with type 2 diabetes at risk of hypoglycaemia (HbA1c ≥ 7% [53 mmol/mol] using sulphonylurea medications and/or insulin in addition to other diabetes medications), who were overweight or obese (body mass index ≥27 kg/m^2) and not pregnant or breastfeeding. Participants selected were otherwise healthy. They were not eligible if blood pressure was >160/100 mm Hg, they had cancer and were undergoing cancer treatment, had end-stage renal disease or previous weight loss surgery. Routine screening blood tests were not performed. Participants must experience ≥1 hypoglycaemic event (interstitial glucose of <3.9 mmol/L for ≥15 min) during the usual diet to continue into the intervention phase of the trial. This criterion was decided after randomisation to maximise the chances of demonstrating a change in hypoglycaemic events after medication reduction.

Eighty-nine participants were screened for eligibility and 42 met the entry criteria and were randomised 1:1 to either the fixed or adjusted medication protocol groups, stratified by medication (sulphonylurea or insulin) and HbA1c below or above 8%, (64 mmol/mol) as a standard level of acceptable vs undesirable glycaemic control (16). Randomisation was completed using an online random number sequence generator the primary investigator was not blinded. Participants received a $100 honorarium to thank them for their time and participation.

2.2. Procedure

HbA1c level was measured at baseline using a point-of-care immunoassay analyser (DCA Vantage Analyser, Siemens Healthcare Diagnostics) calibrated every 2 weeks. Participants followed their usual diet while wearing a flash glucose monitor (FreeStyle Libre) on the back of their arm, which monitored blood glucose levels 24hrs/day for approximately 14 days and automatically stored blood glucose data every 15 min. If the participant experienced a hypoglycaemic event, they continued into the intervention diet phase of the trial. During the intervention period participants followed the 5:2 diet; 2 non-consecutive very-low-calorie days (500–600 kcal) [2100–2500 kJ/day] with a minimum of 50 g of protein/day in accordance with the very-low-calorie-diet guidelines [17] with 5 habitual eating days per week for 14 days, again wearing a flash glucose monitor following either the fixed or adjusted medication protocol assigned at randomisation. The 14-day active duration of the flash glucose sensor determined the length of usual diet and 5:2 diet periods. Finger-prick glucose was not measured during the study, and the glucose monitor was not blinded; participants were able to review their glucose data. Participants were provided with dietary information booklets with portion advice and sample menus; no food or meal replacements were provided. Carbohydrate

was recommended to be <50 g/day. Participants were given digital kitchen scales and encouraged to weigh foods to ensure accuracy of intake. Diet checklists were utilised to monitor the usual diet and the 5:2 diet days. The usual diet days were analysed using FoodWorks, version 9 (Xyris Software Australia) on days with a hypoglycaemic event and matched days without events. The 5:2 diet days were also analysed for compliance to the desired energy intake. Medication diaries were used to monitor medication changes. Daily step count was monitored via a waistband pedometer (G-sensor, Pocket Pedometer, Walking with Attitude, WA, Australia).

2.3. Medication management

Only medications likely to cause hypoglycaemia (sulphonylureas and/or insulin) were altered using either the fixed or adjusted medication protocol during the 5:2 diet intervention. All other oral medications remained the same as at baseline (Table 2). See supplementary table 1 for dose information and detailed medication changes.

The fixed medication management protocol (Table 1), similar to that used in our long-term trial [11], required discontinuation of sulphonylureas and/or insulin for all participants if baseline HbA1c was <7% (53 mmol/mol). If >7% but <8% (>53 mmol/mol but <64 mmol/mol) then sulphonylureas and insulin were discontinued on intermittent days only and long and intermediate-acting insulin the night before an intermittent day. If >8% but <10% (>64 mmol/mol but <86 mmol/mol) then sulphonylureas and insulin were discontinued on intermittent days only. If >10% but <12% (>86 mmol/mol but <108 mmol/mol), sulphonylurea medications remained unchanged but short-acting insulin was discontinued, intermediate-acting insulin was reduced by half and long-acting insulin was reduced by 10 units or 10% whichever was greater on IER days only. If >12% (>108 mmol/mol), sulphonylurea medications remained unchanged, short-acting insulin was discontinued on IER days only. The adjusted medication protocol (Table 1) took into account hypoglycaemic events during the usual diet and recommended medication changes one level greater than appropriate if solely based on HbA1c. For example, if HbA1c is >7 but <8% (>53 mmol/mol but <64 mmol/mol) at baseline then the participant followed the <7% (<53 mmol/mol) protocol. Medication dosages were recorded daily, and the medication effect score (MES) was used to quantify changes. The MES is calculated as (actual drug dose/maximum drug dose) × drug mean adjustment factor [18].

2.4. Outcome measures

The primary outcome was to determine if the adjusted protocol was superior to the fixed protocol at reducing hypoglycaemic events during 5:2 diet treatment. This was

Table 1 – Fixed and adjusted medication protocol.

HbA1c	Fixed medication protocol		Adjusted medication protocol
	Sulphonylureas	Insulin	Hypoglycaemia
<7% (<53 mmol/mol)	Discontinue at baseline	Discontinue at baseline	One or more events (<3.9 mmol/L for ≥15 min) over 2 weeks then follow protocol 1 level greater than appropriate. *E.g: If HbA1c is >7–8% then the participant should follow the <7% protocol.*
>7–8% (>53–64 mmol/mol)	Discontinue on IER days only	Long and intermediate-acting insulin discontinued the night before the IER. All insulin discontinued on the day of the IER. Insulin will not be resumed until a full day's caloric intake is planned (if taken in the morning) or achieved (if taken in the evening).	
>8–10% (>64–86 mmol/mol)	Discontinue on IER days only	All insulin discontinued on the day of the IER. Insulin will not be resumed until a full day's caloric intake is planned (if taken in the morning) or achieved (if taken in the evening).	
>10–12% (>86–108 mmol/mol)	Continues	Short-acting insulin is discontinued, intermediate-acting is halved and long-acting insulin is reduced by 10 units or 10% whichever is greater, on IER days only.	
>12% (>108 mmol/mol)	Continues	Short-acting insulin is discontinued and long-acting insulin continued.	

IER; intermittent energy restriction.

determined by comparing the change in hypoglycaemic events from the baseline 2 weeks on usual diet to the 2 weeks on the 5:2 diet with each protocol. Secondary outcomes were to determine factors that predicted hypoglycaemia and assess changes to glycaemic control over 14 days using mean daily glucose and percentage in optimal range (4–10 mmol/L).

Severe hypoglycaemia was defined according to Diabetes Australia's guidelines as, an event requiring the assistance of another person or episodes associated with coma or seizure as defined by Danne et al [19]. All participants were provided with standard hypoglycaemic treatment advice at the start of the trial.

2.5. Statistical analysis

Analysis was performed using SPSS, version 25 (IBM SPSS Statistical Software). Non-parametric testing was used due to small sample size. All data were reported as the median and IQR. A 2-tailed $P = 0.05$ was considered statistically significant. Mann-Whitney U and Pearson X^2 tests were used to analyse differences between groups at baseline. Wilcoxon signed-rank test was used to determine change over time within groups. Mann-Whitney U was used to assess differences between groups and difference over time in each group. Factors significant in a Kendall's tau-b correlation were entered into linear regression to determine independent factors associated with hypoglycaemic events.

3. Results

Eighty-nine Australian adults with type 2 diabetes were assessed for eligibility. Forty-two were randomly assigned to medication protocol groups and those who experienced ≥1 hypoglycaemic event (n = 26, 13 women and 13 men) over 14 days on their usual diet entered the intervention treatment phase. All 26 participants completed the 14-day diet intervention period and were included in the analysis (Fig. 1). Participants had a median [IQR] age of 66 years [60.8–71.5 years]; HbA1c level of 7.8% (62 mmol/mol) [7.3–8.8% (56–73 mmol/mol)]; and body mass index of 34.1 kg/m^2 [32.9–36.8 kg/m^2]). There were no significant differences between groups at baseline. However, of the 26 participants who were eligible to continue into the intervention phase, HbA1c was significantly higher in the fixed protocol group compared to the adjusted protocol (Table 2).

3.1. Compliance

The glucose sensor was scanned a median of 6.25 times per day (5.5 to 10.6) collecting 91.5% of the glucose data (88.5 to 94.5%) with no difference between groups ($P = 0.8$ and $P = 0.3$ respectively). The median energy intake on the 5:2 diet days was 656 kcal (526 to 695 kcal) in the fixed group and 583 kcal (461 to 728 kcal) in the adjusted group ($P = 0.4$). Carbohydrate intake was also similar between groups (48 g (37 to 59 g) fixed vs 53 g (34 to 75 g) adjusted; $P = 0.6$). Energy and carbohydrate intake was not related to hypoglycaemic events ($P = 0.5$ and $P = 0.3$ respectively). Median weight loss from baseline to the completion of the 14-day 5:2 diet was −3.4 kg (−4.5 to −1.1 kg) in the fixed group and −2.2 kg (−5.4 to −1.1 kg) in the adjusted group ($P = 0.9$). Weight loss was not correlated with hypoglycaemic events ($P = 0.4$).

Five participants (n = 2 Fixed, n = 3 Adjusted) did not follow the medication protocol guidelines as advised; all participants had more insulin than required which caused more hypoglycaemic events during treatment for 1 participant in the fixed group and 2 participants in the adjusted group. Participants who did not comply with medication changes were not excluded from analysis.

3.2. Hypoglycaemia

The median number of hypoglycaemic events occurring in the fixed medication group reduced from 2.5 during the usual diet to 1.0 during the 5:2 diet period ($P = 0.3$). In the adjusted medication group, hypoglycaemic events reduced from 4.5 to 0.0 during the 5:2 diet period ($P = 0.01$). A Mann-Whitney U test revealed a significant difference in change in the number of hypoglycaemic events between fixed and adjusted medication protocols (−1.0 event in the fixed group vs. −3.5 events in the adjusted group; $P = 0.04$).

Overall there were 127 hypoglycaemic events during the 14-day usual diet period compared to 56 hypoglycaemic events during the 14-day 5:2 diet period affecting 12 of 26 participants. Fourteen participants had no hypoglycaemic events during the 5:2 diet period, 5 participants (41.7%) in the fixed group compared to 9 participants (64.3%) in the adjusted group ($P = 0.3$). A total of 12 hypoglycaemic events occurred over the 4 very-low-calorie diet days, 7 events affecting 4 participants in the fixed group and 5 events affecting 3 participants in the adjusted group ($P = 0.6$). Forty-four hypoglycaemic events occurred on the 10 habitual eating days, 27 events affecting 5 participants in the fixed group and 17 events affecting 5 participants in the adjusted group ($P = 0.6$). Duration of hypoglycaemic events were not significantly different between groups during either diet period. The adjusted group experienced an increase in duration between the usual diet and the 5:2 diet period ($P = 0.04$). Level 2 hypoglycaemic events (<2.9 mmol/L) occurred at a similar rate between groups with no difference between groups. There were no severe hypoglycaemic events. The majority (85%) of hypoglycaemic events occurred fasting, 65% of these occurred overnight, and 15% of events were postprandial, there was no difference between groups ($P = 0.6$) and no change within groups between diets.

There was a greater reduction to medications in adjusted group compared to the fixed group ($P = 0.01$), and although this resulted in slight reductions in glycaemic control, there were no significant differences in change to above, below, in-target, average blood glucose levels or glucose variability between groups (Table 3).

3.3. Predicting hypoglycaemic events

Including all participants (n = 42) who used a flash glucose monitor during their usual diet, hypoglycaemic events were inversely correlated with above target percent ($r = −0.3$, $P = 0.03$) and average blood glucose levels ($r = −0.4$, $P = 0.001$) and directly correlated with MES total ($r = 0.4$, $P = 0.001$). The

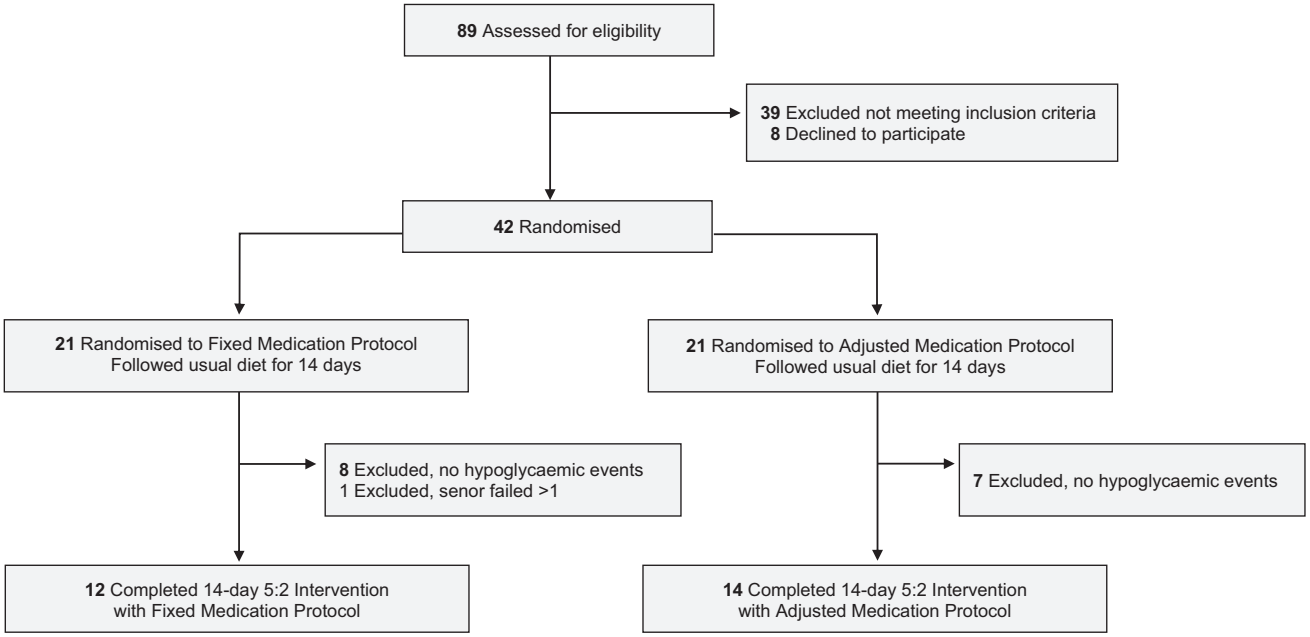

Fig. 1 – Flow diagram.

Table 2 – Median (IQR) participant characteristics during usual diet.[†]

	All participants total (n = 42)	≥1 Hypoglycaemic event		
		Fixed (n = 12)	Adjusted (n = 14)	Total (n = 26)
Age, y	64.0 (57.5–70.3)	64.5 (55.0–70.8)	68.5 (62.5–73.0)	66.0 (60.8–71.5)
Gender, n (%)				
Female	20 (48)	7 (58)	6 (43)	13 (50)
Male	22 (52)	5 (42)	8 (57)	13 (50)
Weight, kg	98 (91, 112)	100 (88, 110)	97 (88, 106)	98 (89, 106)
Glycaemic control UD				
HbA_{1c}, %	7.9 (7.3–9.0)	8.6 (7.6–10.1)	7.6 (7.1–8.3)*	7.8 (7.3–8.8)
HbA_{1c}, mmol/mol	63 (56–75)	70 (60–87)	60 (54–67)*	62 (56–73)
Duration of diabetes, y	11 (7.0–18.0)	12.5 (10.0–24.8)	12.5 (6.0–16.5)	12.5 (10.0–20.0)
Hypoglycaemic events	1.0 (0.0–5.5)	2.5 (1.0–6.8)	4.5 (1.8–10.3)	3.5 (1.0–8.0)
Above target, %	32.0 (18.5–55.0)	25.0 (18.0–40.8)	29.5 (12.0–52.5)	26.5 (18.0–41.8)
In-target, %	64.0 (44.0–76.5)	70.0 (58.3–79.8)	59.0 (45.8–84.5)	66.0 (53.5–81.0)
Below target, %	1 (0.0–4.0)	1.5 (1.0–5.5)	3.0 (1.0–6.3)	2.0 (1.0–6.0)
Average BGLs	9.0 (7.9–10.9)	8.2 (7.8–9.5)	8.4 (7.6–10.8)	8.2 (7.7–9.7)
Glucose variability	1.1 (0.8–1.5)	1.2 (1.0–1.4)	1.1 (0.8–1.6)	1.2 (0.9–1.5)
Diabetes medications				
Metformin, n (%)	35 (83)	9 (75)	11 (79)	20 (77)
DPP-4 inhibitor, n (%)	4	2 (17)	2 (14)	4 (15)
SGLT2 inhibitor, n (%)	7	3 (25)	4 (29)	7 (27)
GLP-1R agonists, n (%)	2	2 (17)	0 (0)	2 (8)
Sulphonylureas, n (%)	17 (40)	3 (25)	8 (57)	11 (42)
Insulin, n (%)	31 (74)	10 (83)	11 (79)	21 (81)
MES				
Sulphonylureas	0.8 (0.4–1.5)	0.8 (0.3-missing)	0.8 (0.5–1.5)	0.8 (0.4–1.5)
Insulin	1.3 (0.8–2.1)	1.1 (0.9–2.0)	1.5 (0.6–2.1)	1.4 (0.9–2.0)
Total	1.3 (0.8–2.0)	0.9 (0.8–1.9)	1.6 (1.2–2.7)	1.5 (0.9–2.1)

HbA1c, haemoglobin A1c (to convert NGSP to IFCC; IFCC = (10.93 * NGSP) − 23.50); UD, usual diet; MES, medication effect score (calculated as [actual drug dose/maximum drug dose] × drug mean adjustment factor).

[†] Data were analysed using Mann-Whitney *U* test (for continuous variables) and X^2 test (for categorical variables) and given as median (IQR) value. There were significant differences in HbA1c between fixed and adjusted medication groups who had ≥1 hypoglycaemic event during the usual diet period (*P = 0.05).

Table 3 – Median (IQR) glycaemic control and medication effect score during the usual diet, 5:2 diet and change between diets.[†]

	Usual Diet		P	5:2 Diet		P	Change from Usual Diet to 5:2 diet		P
	Fixed (n = 12)	Adjusted (n = 14)		Fixed (n = 12)	Adjusted (n = 14)		Fixed (n = 12)	Adjusted (n = 14)	
Weight, kg	100 (88, 110)	97 (88, 106)	0.9	96 (85, 107)	95 (86, 104)	1.0	−3.4 (-4.5, −1.1)	−2.2 (-5.4, −1.1)	1.0
Glycaemic control									
Hypoglycaemic events (<3.9 mmol/L)	2.5 (1.0, 6.8)	4.5 (1.8, 10.3)	0.2	1.0 (0.0, 7.3)	0.0 (0.0, 2.3)	0.3	−1.0 (-2.8, 0.0)	−3.5 (-7.8, −1.0)	0.04
Hypoglycaemic events (<2.9 mmol/L)	1.0 (0.0, 1.8)	1.0 (0.0, 1.8)	0.9	0.0 (0.0, 1.8)	1 (0.0, 0.3)	0.5	0.0 (-1.0, 0.0)	−0.5 (-1.8, 0.0)	0.8
Correlation with baseline HbA1c				r = 0.4; P = 0.1	r = 0.7; P = 0.003				
				r = 0.6; P = 0.001					
Total number of events	44	83	0.2	34	22	0.3	−10	−61	0.04
Event duration, mins	143 (121, 185)	137 (79, 219)	0.9	110 (91, 226)	170 (111, 204)	0.9	−5.0 (-58, 70)	50 (19, 79)	0.3
Above target, %	25.0 (18.0, 40.8)	29.5 (12.0, 52.5)	0.7	23.5 (13.0, 51.0)	49.0 (19.5, 69.0)	0.9	1.5 (-10.3, 13.0)	11.0 (-3.0, 32)	0.3
In-target, %	70.0 (58.3, 79.8)	59.0 (45.8, 84.5)	0.4	73.5 (47.3, 81.8)	50.0 (29.5, 80.5)	0.2	−2.0 (-8.5, 8.3)	−7.5 (-24.0, 7.0)	0.4
Below target, %	1.5 (1.0, 5.5)	3.0 (1.0, 6.3)	0.3	1.0 (0.0, 4.3)	0.0 (0.0, 2.0)	0.2	−1.0 (-3.3,1.5)	−2.5 (-2.5, −1.0)	0.06
Average BGL	8.2 (7.8, 9.5)	8.4 (7.6,10.8)	0.9	8.6 (7.4,10.1)	10.2 (8.3, 11.8)	0.1	0.4 (-1.2, 1.5)	1.0 (-0.2, 2.9)	0.3
Glucose variability	1.2 (1.0, 1.4)	1.1 (0.8, 1.6)	1.0	1.2 (1.1, 1.7)	1.5 (0.8, 2.1)	0.4	0.1 (-0.03, 0.4)	−0.001 (-0.3, 1.0)	1.0
MES									
Sulphonylureas	0.8 (0.3, missing)	0.8 (0.5, 1.5)	0.6	0.8 (0.2, missing)	0.0 (0.0, 0.4)	0.06	−0.1 (-0.4, −0.1)	−0.6 (-1.3, −0.4)	0.09
Insulin	1.1 (0.9, 2.0)	1.5 (0.6, 2.1)	0.8	0.7 (0.5, 1.5)	0.0 (0.0, 0.6)	0.04	−0.5 (-0.6, −0.2)	−0.8 (-1.8, −0.6)	0.02
Total	0.9 (0.8, 1.9)	1.6 (1.2, 2.7)	0.08	0.7 (0.4, 1.5)	0.0 (0.0, 1.0)	0.03	−0.4 (-0.4, −0.2)	−1.4 (-1.4, −0.7)	0.01
Dietary compliance[††]									
Energy, kcal				656 (526, 695)	583 (461, 728)				
Carbohydrate, g				48 (37, 59)	53 (34, 75)				

BGL, blood glucose level; Above target (>10 mmol/L), In-target (4–10 mmol/L), Below target (<3.9 mmol/L); Glucose variability (calculated as total SD of daily average blood glucose levels); MES, medication effect score (calculated as [actual drug dose/maximum drug dose] × drug mean adjustment factor).

[†] Data were analysed using Mann-Whitney *U* test and given as median (IQR) value. *P* value by treatment, between-group difference.

[††] Dietary data is presented for the 5:2 diet days only (total of 4 days).

difference in steps within groups on days with and without hypoglycaemic events was not significantly different in either group (P = 0.2 for both groups), and step count did not correlate to hypoglycaemic events (P = 0.8). The difference in energy intake within groups on days with and without hypoglycaemic events was not significantly different in either group (P = 0.2 for both groups). Carbohydrate intake was greater on days with no hypoglycaemic events compared to days with events in the fixed group (19 g (9 to 66); P < 0.05) but not in the adjusted group (−18 g (−77 to 58); P = 0.2) and the difference did not correlate to hypoglycaemic events (P = 0.7).

Only HbA1c was correlated with hypoglycaemic events during 5:2 diet period (r = 0.6, P = 0.001) accounting for 27% of the variance (P = 0.004). Significance was lost in the fixed group (adjusted r^2 = 0.1, P = 0.2) but not for the adjusted group accounting for 38% of the variance (P = 0.01). Thirteen of the 14 participants (n = 4 fixed, n = 9 adjusted) who did not experience a hypoglycaemic event during the 5:2 period had a baseline HbA1c < 8% (<64 mmol/mol). All participants who had ≥5 hypoglycaemic events during the 5:2 diet period (n = 4 fixed, n = 2 adjusted) had a baseline HbA1c > 8% (>64 mmol/mol). To adjust for the difference in HbA1c at baseline, 3 participants from the fixed group with HbA1c > 10% were removed for the analysis (unmatched by similar participants in the adjusted group). As a result, the significance in change in hypoglycaemic events was lost (−1.0 event in the fixed group vs. −3.5 events in the adjusted group; P = 0.12).

4. Discussion

The results of this exploratory pilot trial confirm, for the first time, the importance of understanding the patient's current risk of hypoglycaemia in order to make further reductions to medications than might otherwise be anticipated to reduce the risk of hypoglycaemia during a 5:2 diet. Hypoglycaemic events were significantly reduced from the usual diet to the 5:2 diet using the adjusted medication protocol (P = 0.01) compared to the fixed medication protocol (P = 0.3) and therefore the adjusted protocol may be most appropriate for patients currently experiencing hypoglycaemic events on their usual diet. In this trial, lower average blood glucose levels and larger doses of medication predicted hypoglycaemic events in the usual diet and may be used to predict risk if glucose monitoring is not available. In both medication groups there were no episodes of severe hypoglycaemia and many participants [42% (n = 5) in the fixed group, 64% (n = 9) in the adjusted group] did not experience hypoglycaemia at all during 5:2 diet period while following the medication protocols. In fact, unlike the findings by Corley et al, which noted a twofold increase in hypoglycaemic events on very-low-calorie days [12] in this study events were more common on ad libitum days. The greater medication reduction required in the adjusted protocol had no adverse effects on overall glycaemic control, although numbers are too low to be completely confident on this point. The fixed protocol may be appropriate for participants who are not currently experiencing hypoglycaemia, as demonstrated in our long-term study [11] although this cannot be demonstrated here. While not significant, time in target increased and time above target decreased during the 5:2 diet period in the fixed medication group. The 5:2 diet days would have contributed to reducing blood glucose levels, but more likely the effect was due to the more moderate medication changes made in this group. Greater medication changes were made in the adjusted group, and this resulted in reduced time in target, increased time above target and greater glucose variability, although not significant. A higher HbA1c was correlated with hypoglycaemic events during the 5:2 diet, an effect which is supported in the literature [16] in people not on a weight loss diet, but a larger cohort is needed to test the effect further. High HbA1c may be caused by both recurrent hypoglycaemia with secondary overeating and endogenous responses causing hyperglycaemia as well as inadequate treatment. In this study the main reason a higher HbA1c was correlated with hypoglycaemia during the 5:2 diet period was the more modest reduction in medication in the high HbA1c group. But it is possible that the difference in HbA1c between groups affected results as significance was lost after removing 3 participants in the fixed group with HbA1c > 10% who were unmatched in the adjusted group. Therefore, randomisation before eligibility was confirmed, is a limitation of this study as is the small number of participants. Lack of blinding of the flash glucose monitoring results may have influenced participant's behaviour while on both their usual diet and the 5:2 diet as participants may have been more aware of foods that increased their blood glucose levels. In addition, there was no confirmation of hypoglycaemic events with finger-prick testing.

The 5:2 diet offers an alternative method to daily dieting for weight loss and blood glucose control for people with type 2 diabetes [11]. Patients using glycaemic agents likely to cause hypoglycaemia (sulphonylureas/insulin) require medication changes to safely follow the 5:2 diet method. In this pilot study we have demonstrated the importance of understanding an individual's risk of hypoglycaemia before starting a 5:2 diet regime and that our adjusted medication protocol is likely the best option for medication changes for these patients. Further investigation with a larger sample size is warranted.

Acknowledgments

We would like to thank all participants and the staff of the Sansom Institute for Health Research. We would like to acknowledge that some participants were contacted via the National Diabetes Services Scheme (NDSS) – an initiative of the Australian Government administered with the assistance of Diabetes Australia. Through the NDSS, Diabetes Australia provides diabetes products and self-management support services to over one million Australians with diabetes.

Conflict of interest

All authors declare no conflict of interest.

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.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.013.

REFERENCES

[1] World Health Organization. Global report on diabetes. World Health Organization, 2016. https://www.who.int/diabetes/global-report/en/ [accessed Oct 15, 2018).
[2] International Diabetes Federation. IDF Diabetes Atlas. 8th ed. 2017. Brussels, Belgium, International Diabetes Federation. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html [accessed Oct 15, 2018).
[3] Omodei D, Fontana L. Calorie restriction and prevention of age-associated chronic disease. FEBS Lett. 2011;6;585 (11):1537–42. https://doi.org/10.1016/j.febslet.2011.03.015.
[4] Middleton KR, Anton SD, Perri MG. Long-term adherence to health behaviour change. Am J Lifestyle Med 2013;7:395–404. https://doi.org/10.1177/1559827613488867.
[5] Acharya SD, Elci OU, Sereika SM, Music E, Styn MA, Turk MW, et al. Adherence to a behavioral weight loss treatment program enhances weight loss and improvements in biomarkers. Patient Prefer Adher 2009;3:151–60.
[6] Johnstone A. Fasting for weight loss: an effective strategy or latest dieting trend? Int J Obes (Lond). 2015;39:727–33. https://doi.org/10.1038/ijo.2014.214.
[7] Seimon RV, Roekenes JA, Zibellini J, Zhu B, Gibson AA, Hills AP, et al. Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials. Mol Cell Endocrinol 2015;418(pt 2):153–72. https://doi.org/10.1016/j.mce.2015.09.014.
[8] Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? Obes Rev 2011;12:e593–601. https://doi.org/10.1111/j.1467-789X.2011.00873.x.
[9] Patterson RE, Laughlin GA, Sears DD, LaCroix AZ, Marinac C, Gallo LC. Intermittent fasting and human metabolic health. J Acad Nutr Diet 2015;115:1203–12. https://doi.org/10.1016/j.jand.2015.02.018.
[10] Carter S, Clifton PM, Keogh JB. The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. Diabetes Res Clin Pract 2016;122:106–12. https://doi.org/10.1016/j.diabres.2016.10.010.
[11] Carter S, Clifton PM, Keogh JB. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. JAMA Netw Open. 2018;1. https://doi.org/10.1001/jamanetworkopen.2018.0756 e180756.
[12] Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. Diabet Med 2018;35:588–94. https://doi.org/10.1111/dme.13595.
[13] Arnason TG, Bowen MW, Mansell KD. Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study. World J Diabetes 2017;8:154–64. https://doi.org/10.4239/wjd.v8.i4.154.
[14] Ash S, Reeves MM, Yeo S, Morrison G, Carey D, Capra S. Effect of intensive dietetic interventions on weight and glycaemic control in overweight men with Type II diabetes: a randomised trial. Int J Obes Relat Metab Disord 2003;27:797–802. https://doi.org/10.1038/sj.ijo.0802295.
[15] Carter S, Clifton PM, Keogh JB. Intermittent energy restriction in type 2 diabetes: a short discussion of medication management. World J Diabetes 2016;7:627–30. https://doi.org/10.4239/wjd.v7.i20.627.
[16] Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. Diabetes Care 2013;36:3535–635. https://doi.org/10.2337/dc13-0610.
[17] Baker S, Jerums G, Proietto J. Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes. Diabetes Res Clin Pract 2009;85:235–42. https://doi.org/10.1016/j.diabres.2009.06.002.
[18] Mayer SB, Jeffreys AS, Olsen MK, McDuffie JR, Feinglos MN, Yancy Jr WS. Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. Diabetes Obes Metab 2014;16:90–3. https://doi.org/10.1111/dom.12191.
[19] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–40. https://doi.org/10.2337/dc17-1600.