

Intermittent energy restriction in type 2 diabetes: A short discussion of medication management

Sharayah Carter, Peter M Clifton, Jennifer B Keogh

Sharayah Carter, Peter M Clifton, Jennifer B Keogh, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5000, Australia

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Correspondence to: Peter M Clifton, Professor of Nutrition, School of Pharmacy and Medical Sciences, University of South Australia, GPO Box 2471, Adelaide, SA 5000, Australia. peter.clifton@unisa.edu.au
Telephone: +61-403-197998

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Abstract

AIM

To discuss type 2 diabetes mellitus (T2DM) medication

changes required during the popular 5:2 intermittent energy restriction (IER) diet.

METHODS

A search was conducted in MEDLINE, EMBASE, AMED, CINAHL and Cochrane library for original research articles investigating the use of very low calorie diets (VLCD) in people with T2DM. The search terms used included "VLCD" or "very low energy diet" or "very low energy restriction" or "IER" or "intermittent fasting" or "calorie restriction" or "diabetes mellitus type 2" and "type 2 diabetes". Reference lists of selected articles were also screened for relevant publications. Only research articles written in English, which also included an explanation of medication changes were included. A recent pilot trial using the 5:2 IER method, conducted by our research group, will also be summarized.

RESULTS

A total of 8 studies were found that investigated the use of VLCD in T2DM and discussed medication management. Overall these studies indicate that the use of a VLCD for people with T2DM usually require the cessation of medication to prevent hypoglycemia. Therefore, the 5:2 IER method will also require medication changes, but as seen in our pilot trial, may not require total cessation of medication, rather a cessation on the 2 IER days only.

CONCLUSION

Guidelines outlined here can be used in the initial stages of a 2-d IER diet, but extensive blood glucose monitoring is still required to make the necessary individual reductions to medications in response to weight loss.

Key words: Diabetes mellitus/therapy; Fasting; Caloric restriction; Diabetes complication; Intermittent energy restriction; Obesity; Very low calorie diet; Medication management; Type 2 diabetes mellitus

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Core tip: Use of the popular 5:2 intermittent energy restriction diet in people with type 2 diabetes requires careful manipulation of oral hypoglycemic agents and insulin to prevent poor blood glucose control. This short review fills a very important gap in the literature, reviewing necessary medication changes required in severe energy restriction and outlining how these changes may apply during the 5:2 diet by sharing our experiences from our recent 5:2 pilot trial.

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INTRODUCTION

Approximately 80% of people with type 2 diabetes mellitus (T2DM) are overweight or obese^[1]. Weight loss is known to reduce glycemia and increase insulin sensitivity^[1] and large amounts of weight loss can lead to remission of T2DM^[2]. However, weight loss for this population group is often difficult^[3], with poor adherence to weight loss programs, suggesting people find continuous energy restriction (CER) difficult to maintain. Recently attention has been given to a new method of weight loss, known as intermittent energy restriction (IER), which in the overweight and obese populations, without diabetes, has shown to be comparable to CER in achieving weight loss^[4,5]. IER uses short periods (usually 2 d) of severe energy restriction, 400-800 kcal/d, followed by longer periods of habitual diet. There are however, very few studies comparing the effects of IER to daily CER in T2DM. Therefore, we have limited information on how to manage diabetes medications to prevent hypoglycemia, which is likely to occur during the short periods of severe energy restriction. We evaluated continuous very low calorie diet (VLCD) trials to provide a starting point for medication management and to provide guidance to future IER weight loss trials for people with T2DM.

MATERIALS AND METHODS

A search was conducted in MEDLINE, EMBASE, AMED, CINAHL and Cochrane library for original research articles investigating the use of VLCD in people with T2DM. The search terms used included "VLCD" or "very low energy diet" or "very low energy restriction" or "IER" or "intermittent fasting" or "calorie restriction" or "diabetes mellitus type 2" and "type 2 diabetes". Reference lists of selected articles were also screened for relevant publications. Only research articles written in English, which also included an explanation of medication changes were included.

VLCDs are defined as diets with an energy intake of

< 800 kcal (< 3344 kJ) per day with at least 50 g of high-quality protein, essential fatty acids, daily requirements of vitamins and minerals as well as the addition of approximately 2 cups of non-starchy vegetables to prevent constipation. VLCDs can be given as a complete liquid formula or if food-based diets are used they often include a multivitamin supplement^[6].

RESULTS

Seven trials using continuous VLCD in participants with T2DM were found, and one controlled trial was found using intermittent VLCD (Table 1). In six trials, including the intermittent VLCD trial, all oral hypoglycemic agents (OHA) were discontinued before the start of the trial^[2,7-11] regardless of the degree of glycemic control. In two trials, medications were reinitiated if blood glucose levels (BGL) were above a pre-determined level^[7,9]. In one trial, medications, including insulin, were restarted if the mean of two weekly fasting BGL averaged > 13.3 mmol/L for two weeks, dosages were increased thereafter on a case-by-case basis^[7]. In the second trial, medications were reinitiated at half the original dose if fasting BGLs increased > 13.9 mmol/L^[9]. In the other four trials, there was no mention of reinitiating medications^[2,8,10,11].

In the two remaining trials, diabetic medications and insulin were reduced by 50% at either the commencement of the VLCD treatment^[12] or in accordance with self-monitored BGLs^[13]. In one trial, participants measured fasting and postprandial BGLs daily for two days before the start of the VLCD and if the mean result was < 8 and < 10 mmol/L, respectively, diabetic medications were halved^[13]. Conversely, if levels were > 9 and > 11 mmol/L, respectively, medications were increased^[13]. Medication changes occurred in the following order; insulin was decreased first followed by sulfonylureas and lastly metformin, and when increasing, medications were increased in reverse order^[13]. In the second trial, medications were halved at the initiation of the VLCD and reduced further if the fasting weekly average was < 8.4 mmol/L or if participants experienced hypoglycemia (< 3.4 mmol/L) and increased if fasting weekly BGLs averaged > 8.4 mmol/L^[12]. All changes to dosages occurred on a case-by-case basis in both trials^[12,13].

One trial used a VLCD in an overweight population with T2DM on an intermittent basis. The severe energy restriction was used at a frequency of either 1 d or 5 d per week over 20 wk. Oral glycemic agents were discontinued 2 wk before the start of the trial and people with fasting glucose > 16.7 mmol/L were excluded. People using insulin were also excluded from this trial. Medication was reinstated, at half the original dose, if fasting BGLs increased to > 13.9 mmol/L; participants were only required to measure their fasting BGLs levels twice per week.

We recently conducted a 3-mo pilot trial testing the effects of a 2-d IER compared to a CER diet in people with T2DM^[14]. Our pilot trial demonstrated that 2 d of

Table 1 Summary of trials

Ref.	Design	Duration	Subjects	Aim	Diet groups	Medication protocol
Wing <i>et al</i> ^[7]	Randomized parallel study	50 wk 1-yr follow-up	<i>n</i> = 93 Male/female: 33/60 Mean age: 51.8 ± 9.7 Mean diagnosis (yr): 6.8 ± 6.1	Effects of a weight control program, with and without 2 × 12-wk VLCD restriction	VLCD = 400-500 kcal <i>via</i> liquid or food-based diet from 1-12 wk and from 24-36 wk. LCD was followed at all other times LCD = 1000-1200 kcal	All medications (inc. insulin) were discontinued at the start of the trial. Insulin was discontinued and monitored for 3 d. Dosages of oral medications or insulin were reinstated if the mean of two fasting blood glucose levels averaged > 13.3 mmol/L over a fortnight. Dosages increased on a case-by-case basis
Kelley <i>et al</i> ^[8]	Single arm study	24 wk	<i>n</i> = 7 Male/female: 2/5 Mean age: 59 Mean diagnosis (yr): N/A	Evaluating the efficacy of VLCD treatment in obese T2DM participants	VLCD = 400-800 kcal <i>via</i> liquid and food-based diet	Discontinued all oral glycemic medication 3 wk before commencement on the VLCD
Williams <i>et al</i> ^[9]	Randomized parallel study	20 wk	<i>n</i> = 54 Male/female: 23/31 Mean age: 51.9 ± 7.8 Mean diagnosis (yr): N/A	Evaluating the efficacy of intermittent VLCD restriction on weight loss and glycemic control compared to moderate calorie restriction	VLCD = 400-600 kcal <i>via</i> food-based diet. LDC (1500-1800 kcals) at all other times 2 groups: 1-d: 1 d/wk plus 5 consecutive days in week 2 5-d: 5 d/wk for 15 wk	Discontinued all oral glycemic medication 2 wk before the trial and people with fasting glucose > 16.7 mmol/L were excluded. People using insulin were also excluded. Medications were only reinstated if fasting BGLs (measured twice weekly) increased > 13.9 mmol/L. Restarted medication occurred at half of the original dose
Uusitupa <i>et al</i> ^[10]	Single arm study	12 wk	<i>n</i> = 10 Male/female: 6/4 Mean age: 51 ± 2.2 Diagnosis (yr): Ranged 4-16	Evaluating the effects of weight loss using a VLCD on metabolic control and cardiovascular risk factors in obese participants with T2DM	VLCD = 500-800 kcals <i>via</i> liquid and food-based diet	Discontinued all oral glycemic medications before the start of the trial

VLCD: Very low calorie diet; LCD: Low calorie diet; T2DM: Type 2 diabetes mellitus; BGL: Blood glucose levels.

IER compared to CER achieves similar reductions in HbA1c ($-0.7\% \pm 0.9\%$; $P < 0.001$) and weight loss (-5.8 ± 3.9 kg; $P < 0.001$)^[14]. In the pilot trial, our protocol was to discontinue OHA likely to cause hypoglycemia (e.g., sulfonylureas) at baseline if HbA1c was < 8%. Medications such as metformin, gliptins, and SGLT2 inhibitors remained unchanged. Participants using insulin were also asked to reduce their dose by 10 units/d if randomized to the CER group or halved on the IER days. If HbA1c was > 8% at baseline OHA remained the same and insulin dose was decreased by 5-10 units on IER days. However, due to low BGLs in some participants we changed the medication protocol in preparation for our 12-mo intervention trial, which is currently ongoing. The new protocol requires discontinuation of sulfonylureas as well as insulin if baseline HbA1c is < 7% for both groups. If HbA1c is > 7% but < 10% then medications are discontinued only on IER days and if HbA1c is > 10% medications remain unchanged. Following this change, there has been a reduction in hypoglycemic events for participants taking insulin on IER days and a reduction in

hyperglycemic events on non-IER days and in the CER group. It is important to note that in addition to changes made based on baseline values, it is also essential to monitor daily BGLs. Each participant requires individual medication changes, especially to insulin units, in response to weight loss.

DISCUSSION

IER is an alternative method to achieve weight loss, which can be used for the management of T2DM. Due to the severe energy restriction required for IER diets to be effective, management of OHA, as well as insulin, requires constant supervision as well as ongoing blood glucose monitoring by the participant to prevent unwanted hypo- or hyperglycemic events. Medication changes will differ depending on the number of days the intermittent restriction is followed and is likely to only require intervention on these days unless glycemic control is excellent. The treatment method promoted by popular media suggests 2 d of restriction. We tested this

method and we suggest baseline medication changes based on HbA1c, as outlined in the second protocol above, as well as individual changes in response to weight loss. Participants, therefore, need to be willing to monitor their BGLs at least twice daily and report any episodes of hypo- or hyperglycemia, which would indicate the need to further adjust medications.

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COMMENTS

Background

Recently attention has been given to a new method of weight loss, known as intermittent energy restriction (IER), which has demonstrated positive results for weight loss in overweight and obese populations.

Research frontiers

For this new diet method to be used safely in the type 2 diabetes mellitus (T2DM) population, medication management protocol must be established.

Innovations and breakthroughs

Very low calorie diets used in the treatment of T2DM provide insight, but as seen from the research, medication changes may only be required on the IER treatment days and after weight loss.

Applications

IER is a successful treatment method for weight loss and glycemic control in T2DM, and with regular blood glucose levels monitoring, medications can be safely adjusted to limit unwanted episodes of hypo-or hyperglycemia.

Peer-review

The review though very short is written well. The authors state that intermittent energy restriction which requires severe energy restriction needs to be discussed as it is a developing concept.

REFERENCES

- 1 **Maggio CA**, Pi-Sunyer FX. Obesity and type 2 diabetes. *Endocrinol Metab Clin North Am* 2003; **32**: 805-822, viii [PMID: 14711063 DOI: 10.1016/S0889-8529(03)00071-9]
- 2 **Lim EL**, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; **54**: 2506-2514 [PMID: 21656330 DOI: 10.1007/s00125-011-2204-7]
- 3 **Wing RR**, Marcus MD, Epstein LH, Salata R. Type II diabetic subjects lose less weight than their overweight nondiabetic spouses. *Diabetes Care* 1987; **10**: 563-566 [PMID: 3677974 DOI: 10.2337/diacare.10.5.563]
- 4 **Keogh JB**, Pedersen E, Petersen KS, Clifton PM. Effects of intermittent compared to continuous energy restriction on short-term weight loss and long-term weight loss maintenance. *Clin Obes* 2014; **4**: 150-156 [PMID: 25826770 DOI: 10.1111/cob.12052]
- 5 **Harvie MN**, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, Cuzick J, Jebb SA, Martin B, Cutler RG, Son TG, Maudsley S, Carlson OD, Egan JM, Flyvbjerg A, Howell A. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond)* 2011; **35**: 714-727 [PMID: 20921964 DOI: 10.1038/ijo.2010.171]
- 6 **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**: 235-242 [PMID: 19560834 DOI: 10.1016/j.diabres.2009.06.002]
- 7 **Wing RR**, Blair E, Marcus M, Epstein LH, Harvey J. Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? *Am J Med* 1994; **97**: 354-362 [PMID: 7942937 DOI: 10.1016/0002-9343(94)90302-6]
- 8 **Kelley DE**, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M. Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1993; **77**: 1287-1293 [PMID: 8077323 DOI: 10.1210/jcem.77.5.8077323]
- 9 **Williams KV**, Mullen ML, Kelley DE, Wing RR. The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. *Diabetes Care* 1998; **21**: 2-8 [PMID: 9538962 DOI: 10.2337/diacare.21.1.2]
- 10 **Uusitupa MI**, Laakso M, Sarlund H, Majander H, Takala J, Penttilä I. Effects of a very-low-calorie diet on metabolic control and cardiovascular risk factors in the treatment of obese non-insulin-dependent diabetics. *Am J Clin Nutr* 1990; **51**: 768-773 [PMID: 2333833]
- 11 **Paisey RB**, Frost J, Harvey P, Paisey A, Bower L, Paisey RM, Taylor P, Belka I. Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes. *J Hum Nutr Diet* 2002; **15**: 121-127 [PMID: 11972741 DOI: 10.1046/j.1365-277X.2002.00342.x]
- 12 **Collins RW**, Anderson JW. Medication cost savings associated with weight loss for obese non-insulin-dependent diabetic men and women. *Prev Med* 1995; **24**: 369-374 [PMID: 7479627 DOI: 10.1006/pmed.1995.1060]
- 13 **Capstick F**, Brooks BA, Burns CM, Zilkens RR, Steinbeck KS, Yue DK. Very low calorie diet (VLCD): a useful alternative in the treatment of the obese NIDDM patient. *Diabetes Res Clin Pract* 1997; **36**: 105-111 [PMID: 9229194 DOI: 10.1016/S0168-8227(97)00038-7]
- 14 **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**: 106-112 [PMID: 27833048 DOI: 10.1016/j.diabres.2016.10.010]

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