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Metabolic and cardiovascular effects of very-low-calorie diet therapy in obese patients with Type 2 diabetes in secondary failure: outcomes after 1 year

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Abstract

Aims To evaluate the short-term and 1-year outcomes of an intensive very-low-calorie diet (VLCD) on metabolic and cardiovascular variables in obese patients with Type 2 diabetes (T2DM) and symptomatic hyperglycaemia despite combination oral anti-diabetic therapy ± insulin, and to assess patient acceptability and the feasibility of administering VLCD treatment to this subgroup of patients in a routine practice setting.

Methods Forty obese patients with T2DM (22 M, mean age 52 years, body mass index (BMI) 40 kg/m^2, duration of T2DM 6.1 years) and symptomatic hyperglycaemia despite combination oral therapy (n = 26) or insulin + metformin (n = 14) received 8 weeks of VLCD therapy (750 kcal/day) followed by standard diet and exercise advice at 2–3-month intervals up to 1 year. Insulin was discontinued at the start of the VLCD, and anti-diabetic therapy was adjusted individually throughout the study, including (re)commencement of insulin as required.

Results Immediate improvements in symptoms and early weight loss reinforced good compliance and patient satisfaction. After 8 weeks of VLCD, body weight and BMI had fallen significantly: 119 ± 19–107 ± 18 kg and 40.6–36.6 kg/m^2, respectively, with favourable reductions in serum total cholesterol (5.9–4.9 mM), blood pressure (10/6 mmHg) and fructosamine (386 ± 73–346 ± 49 μM) (equates to an HbA_{1c} reduction of approximately 1%). Sustained improvements were evident after 1 year, with minimal weight regain, e.g. mean body weight 109 ± 18 kg and BMI 37 ± 4 kg/m^2. Glycaemic control tended to deteriorate after 1 year.

Conclusions The absence of a control group is a major limitation, but the results indicate that 8 weeks of VLCD treatment may be effective and well tolerated in symptomatic obese patients with T2DM in secondary failure, producing sustained cardiovascular and metabolic improvements after 1 year. VLCD therapy is a treatment option that deserves greater consideration in this difficult-to-treat patient population.

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Keywords VLCD, secondary failure, obesity, Type 2 diabetes, hyperglycaemic symptoms

Introduction

The clinical management of obese patients with Type 2 diabetes (T2DM) and symptomatic hyperglycaemia despite combination oral anti-diabetic therapy can be particularly difficult. Few, if any, therapeutic strategies optimally achieve the desired outcomes of promoting weight loss and improving glycaemic control. Energy restriction and weight reduction have independent, additive effects on metabolic and cardiovascular function [1]; for example, projections based on observational data suggest that a sustained 10-kg weight loss would result in a 15% reduction in HbA_{1c}, 10–20 mmHg fall in blood

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pressure (BP) and a 20–25% reduction in total mortality [2,3], but aggressive weight reduction programmes are not routinely provided in many diabetes services, especially in the UK, often because of concerns about early weight regain and the lack of evidence of sustained medium to long-term benefit [4].

Very-low-calorie diets (VLCDs) are defined as diets of < 800 kcal/day [5]. They were developed to achieve maximum weight loss while preserving lean body mass, and are usually given for 8–12 weeks as a liquid formula containing high levels of protein enriched with vitamins, minerals, electrolytes and fatty acids. First-generation VLCDs were associated with sudden cardiovascular collapse [6], but the safety and tolerability of newer formulations have been well established, albeit mainly in healthy non-diabetic subjects > 30% above ideal body weight [5,7]. Favourable effects of VLCD therapy on body weight and glycaemic control have also been reported in patients with T2DM [8–10], but mostly in short-term studies and following use of a VLCD as primary therapy in newly diagnosed patients [11,12]. In contrast, there is relatively little information about metabolic and cardiovascular outcomes following VLCD treatment among symptomatic patients with T2DM in secondary failure and/or those recently commenced on insulin with suboptimal glycaemic and symptom control. Thus, the purpose of this study was to evaluate short-term and 1-year outcomes of an intensive 2-month VLCD as part of the routine care of obese patients in secondary failure.

Patients and methods

Consecutive obese patients with hyperglycaemic symptoms and poorly controlled T2DM despite maximum tolerated doses of oral anti-diabetic therapy (sulphonylurea and metformin) ± insulin were invited to participate in a 12-month study divided into two phases: (i) 8 weeks of VLCD therapy with review by the dietician after 2, 4 and 8 weeks (patients also had telephone access between visits); and (ii) a follow-up phase (week 8 to week 52) in which a standard low-calorie weight-maintenance diet was recommended together with simple advice about exercise at bi-monthly visits to the Diabetes Centre. Clinical, biochemical and haemodynamic parameters were recorded at baseline, 8 weeks and 1 year. The effects of VLCD therapy on glycaemic control after 8 weeks and during subsequent follow-up were assessed by measurements of serum fructosamine (normal range 205–285 μm/l; a serum fructosamine of 400 μm/l is approximately equivalent to an HbA_{1c} of 10%). Patients gave informed consent and a detailed protocol was approved by the institutional ethics committee.

VLCD treatment

Patients were instructed to replace their entire diet with Slimfast, a commercially available liquid meal replacement, for 8 weeks. In addition to three Slimfast meal replacements per day, patients were allowed one bowl of low-calorie vegetable soup, one bowl of vegetables or salad, two portions of fresh fruit and 300 ml of skimmed milk for drinks. This provided approximately 750 calories and 50 g of protein per day. Patients were also instructed to drink at least 1.5 l of calorie-free fluid per day.

Blood glucose monitoring and adjustment of anti-diabetic treatment

All patients were regularly performing home blood glucose monitoring throughout the study, and those on insulin therapy at baseline had their insulin discontinued at the start of the VLCD. Insulin was commenced or recommenced, as required, during subsequent follow-up, and similarly oral anti-diabetic treatments (metformin and sulphonylureas only) were adjusted to individual patient needs in accordance with routine practice. Other medical therapies were unchanged during the 8-week VLCD.

Statistical analysis

Clinical and biochemical parameters at baseline, following 8 weeks of VLCD and at 1 year, were compared by repeated measures analysis of variance. All data are expressed as mean ± SD.

Results

Forty-four patients agreed to participate in the study (approx. half of all consecutive obese patients in secondary failure attending our service during recruitment); four withdrew, all within the first 5 days of starting the VLCD, mainly because of distaste and poor compliance, but there were no further drop-outs. Thus, 40 obese patients with a mean duration of T2DM of 6.1 years (22 male, mean age 52 years, range 33–69 years) completed the study; one-half had evidence of micro- or macrovascular complications. All patients were symptomatic of poor glycaemic control despite treatment with combined (sulphonylurea and metformin) oral anti-diabetic therapy ($n = 26$) or insulin + metformin ($n = 14$). The average dose of insulin was 102 ± 26 U/day among insulin-treated patients ($n = 14$). Baseline clinical parameters for the group were was follows: body weight 115 ± 15 kg, body mass index (BMI) 40 ± 9.4 kg/m^2, BP 152/82 ± 17/9 mmHg, serum triglycerides 3.4 ± 1.7 mM, total cholesterol 6.0 ± 1.2 mM, and fructosamine 387 ± 71 μM.

Tolerability

Four patients were unable to tolerate the VLCD and withdrew in the first week of the study. There were no subsequent withdrawals, and the VLCD was generally well tolerated with favourable early effects on glycaemic symptoms and body weight reinforcing patient compliance. There were no significant electrolyte disturbances.

Short-term effects on body weight, metabolic and cardiovascular parameters

Following 8 weeks of VLCD therapy the average weight loss was 12 kg, and mean BMI had fallen from 40 to 36 kg/m^2. Hyperglycaemic symptoms were improved considerably

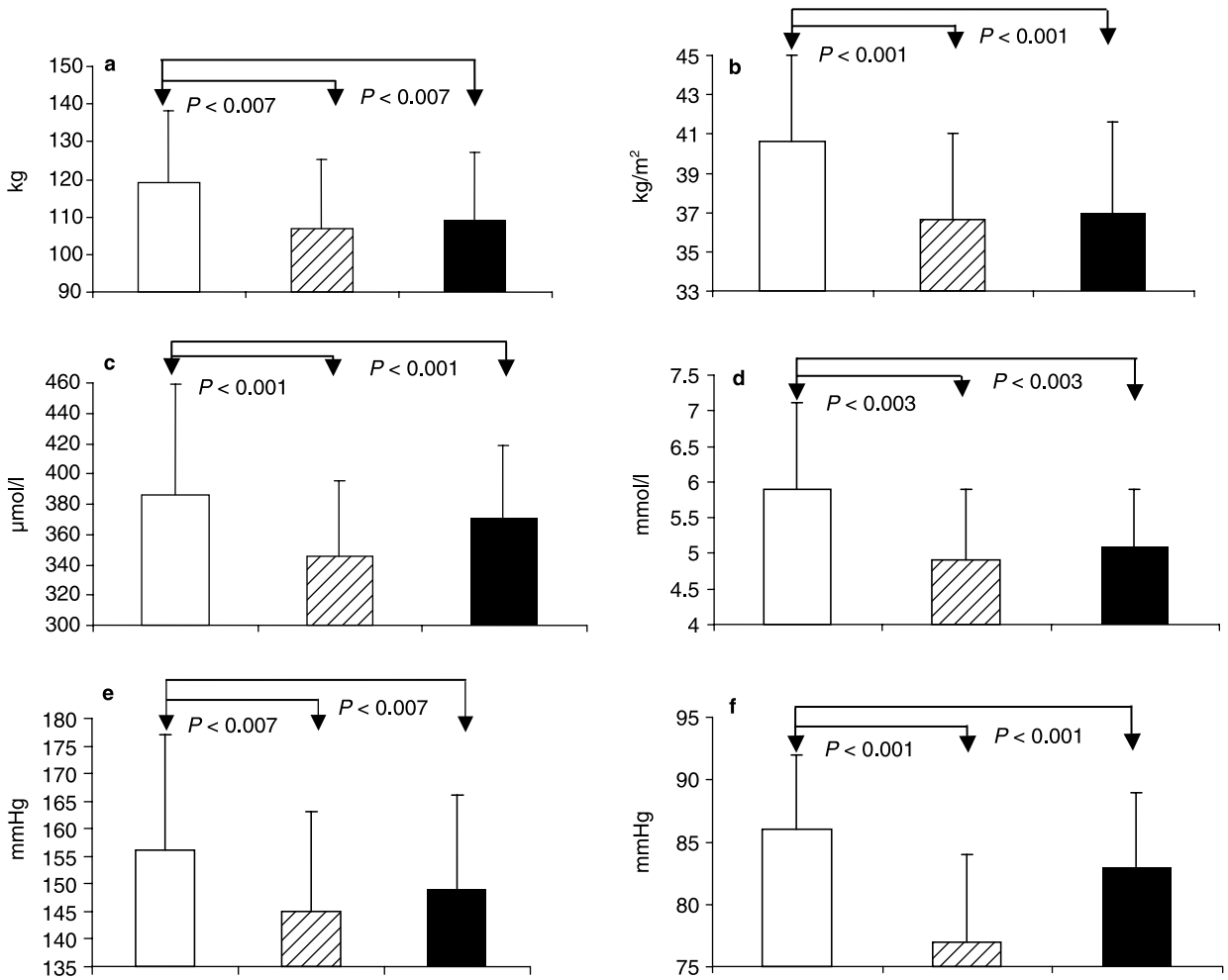

Figure 1 Mean values at baseline (□), after 2 months very-low-calorie diet (hatched) and after 1 year (■) for (a) body weight, (b) body mass index, (c) serum fructosamine, (d) total cholesterol, (e) systolic blood pressure (BP), and (f) diastolic BP (n = 40).

following the VLCD and serum fructosamine was reduced from 386 to 341 µM (Fig. 1). There were additional improvements in serum lipids (e.g. 1.0 mmol/l reduction in total cholesterol) and BP (average reduction 10/6 mmHg) (Fig. 1).

Outcomes at 1 year

Average body weight and BMI after 1 year were 109.5 kg and 37 kg/m^2, respectively. Mean fructosamine for the group was 371 ± 41 µM, and 15 patients were on insulin (average dose 41 U/day). Improvements in total cholesterol and BP were maintained at 1 year (Fig. 1).

Effects of VLCD on insulin requirements

Fourteen patients were treated with metformin + insulin prior to starting the VLCD (average insulin dose 102 U/day). After 8 weeks, 10 patients had (re)commenced insulin (average dose 36 U/day), and after 1 year 15 patients were treated with insulin (Fig. 2). The effects of the VLCD on home blood glucose levels for a typical patient who stopped and restarted insulin (at a much lower dose) are illustrated in Fig. 3.

Discussion

VLCDs have become widely established in the treatment of uncomplicated obesity [5], but historical concerns about cardiovascular safety in patients with co-morbid conditions, and somewhat pessimistic assumptions about early weight regain, have greatly limited the consideration of VLCDs as a treatment option in patients with diabetes, especially in the UK. Most previous studies have evaluated VLCDs as primary weight-loss therapy in small numbers of patients with newly diagnosed diabetes [11,12], but this is the first report describing the short-term and 1-year outcomes of VLCD therapy in symptomatic patients with obesity and T2DM in secondary failure, including a subgroup who had recently switched to insulin and metformin with a suboptimal effect on glycaemic and symptom control. Compliance with three liquid meal replacements per day and only a small amount of solid foodstuff represents a

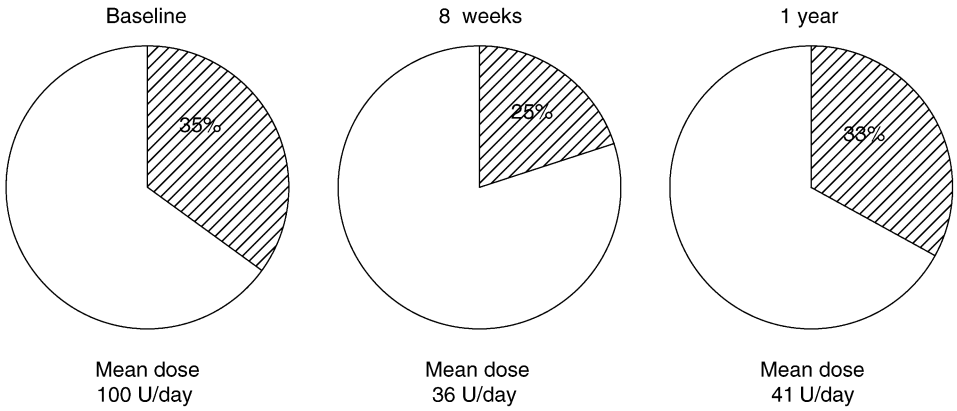

Figure 2 Proportion of patients treated with insulin (and average daily dose) at baseline, after 2 months' very-low-calorie diet (VLCD) and after 1 year.

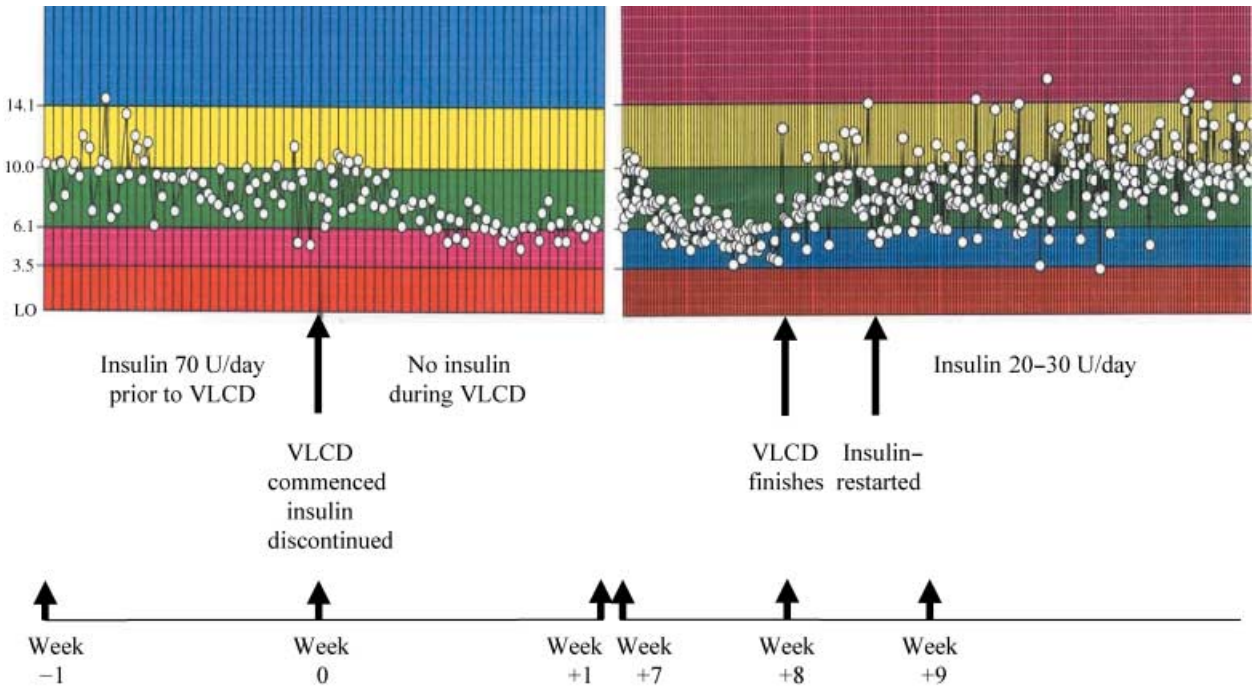

Figure 3 Home blood glucose recordings for an individual patient who was taking 70 U/day of insulin prior to commencing the very-low-calorie diet (VLCD). Insulin was discontinued on starting the VLCD and recommenced 9 weeks later. However, during follow-up, blood glucose levels were considerably better on less than half the pre-VLCD dose of insulin (20–30 U/day), illustrating sustained improvements in insulin sensitivity and dose requirements following the VLCD.

major challenge, but these patients were highly motivated by their symptoms, lack of success with previous therapeutic and dietary interventions, and a realization that energy restriction in the short term and major weight loss in the medium term were unavoidable objectives for improved well-being and glycaemic control. Patients reported an almost immediate improvement in diabetic symptoms which, combined with early weight loss even in the first week, probably encouraged good compliance with the VLCD and explains why there were no drop-outs beyond the first few days. Feelings of hunger during VLCD treatment are generally less than might be expected, and there is evidence that VLCDs have a modest satiating effect due to the high protein content and the ketosis induced by lipolysis [13].

The VLCD was generally well tolerated and highly effective in reducing body weight (on average by 12 kg) and BMI, with favourable reductions in BP (10/6 mmHg) and levels of serum cholesterol (17%) and fructosamine (40 μM, equivalent to 0.8–1% HbA_{1c}) after 2 months. The short-term metabolic and haemodynamic changes are entirely consistent with improved peripheral and hepatic insulin sensitivity [14], although energy restriction, independent of weight loss, has an important effect

on glycaemic control, especially in the early phase of VLCD treatment [15]. There were no gender-related differences in weight loss in the present study, even though some evidence has suggested that male (non-diabetic) subjects lose more weight than women [7]. The secondary benefits on other cardiovascular risk factors, especially BP, should not be underestimated. For example, a reduction of 10/6 mmHg is equivalent to the difference in average BP (10/5 mmHg) between the 'tight' and 'less-tight' BP control groups of the UK Prospective Diabetes Study, an effect which, maintained over 10 years, produced a 32% reduction in diabetes-related deaths [16].

In the post-VLCD follow-up period, patients received standard levels of diabetes care, including diet and exercise advice from a specialist dietician at 2–3-month intervals. Even without intensive behavioural or dietary counselling, sustained improvements in various parameters were still apparent after 1 year. In particular, although there had been some weight regain and a deterioration in glycaemic control, levels of body weight, BMI and fructosamine were still significantly lower than baseline pre-VLCD values. This also applied to those patients on insulin, who had better glycaemic control despite requiring a much lower daily dose of insulin. It has been suggested that obese patients with T2DM regain weight more readily than non-diabetic subjects following an intensive period of dietary intervention [17], implying that short-term VLCD treatment is less appropriate in diabetes, but the time-course and magnitude of weight regain may have been overestimated to the extent that many patients with T2DM are not considered for what is a potentially worthwhile treatment with lasting benefits.

It should be acknowledged that the lack of a parallel control group compromises the interpretation of this study, particularly the magnitude of effects attributable to VLCD therapy. Various factors may have augmented the apparent response to VLCD. These patients were symptomatic and unwell, and therefore practical as well as ethical considerations compromised the design of a 1-year study. Nevertheless, obese patients in secondary failure are notoriously difficult to manage in terms of weight control, symptoms and glycaemic control, and this pragmatic study in a large group of patients indicates that VLCD therapy is a treatment option that perhaps deserves greater consideration in routine clinical practice.

More information is needed on how best to preserve the benefits of short-term VLCD-induced weight loss after resuming a standard diet. There is evidence that individuals who begin exercising (having been unable to exercise prior to the VLCD) maintain weight loss more effectively [18], and oral anti-obesity agents such as sibutramine may be of some benefit [19]. In addition, the idea of intermittent or 'pulsed' VLCD therapy requires further consideration [20]. Outcomes at 1 year were better among patients with T2DM who received intermittent VLCDs (two 3-month periods, months 1–3 and 6–9) compared with those on an ordinary low-calorie diet (1000–1200 kcal/day) with prescribed behavioural therapy [21]; however, the authors of this study concluded that a modest difference in body weight (3.5 kg favouring the VLCD group) did not justify further use of pulsed VLCDs, but alternative VLCD regimes, e.g. frequent short periods of 1–5 days, deserve further evaluation [20].

There has been a long history of debate over the safety and utility of VLCDs in routine clinical practice [6,7], but modern formulations are effective, well tolerated and associated with high levels of patient satisfaction. Importantly, in the present study VLCD therapy was administered and supervised by a specialist dietician working within the framework of a routine diabetes service using an agreed protocol. Dieticians have often been reluctant to use VLCDs without close medical supervision, but this study has demonstrated the feasibility of a dietician-led programme of VLCD education and treatment for those obese patients with T2DM in secondary failure in whom the physician has made a referral. There should be greater consideration given to VLCDs as a treatment option in this difficult-to-manage and symptomatic patient group.

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