

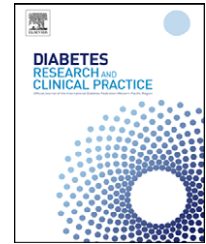


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International Diabetes Federation



Review

Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes^{☆,☆☆}

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ABSTRACT

A recent study has shown that obese patients with newly diagnosed type 2 diabetes who lose 10% of their body weight are more likely to achieve glycaemic and blood pressure targets, despite weight regain. A well-established non-surgical method for achieving weight loss $\geq 10\%$ within 3 months is the use of very-low-calorie diets (VLCDs). In patients with diabetes, VLCDs are associated with rapid improvement in glycaemia and cardiovascular risk factors. The present review analyses the evidence from available trials on the effects of VLCDs on body weight, glycaemic control and complications, and their potential for clinical use in diabetes management.

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Contents

1. Weight loss as a treatment for type 2 diabetes (T2D)	000
2. VLCDs as a weight loss intervention in obesity	000
3. VLCDs and diabetes prevention	000
4. VLCDs as a weight loss intervention in T2D	000
5. VLCDs effect on glycaemia in T2D	000
6. VLCDs on cardiovascular risk factors in T2D	000
7. Current recommendations for the use of VLCDs in T2D	000
8. Further research in VLCDs and T2D	000
References	000

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1. Weight loss as a treatment for type 2 diabetes (T2D)

Obesity is the major risk factor for type 2 diabetes (T2D), accounting for 60–90% of cases [1]. Approximately 80% of people with T2D are overweight or obese, and obesity compounds the cardiovascular risk of T2D, such that T2D individuals 20–30% above their ideal body weight have 2.5–3-fold higher mortality compared to people with diabetes at their ideal weight. Mortality rises to greater than fivefold for individuals >40% above their ideal weight [1]. Weight loss produces numerous benefits in T2D including improved glucose metabolism, reduction in glycaemia and fasting insulin levels and increased insulin sensitivity, reduction in blood pressure, and improvements in lipid profile with decreased triglycerides, increased high density lipoprotein cholesterol (HDL-C) and fewer small, dense low density lipoprotein cholesterol (LDL-C) particles [2]. Observational data suggest weight loss increases life expectancy in T2D by 3–4 months per kilogram lost [3].

Large weight losses (e.g. 10% or more of the baseline body weight), such as with bariatric surgery, can lead to marked improvements in or remission of T2D [4]. A randomised study in recently diagnosed obese T2D patients showed laparoscopic adjustable gastric banding is superior to conventional lifestyle intervention in achieving remission of diabetes at 2 years, largely due to the degree of weight loss (20.7% versus 1.7%) [5]. In the absence of surgical intervention, a retrospective cohort study in 2574 people with newly diagnosed T2D found that those who lost close to 10% of their body weight after diagnosis were more likely to achieve glycaemic and blood pressure targets despite weight regain by year 4, compared to patients who maintained their weight or gained weight post-diagnosis [6]. Weight loss seems more achievable in T2D patients early in their disease [7], and one large study investigating intensive lifestyle intervention and major cardiovascular events is ongoing [2].

2. VLCDs as a weight loss intervention in obesity

Very-low-calorie diets (VLCDs) are defined as diets limiting energy intake to 1.88–3.35 MJ (450–800 kcal) per day while providing at least 50 g of high-quality protein and amino acids, essential fatty acids and daily requirements of trace elements, vitamins and minerals. They are recommended only in the obese (body mass index (BMI) ≥ 30 kg/m²) or in individuals with BMIs >27 kg/m² plus one or more co-morbidities. Generally, they involve an intensive phase (three meal replacements) usually lasting 8–16 weeks. In addition, two cups of salad or low-starch vegetables are eaten to provide fibre to lessen hunger and reduce constipation [8]. A tablespoon of oil or butter is also consumed to prevent gallstones [9]. They are most often commenced in the outpatient setting, as efficacy is not improved by admitting patients for the commencement of these diets [10,11]. A period on a low-calorie diet prior to the VLCD is not recommended. In our clinic we allow patients to eat out at restaurants or socially (avoiding potato, rice, pasta and bread), however one study suggested less weight loss at

Table 1 – Absolute and relative contraindications to the use of very-low-calorie diets.

Absolute contraindications	Relative contraindications
BMI <25 kg/m ²	Age >65 years
Pregnancy/lactation	Child <16 –18 years
Clinical eating disorder	BMI 25–30 kg/m ²
Major psychiatric illness	Type 1 DM
Severe systemic or organ disease, e.g.:	Cholelithiasis
Recent myocardial infarct/angina/stroke	Gout
Major dysrhythmia	
Severe renal/hepatic disease	
Malignancy	
Wasting disorders, such as Cushing's syndrome	

12-weeks and 1-year with a 'liberal' (two small extra meals/week) compared to a strict regimen [11]. Contraindications to VLCD use are shown in Table 1. Type 1 diabetes is often listed as an absolute contraindication to VLCD use; however, in our experience VLCDs in selected obese patients with type 1 diabetes can be used with appropriate education and close supervision.

Modern VLCDs are extremely safe with no increased rate of cardiac arrhythmias [12] or electrolyte abnormalities [13,14] seen in large trials. While early VLCDs were associated with gallstone formation due to inadequate intake of fat, the incidence of cholelithiasis with current day VLCDs incorporating fat is unknown. Increases in serum uric acid are often seen [15], however acute attacks of gout are rare. Reductions in bone mineral density are associated with use of VLCDs [16]; however, there are no data to suggest this increases long-term fracture risk. Side effects tend to be mild and/or transient, and may include dizziness, headache and fatigue, cold intolerance, dry skin, temporary rash, altered bowel habit, hair loss, muscle cramps, menstrual disturbance in women, transient hepatic transaminase rise and halitosis (ketone breath) [17].

VLCDs are associated with ketosis via the production of acetoacetate and beta-hydroxybutyrate from the breakdown of circulating fatty acids. During ketogenic diets, including VLCDs, it appears to be more dependent on the total carbohydrate intake rather than the degree of calorie restriction, although the literature is inconsistent on the level of carbohydrate restriction required to allow ketogenesis (<50 g of carbohydrate up to 192 g/day) [18]. Quantities of other macronutrients may influence this, as up to 57 g of glucose can be produced from 100 g of dietary protein [19]. Typically, the serum ketone levels seen are between 0.33 and 0.72 mmol/L, a rise above a baseline level of <0.10 mmol/L, but much lower than the levels seen in diabetic ketoacidosis, which may be up to 25 mmol/L [18]. Some evidence exists for an appetite-suppressive effect of ketone bodies [20,21], although there is conflicting literature [22] and definitive evidence for a reduction in hunger with the onset of ketosis in VLCDs remains to be shown.

The advantages of VLCDs include rapid weight loss that acts as a motivating factor, calorie restriction-associated diuresis that can alleviate fluid retention, preservation of lean body mass and probably hunger suppression by mild ketosis. Perhaps paradoxically, the convenience of meal

replacements and restriction of foods improves acceptability and adherence [17].

VLCDs produce an initial large weight loss, in the order of 1.5–2.5 kg per week, and weight losses during the intensive phase may range from 12 to 35 kg [10]. While weight regain is usual, there is no good evidence that regain is more rapid compared with other dietary means of weight reduction [10]. A 2001 meta-analysis found a mean weight loss of 6.6% after VLCD at 4.5 years (compared to 2.1% using a hypocaloric balanced diet) [23]. Some data have suggested a gender difference, whereby males do better on VLCDs and women on non-VLCD programs [24]. Long-term mean weight losses for VLCDs versus non-VLCDs show little difference [23], however, some patients maintain significant weight loss following VLCD programs. One study of 112 patients who achieved >10 kg weight loss with VLCD at 12-weeks, showed 40% maintained >5% weight loss, and 25% >10% at 7 years [25].

Behavioural therapy (keeping food diaries, employing shopping strategies, dietary and exercise education, and so on) is often employed in studies of VLCDs. In a study of 76 obese women, 27% maintained >5 kg weight loss at 5 years with VLCDs plus behavioural therapy (BT) compared to 11% with VLCDs alone and 13% with LCDs plus BT, suggesting a role of BT in decreasing weight regain [26]. Exercise may also assist with reducing weight regain, and we recommend low intensity, aerobic exercise in combination with VLCD to promote weight maintenance. In a study of 30 women, addition of exercise to VLCD plus BT did not increase initial weight loss but improved weight maintenance at 1 and 2 years (−9.1 kg versus −0.8 kg) [27]. It should be recognised that there is a paucity of quality data looking specifically at exercise and VLCDs combined with regard to weight loss and health outcomes versus LCD/BT plus exercise [28].

3. VLCDs and diabetes prevention

To date, diabetes prevention programs using non-surgical or pharmacological intervention have focused on exercise and dietary modification and have achieved modest weight loss of the order of 5–7% [29–31]. The Finnish Diabetes Prevention Study used adjuvant VLCDs in 48 patients with unsatisfactory weight loss at 6 months and showed a benefit in terms of weight loss but no difference in diabetes incidence compared to the non-VLCD group [30]. No randomised studies have specifically addressed the question of diabetes prevention in obesity or pre-diabetes using VLCDs. A consensus statement from the International Diabetes Federation does not recommend the use of VLCDs in diabetes prevention due to the lack of evidence for benefit in achieving long-term reductions in weight [32].

4. VLCDs as a weight loss intervention in T2D

A Cochrane review published in 2004 (amended in 2007) concluded that insufficient quality data exist to recommend VLCDs over other diets in T2D and called for studies to address this question [28]. Furthermore, people with T2D may find it harder than people without diabetes to lose weight, including

using VLCDs. A small study of 12 diabetic individuals and their spouses undergoing behaviour modification suggested less weight loss in the diabetic group, likely due to dietary non-adherence in the diabetes group [33]. Other studies support the notion that individuals with T2D have greater difficulty initiating or maintaining weight loss using dietary and behavioural therapy [34], pharmacotherapy [7,35,36], and bariatric surgery [37] although the literature is conflicting [38]. Reasons often given for the decreased efficacy of weight loss interventions in T2D include antidiabetic therapies, especially insulin and thiazolidinediones, which promote adipose tissue deposition and fluid retention, increased food intake to avoid hypoglycaemia, and reduced calorie loss via reductions in glycosuria.

With VLCDs as the intervention, a study with 15 participants showed less weight loss in the T2D VLCD group compared to the non-diabetic VLCD group, but the T2D group was less obese at baseline [14]. One study comparing 7 insulin treated diabetic patients to 11 on sulfonylureas and 12 non-diabetic controls suggested that use of insulin may impair weight loss with VLCDs in individuals with diabetes [39]. However, conclusions were limited by the small numbers and proportionally more women in the insulin-treated group. Theoretically, the use of exogenous insulin or an insulin secretagogue may reduce diet tolerability and thus efficacy through non-adherence, as insulin directly inhibits ketogenesis in the liver [40]. The risk of hypoglycaemia may also promote greater food intake, decreasing adherence. Insulin inhibits lipolysis in adipose tissue; hence elevated levels such as with high doses of exogenous insulin or sulfonylureas may lead to reduced weight losses with VLCDs. However, differences in weight loss, hunger and ketone levels in patients with T2D on therapies that raise insulin levels have not been demonstrated so far. Thus, firm evidence for reduced efficacy of VLCDs in obese individuals with diabetes is lacking.

Weight regain is frequent in individuals with T2D undergoing weight loss regimens including VLCDs, as it is in non-diabetic obese individuals. Little data exist to show a difference in weight regain following VLCD between non-diabetic patients and individuals with T2D. Homeostatic mechanisms of weight regulation post-weight loss, such as reductions in leptin [41,42], cholecystokinin [43] levels and triiodothyronine (T3) and rises in reverse triiodothyronine (rT3) [14] and circulating ghrelin [44] levels, are potential modulators in weight regain through effects on satiety and appetite and energy expenditure, both in obesity and T2D. Studies investigating appetite suppression via pharmacotherapy in obese and T2D individuals in the post-VLCD period are ongoing.

Practical considerations in people with diabetes undergoing VLCDs include the risk of hypoglycaemia with sulfonylureas and insulin, and doses are generally halved at commencement of VLCDs. Further adjustment and close glycaemia monitoring is mandatory. Antihypertensives and diuretic therapies often need adjustment to prevent hypotension and dehydration. The co-existence of renal impairment should also be considered. While end-stage renal failure is an absolute contraindication, lesser degrees of chronic renal impairment may benefit. No deterioration in renal function was seen in one study including 11 patients with T2D and

serum creatinine $>130 \mu\text{mol/L}$ [45], while another study showed increased creatinine clearance and reduced proteinuria in 24 patients with T2D undergoing a VLCD [46]. Prior to commencement of a VLCD in the diabetic patient screening investigations therefore should include markers of glycaemic control such as glycosylated haemoglobin A1c (HbA1c), serum electrolytes and renal function, liver function tests, thyroid function, lipid profile and uric acid level, urinary albumin, and an electrocardiogram (ECG).

5. VLCDs effect on glycaemia in T2D

Effects of VLCDs on plasma glucose levels occur rapidly, with falls in mean glucose levels seen within days and reaching near-nadir after 1–2 weeks [47]. The majority of the glucose-lowering effect seems related to calorie restriction, whereas weight loss has an increasing contribution with time via reductions in intraabdominal (visceral) adipose tissue [48–50]. In a 12-week study of 14 obese patients with T2DM using VLCDs, marked improvement was seen in glycosylated HbA1c [51]. Twelve-month follow-up data in nine individuals showed a rise in HbA1c but this remained below baseline (8.8% versus 8.1%, $p < 0.05$) [52]. Another study in 36 obese subjects with T2D compared the addition of a VLCD or LCD to a 20-week behavioural program [53]. At 20 weeks significantly more weight was lost in the VLCD group (18.6 kg versus 10.1 kg), however this was not sustained over the next 12 months (8.6 kg versus 6.8 kg). Significant differences were maintained, however, with respect to fasting glucose levels (9.17 mmol/L versus 11.78 mmol/L) and HbA1c while antidiabetic medication use at 72 weeks was similar between groups. However, a

subsequent study looking at intermittent use of VLCD in 93 people with T2DM led to only modestly better weight loss at 1 year (14.2 kg versus 10.5 kg) and no improvement in HbA1c, glucose or insulin levels compared to yearlong LCD [54]. A 5-year study of 15 obese patients with T2D (two with recent onset) showed no significant differences by study's end in fructosamine or fasting glucose levels, although one patient sustained >10 kg weight loss and remained in remission from diabetes at 5 years [55].

Beta-cell function in people with T2D undergoing VLCD treatment improves but remains significantly impaired [56]. Both people without diabetes and people with T2D show a fall in fasting plasma insulin/c-peptide levels [57]. In T2D patients no return of the first-phase insulin response is seen. However, there are improvements in dynamic insulin secretion and overall insulin production, modulation of pulsatility and improved synchrony [58]. High-ketogenic VLCDs lower glucose more than low-ketogenic VLCDs in obese T2D patients, possibly by reducing hepatic glucose output [59]. It has been demonstrated that ketone bodies can stimulate insulin secretion in normal humans [60] but it is unlikely that this has a significant clinical effect in people with diabetes on ketogenic diets, firstly as levels are relatively low and secondly there is evidence of reduced effects in diabetes [61]. Ketones can, however, directly suppress the elevated hepatic glucose output in T2D [59]. It has been hypothesised that mild ketosis may improve peripheral insulin resistance, as studies on cardiac muscle have shown that – within limits – ketones can mimic the acute effects of insulin on the myocardium, including increasing intracellular glucose concentrations, mitochondrial energy production and the efficiency of the working heart [62]. Other investigators suggest a reduction in

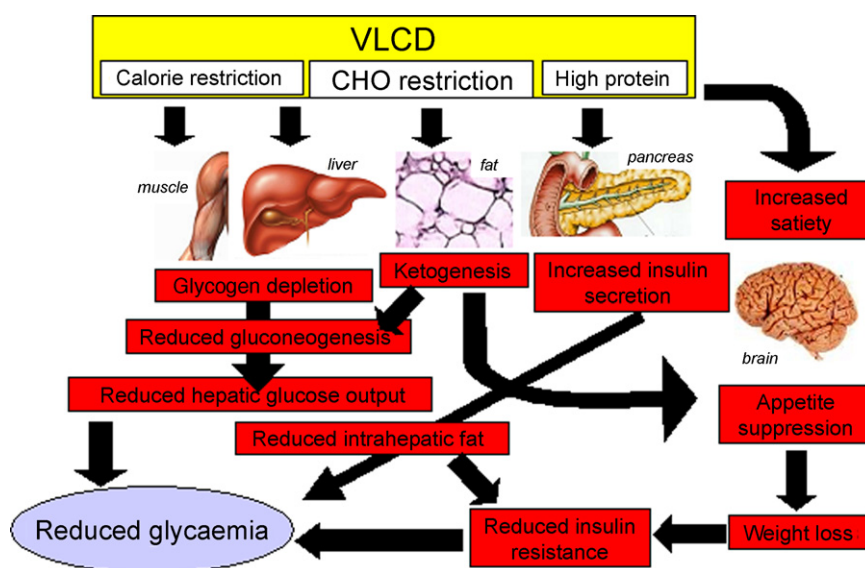


Fig. 1 – Schema for the effects of VLCDs on glycaemia. Calorie restriction leads to glycogen depletion in muscle and liver. Restriction of carbohydrate (CHO) leads to lipolysis and the formation of ketone bodies by the liver [18]. Together, these lead to reductions in hepatic glucose output via inhibition of gluconeogenesis and reduced glycogenolysis [59,61,62]. High protein stimulates insulin secretion [64] and increases satiety [65]. Circulating ketone bodies probably contribute to tolerability of the diet by suppressing appetite in the hypothalamus [20]. Weight loss and diminution of fat depots in the liver, muscle and peri-visceral space lead to reductions in insulin resistance [49,50]. Improved insulin sensitivity, dynamic insulin secretion and reduced hepatic glucose output lead to reductions in blood glucose levels [57,58].

cardiac insulin sensitivity with chronic ketone body exposure [63]. The effects of VLCDs on glycaemia are summarised in Fig. 1.

6. VLCDs on cardiovascular risk factors in T2D

VLCDs produce multiple beneficial effects on metabolic parameters in patients with T2D by virtue of both calorie restriction and weight loss. Generally, blood pressure (systolic and diastolic) falls. Orthostatic hypotension can occur early due mainly to dehydration caused by glycogen depletion-related diuresis and sodium losses [56]. Triglycerides fall by around 25%, and total cholesterol and LDL-C generally also are reduced [56]. HDL-C results are variable, and seem dependent on the degree of weight loss and the time frame. Typically, there is little change in HDL-C levels during the VLCD period, with a subsequent rise with sustained weight loss [66].

Weight loss in obesity and diabetes has been shown to improve left ventricular systolic and diastolic function and reduce left ventricular mass [67,68]. Short-term (under 1 week) VLCD was shown to be associated with increased intracardiomyocellular triglyceride and decreased left ventricular diastolic function in healthy and T2D patients [69,70], however over the intermediate term this resolved and net improvements in myocardial function in diabetic patients were seen [71].

In non-alcoholic fatty liver and steatohepatitis, VLCDs produce a reduction in liver size and fat volume within 6 weeks [72]. Transient rises in liver enzymes – possibly due to rapid mobilisation of intracellular triglycerides and fatty acid release causing portal inflammation – are reversed with weight loss [73] and fall below baseline with weight maintenance [10].

The patient population with diabetes has a threefold higher prevalence of obstructive sleep apnoea [74]. VLCDs have been shown to significantly improve sleep apnoea even with only very modest weight loss, and favourable effects on baroreflex sensitivity may have prognostic implications [75].

7. Current recommendations for the use of VLCDs in T2D

No body currently recommends VLCDs for use in T2D or in obese patients at high risk of diabetes for diabetes prevention, citing the lack of evidence for better long term weight loss compared with other non-surgical interventions [4,28,32]. The long-term effects of VLCDs on glycaemic control, cardiovascular risk and diabetic complications are generally small or absent, and there are no data on the long-term effect on complications and mortality. Therefore, in whom should VLCDs be used? Outside of the fairly well-established pre-bariatric surgery indication, consideration could be given to individual patients with multiple obesity-related comorbidities requiring burdensome polypharmacy, patients with obesity-related end-organ dysfunction such as renal hyperfiltration or cardiac diastolic dysfunction, or those with difficult to control diabetes despite multiple oral agents (perhaps as an alternative to commencement of insulin therapy) or very high doses of exogenous insulin. VLCDs

should be utilised as part of an effort to institute lifestyle change, especially commencement of an exercise programme, and with dietary education reviewing standard tenets of the diabetes diet and also focussing on food choice and behavioural modification. In our experience, particularly in obese patients with diabetes and comorbidities inhibiting lifestyle interventions (such as sleep apnoea and osteoarthritis), the rapid weight loss achieved with VLCDs can be both a catalyst to implement necessary lifestyle changes and can also facilitate the implementation of such changes by improving well-being, energy levels and factors such as sleep quality, symptomatic hyperglycaemia and joint pain. While the literature shows that the long-term effect on weight loss is generally disappointing, individual cases show significant beneficial effects from this approach [76].

8. Further research in VLCDs and T2D

Further long-term randomised trials in obesity looking at weight loss durability with VLCDs versus other interventions are warranted. However, it is likely that most research will focus on novel weight maintenance strategies, especially pharmacological, post-VLCDs. The efficacy of VLCDs in T2D versus the non-diabetic obese remains to be clearly elucidated, in particular the effect of exogenous insulin therapy or insulin secretagogues on weight loss with VLCDs in T2D. Specific areas for further research include use of VLCDs for diabetes prevention in high-risk populations, such as individuals with impaired glucose tolerance or women with polycystic ovarian syndrome. In addition, a comparison of the efficacy of VLCDs in newly diagnosed T2D versus conventional lifestyle intervention or bariatric surgery should be performed. The current absence of data on long-term glycaemic control and micro- and macro-vascular complications following VLCD use in T2D highlights the need for quality trials in this area.

Conflict of interest

Joseph Proietto is Chair of the Optifast Medical Advisory Committee for Nestle Nutrition and serves on the Medical Advisory Board for Abbott Pharmaceuticals.

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