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Insulin resistance in obese patients with type 2 diabetes mellitus : effects of a very low calorie diet

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CHAPTER 9

Sustained beneficial metabolic effects 18 months after a 30-day very low calorie diet in severely obese patients with type 2 diabetes.

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Submitted

ABSTRACT

Very low calorie diets (VLCDs) induce rapid weight loss and improve glycaemia, dyslipidaemia and blood pressure in obese patients with type 2 diabetes mellitus. It is unclear how long the beneficial effects of a once-only VLCD will last in these patients.

We therefore looked at the long-term effect (18 months) of a once-only 30-day VLCD (450 kCal/day) on body weight, glycaemic regulation, hypertension and dyslipidaemia in 22 obese (BMI 37.7 ± 1.1 kg/m², mean $\pm$ SEM) type 2 diabetic patients (mean duration of diabetes 7.4 ± 1.0 years, fasting plasma glucose [FPG] 12.4 ± 0.8 mmol/L, HbA_{1c} $8.3 \pm 0.3\%$), who participated in 2 other studies in which a 30-day VLCD was the intervention. During the 30-day VLCD, all blood glucose-lowering medication (including insulin) was stopped. After the 30-day VLCD, caloric intake was slowly increased to eucaloric and patients were encouraged to maintain weight loss. Medication for their diabetes, blood pressure or dyslipidaemia was reinstituted if deemed necessary by their own physician. On day 0 and 30 of the VLCD and after 18 months follow-up, anthropometric measures, blood pressure, glucose, HbA_{1c}, insulin, C-peptide and lipid levels were measured.

The 30-day VLCD significantly reduced body weight (-11.4 ± 0.6 kg) with an improvement in dyslipidaemia, hypertension and glycaemia (although all blood glucose-lowering medication was discontinued). As a group, patients had sustained loss of body weight and improvement in blood pressure and lipids, at 18 months follow-up. HbA_{1c} levels were also significantly lower (-0.7% compared to day 0), although patients used less blood glucose-lowering medication, especially insulin (18 patients on day 0 [112 ± 21 units/day]; 6 patients at 18 months [23 ± 9 units/day]). The 6 patients on insulin therapy at 18 months all had regained weight to prediet levels, but still had a better cardiovascular risk profile as compared to before the dietary intervention.

In conclusion, a once-only 30-day VLCD leads to a sustained improvement in glycaemia, dyslipidaemia and blood pressure up to 18 months follow-up in obese type 2 diabetic patients, even, although to a lesser extent, in patients who regained body weight.

INTRODUCTION

Type 2 diabetes mellitus is a major health problem, both qualitatively and quantitatively. The number of patients with type 2 diabetes is increasing steadily worldwide with an estimated 366 million patients in 2030¹. Especially worrisome is the increasing number of children and adolescents with type 2 diabetes mellitus^{2,3}. It is estimated that over 80% of adult patients with type 2 diabetes are overweight (defined as a body mass index [BMI] between 25 and 30 kg/m²) or obese (BMI > 30 kg/m²)⁴ and almost all children and adolescents who develop type 2 diabetes are overweight or obese^{2,5}. Genetic factors are without doubt of major significance in the development of type 2 diabetes but environmental and social factors, like a lack of physical exercise and high caloric intake, are equally important and are pivotal targets for therapy.

Both impaired insulin secretion and insulin resistance of target organs are involved in the cause of type 2 diabetes mellitus. Insulin resistance is thought to be of major pathogenetic importance in obese type 2 diabetic patients⁶, making it often difficult to achieve adequate glycaemic regulation. Insulin therapy in this patient group induces further weight gain, hence aggravating insulin resistance. Weight loss reduces insulin resistance and its associated metabolic abnormalities (hyperglycaemia, hyperinsulinaemia, dyslipidaemia and hypertension)⁷⁻⁹ and, therefore, the only reasonable approach in (very) obese patients with type 2 mellitus is weight reduction.

Caloric restriction remains the hallmark for weight loss. However, only substantial caloric restriction or less severe caloric restriction of longer duration, will lead to the considerable weight loss (≥ 5 -10 kg) needed to improve peripheral insulin sensitivity in morbidly obese¹⁰ and obese type 2 diabetic patients¹¹. Substantial caloric restriction has the advantage of rapid weight loss, which stimulates patients to adhere to their diet. Very low calorie diets (VLCD, < 800 kCal/day) can be used for this purpose. Nowadays, these diets are commercially available and safe¹². Several strategies can be followed: continuously for several weeks to months or intermittently^{13,14}. Both these regimens will lead to weight loss and improvement of blood glucose levels. However, the question is: how long will these effects of a VLCD on body weight, glycaemic control and other metabolic derangements last in obese type 2 diabetic patients?

The purpose of this study was to evaluate the long-term (18 months) effect of a once-only 30-day VLCD (Modifast®, 450 kCal/day) on body weight and glycaemic control in obese type 2 diabetic patients with inadequate glycaemic regulation, despite the fact that most patients used large doses of insulin before the dietary intervention, in addition to oral blood glucose-lowering agents. The effects on dyslipidaemia and blood pressure were also evaluated.

PATIENTS AND METHODS

Patients

Twenty-two obese (BMI 37.7 ± 1.1 kg/m², mean $\pm$ SEM) patients (12 female and 10 male) with type 2 diabetes mellitus (mean duration 7.4 ± 1.0 years, fasting plasma glucose (FPG) level 12.4 ± 0.8 mmol/L, HbA_{1c} $8.3 \pm 0.3\%$), age 56 ± 2 years, who participated in 2 different studies^{15,16}, in which a 30-day VLCD was either used as the intervention or offered as a therapy after finishing the initial study, were followed (as an observational study) for 18 months after they completed these 2 studies. The 2 studies were approved by the Medical Ethical Committee of Leiden University Medical Centre. Inclusion criteria for these 2 studies were a diagnosis of type 2 diabetes mellitus and obesity (BMI > 30 kg/m²). In addition, glycaemic regulation had to be poorly controlled, defined as an HbA_{1c} level $> 7\%$ and FPG levels > 10 mmol/L. Eighteen of the twenty-two patients used insulin (mean dosage 112 ± 21 units/day) with or without oral blood glucose-lowering agents.

All patients underwent a medical screening, including a physical examination, blood chemistry testing and an electrocardiogram. None of the patients had a history of cardiovascular disease, nor did they have liver or kidney function abnormalities. The use of antihypertensive or lipid-lowering medication was allowed. None of the patients used other drugs, were smokers or suffered from any other disease that might interfere with the study.

Protocol

Study measurements, as outlined in the methods, were performed on day 0 and 30 of a 30-day VLCD and 18 months after the completion of the VLCD. All measurements were performed in the morning after an overnight fast while patients were still in the fasting state. Three weeks before the start of the study, all oral blood glucose-lowering agents were discontinued. If patients also used insulin, the insulin dosage was adjusted if necessary after the discontinuation of the oral blood glucose-lowering agents. On day 0, a VLCD (Modifast®, 450 kCal/day) was started and from that moment on insulin therapy was discontinued as well, at least for

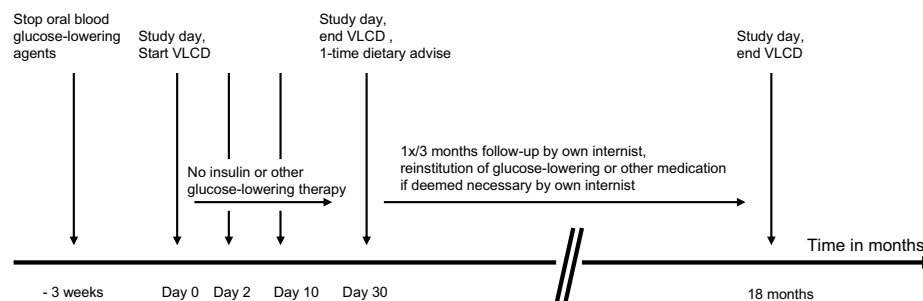


Figure 1

the duration of the 30-day VLCD. Patients followed the VLCD for 30 days. During the 30-day VLCD, patients visited the outpatient clinic every week for support to keep up with their diet and control of body weight, blood pressure and blood glucose levels. After the 30-day VLCD, a normal diet was slowly reintroduced (reinstitution of 1 normal meal per 2-4 weeks, with an increase of 200 kCal/ 2-4 weeks until a caloric intake aimed at weight maintenance (energy requirements measured by bioelectrical impedance measurement) was achieved (around 1500 kCal/day) and patients were advised to maintain their weight loss. Thereafter patients were seen every 3 months at the outpatient clinic (Fig. 1).

The VLCD consisted of three sachets of Modifast® (Nutrition & Santé, Antwerpen, Belgium) per day (450 kCal/day), providing about 50 g protein, 50-60 g carbohydrates and 7 g lipids daily. During the diet patients were allowed to drink calorie-free substances *ad libitum*.

METHODS

Length (meters [m]), weight (kilograms [kg]), body mass index (BMI= weight (kg) / length² (m)) and waist/hip circumference were measured according to WHO recommendations¹⁷.

Blood pressure was measured with an Omron 705IT blood pressure device (Omron Matsushita, Mie, Japan) and recorded with 1 mmHg accuracy.

Serum insulin was measured with a radioimmunoassay (RIA) (Medgenix, Fleurus, Belgium), with an interassay coefficient of variation (CV) below 5%.

Serum glucose, total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured with a fully automated Modulari system consisting of a P800, an I800 and an E170 (Roche, Almere, The Netherlands). HbA_{1c} levels were measured with an HPLC system (Variant, Biomed, Hercules, CA, USA). C-peptide levels were measured with a radioimmunoassay (Linco Research, St. Charles, MO, USA). The interassay CV was 4.2 to 6.0% with a sensitivity of 0.03 ng/mL.

Calculations

Data are presented as mean $\pm$ SEM.

Homeostatic Model Assessment (HOMA) of insulin resistance (IR, normal values approach 1) and β -cell function (% β , 100% is normal) were calculated with the updated computer version (HOMA2) of the formulae of Matthews *et al.*¹⁸.

10 year coronary heart disease (CHD) risk was calculated according to both the Framingham risk score¹⁹ and the United Kingdom Prospective Diabetes Study (UKPDS) risk engine²⁰.

Differences between study days were calculated with the Student's *t*-test for paired samples. Differences between groups were calculated with the Student's *t*-test for independent samples. A non-parametric test (Wilcoxon signed-rank test) was performed when appropriate. All analyses were performed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Intervention period (day 0 to day 30 of the VLCD)

Baseline characteristics of the patients, as well as changes after 30 days VLCD and 18 months follow-up are given in Table 1. All 22 patients completed the 30-day VLCD without problems, no deterioration of glycaemic control occurred and no side effects were noted. Neither oral blood glucose-lowering agents nor insulin therapy had to be restarted during the VLCD.

Patients lost 11.4 ± 0.6 kg ($p = 0.0001$) and waist circumference decreased 8.6 ± 1.0 cm ($p = 0.0001$). Despite the fact that all blood glucose-lowering medication was discontinued, both FPG levels as well as HbA_{1c} levels decreased, although not significant. Fasting serum insulin concentrations declined from 19.7 ± 3.0 mU/L on day 2 to 15.0 ± 2.0 mU/L on day 30 ($p = 0.013$). HOMA-IR decreased from 3.4 ± 0.4 to 2.4 ± 0.3 ($p = 0.001$), whereas HOMA- β increased from 39.4 ± 6.0 to 53.4 ± 10.0 ($p = 0.031$). We used day 2 for the measurement of the serum insulin concentration to avoid interference with long-acting insulin, which had been used until one day before the start of the VLCD.

Systolic and diastolic blood pressure decreased significantly. Total cholesterol and triglyceride concentrations also decreased significantly. HDL-cholesterol, as is often seen at the initiation of weight loss, decreased a little.

Post-intervention period (day 30 to 18 months following the VLCD)

As the patients were free to choose their diet, we were not informed about their caloric intake during this period. No patient was lost to follow-up. As a group, patients did not gain weight

Table 1. Anthropometric measures, glycaemic regulation, lipid levels and blood pressure before, at the end and 18 months after a 30-day VLCD in obese type 2 diabetic patients.

	Day 0	Day 30	18 months
Weight (kg)	111.4 $\pm$ 3.5	99.3 $\pm$ 3.3 [*]	99.1 $\pm$ 3.4 [†]
BMI (kg/m ²)	37.7 $\pm$ 1.1	33.8 $\pm$ 1.0 [*]	33.4 $\pm$ 1.1 [†]
Waist circumference (cm)	122 $\pm$ 2	113 $\pm$ 2 [*]	114 $\pm$ 2 [†]
FPG (mmol/L)	12.4 $\pm$ 0.8	10.7 $\pm$ 0.9	10.9 $\pm$ 1.0
HbA _{1c} (%)	8.3 $\pm$ 0.4	7.9 $\pm$ 0.4	7.6 $\pm$ 0.4 [‡]
Systolic blood pressure (mmHg)	168 $\pm$ 7	143 $\pm$ 7 [§]	145 $\pm$ 4
Diastolic blood pressure (mmHg)	95 $\pm$ 4	83 $\pm$ 3 [§]	81 $\pm$ 2
Total cholesterol (mmol/L)	5.9 $\pm$ 0.4	4.7 $\pm$ 0.2 [§]	5.4 $\pm$ 0.2 ^{**}
HDL-cholesterol (mmol/L)	1.1 $\pm$ 0.05	1.0 $\pm$ 0.05 [§]	1.3 $\pm$ 0.07 ^{,††}
Cholesterol/HDL-cholesterol ratio	5.6 $\pm$ 0.4	5.1 $\pm$ 0.4	4.6 $\pm$ 0.3 ^{‡‡}
Triglycerides (mmol/L)	4.9 $\pm$ 1.5	1.9 $\pm$ 0.3 ^{§§}	2.5 $\pm$ 0.4 ^{, ,##}
Units of insulin (no. of patients treated with insulin)	112 $\pm$ 21 (n=18)	0	23 $\pm$ 9 (n=6)

^{*} $p = 0.0001$, [§] $p = 0.004$, [†] $p = 0.007$, ^{§§} $p = 0.001$: day 30 as compared to day 0.

^{††} $p = 0.0001$, [‡] $p = 0.027$, ^{||} $p = 0.0001$, ^{|||} $p = 0.009$: 18 months versus day 0.

^{**} $p = 0.007$, ^{††} $p = 0.0001$, ^{‡‡} $p = 0.004$, ^{##} $p = 0.014$: 18 months versus day 30

from the end of the VLCD up to 18 months follow-up. In addition, waist circumference, as a measure of visceral fat mass, also remained the same. During the follow-up period, 1 patient experienced an acute coronary syndrome, and 1 patient developed prostate cancer. Some patients intermittently used a hypocaloric (1 sachet of Modifast for breakfast in combination with 2 normal meals a day) but not a very low calorie diet. Furthermore, no weight-control drugs were used.

FPG levels and HbA_{1c} levels did not increase during the follow-up period and although most patients were restarted on oral blood glucose-lowering therapy, the dose was less than before the diet. Since 6 patients were on insulin therapy again at 18 months follow-up and, hence, their fasting serum insulin level would not be accurate, we did not use their data for comparison with the fasting serum insulin concentration on day 30 (and day 2, next section). In addition, serum insulin levels at 18 months were lacking in 2 patients. We can therefore only compare data on endogenous insulin levels of 14 patients and, hence, HOMA-IR and HOMA- β could also only be calculated for 14 patients. Nevertheless, in these 14 patients serum insulin (15.3 ± 2.3 mU/L on day 30 to 14.4 ± 2.1 mU/L at 18 months), HOMA-IR (2.4 ± 0.3 on day 30 to 2.2 ± 0.3 at 18 months) and HOMA- β (53.4 ± 10.0 on day 30 to 55.7 ± 9.0 at 18 months) did not change significantly between day 30 and 18 months follow-up.

Systolic and diastolic blood pressure did not differ between day 30 and 18 months follow-up. Total cholesterol and triglyceride levels increased to some extent whereas HDL-cholesterol levels were significantly higher at 18 months as compared to day 30 ($p = 0.007$). (Table 1)

When looking more closely at the data, 8 patients had stable body weight (plus or minus 5 kilogram [kg]), 6 patients lost more than 5 kg of body weight and 8 patients regained more

Table 2. Cardiovascular risk factors at 18 months, according to post-intervention (day 30 to 18 months follow-up) weight changes.

	From day 30-18months :		
	Stable weight (n=8)	Weight loss > 5 kg (n=6)	Weight gain > 5 kg (n=8)
FPG (mmol/L)	10.1 $\pm$ 1.2	10.2 $\pm$ 2.6	12.5 $\pm$ 1.6
HbA _{1c} (%)	7.8 $\pm$ 0.4	7.1 $\pm$ 0.9	8.1 $\pm$ 0.6
Systolic blood pressure (mmHg)	148 $\pm$ 4	132 $\pm$ 6*	153 $\pm$ 7*
Diastolic blood pressure (mmHg)	84 $\pm$ 2	75 $\pm$ 3 [‡]	82 $\pm$ 4
Total cholesterol (mmol/L)	5.3 $\pm$ 0.5	5.2 $\pm$ 0.4	5.6 $\pm$ 0.3
HDL-cholesterol (mmol/L)	1.3 $\pm$ 0.1	1.4 $\pm$ 0.2	1.2 $\pm$ 0.1
Triglycerides (mmol/L)	2.5 $\pm$ 0.8	1.7 $\pm$ 0.1	3.1 $\pm$ 0.4 [§]
C-peptide (ng/mL)	1.2 $\pm$ 0.2	0.9 $\pm$ 0.1	0.8 $\pm$ 0.2
Insulin (mU/L)	16.0 $\pm$ 4.1	12.5 $\pm$ 1.9	13.0 $\pm$ 0.6
HOMA-IR	2.4 $\pm$ 0.6	1.7 $\pm$ 0.2	2.4 $\pm$ 0.4
HOMA- β	53.5 $\pm$ 9.6	85.4 $\pm$ 17.9	21.4 $\pm$ 4.1 [¶]

Data are presented as mean $\pm$ SEM

* $p = 0.033$, [‡] $p = 0.017$

weight stable versus weight loss

[†] $p = 0.022$, [§] $p = 0.011$, [¶] $p = 0.031$

weight gain versus weight loss

^{||} $p = 0.016$

weight stable versus weight gain

Table 3. Use of blood glucose-lowering, lipid-lowering and antihypertensive agents before and 18 months after a 30-day VLCD in obese type 2 diabetic patients.

	Day 0	18 months
	number of patients	number of patients
Insulin only	6	1
Insulin + oral blood glucose lowering agent	12	5
Metformin only	1	7
Metformin + SU-derivative	3	5
No blood glucose lowering therapy	0	4
Statin	6	4
Fibrate	3 (1 also statin)	1
Beta-blocker	9	7
ACE-inhibitor of ATII-antagonist	11	11
Diuretic	10	3
Number of antihypertensive agents	Day 0	18 months
	number of patients	number of patients
0 antihypertensive agents	6	9
1 antihypertensive agent	7	7
2 antihypertensive agents	5	5
3 antihypertensive agents	4	2
4 antihypertensive agents	1	0

than 5 kg of body weight from day 30 to 18 months follow-up (see Table 2). When these 3 groups were compared, the patients that had gained body weight had worse glycaemic control and dyslipidaemia and a higher (systolic) blood pressure as compared to the other 2 groups. Because the groups were small, significance was not always reached.

Day 0 versus 18 months follow-up

As a group, body weight and waist circumference were significantly lower at 18 months follow-up as compared to day 0.

FPG and HbA_{1c} levels for the whole group were also significantly lower at 18 months, despite the fact that patients used less blood glucose-lowering medication (see Table 3). Four patients used no blood glucose-lowering therapy at all at 18 months. Most of the patients on oral blood glucose-lowering therapy were on metformin only. In addition, only 6 patients were on insulin therapy at 18 months (5 patients had already been on insulin therapy before the VLCD, 1 patients used insulin for the first time) with a mean dose of 23 ± 9 units per day, whereas before the VLCD 18 patients were on insulin therapy with a mean dose of 112 ± 21 units/day.

Fasting serum insulin concentrations and HOMA-IR and HOMA- β could be compared in 14 patients (see section above). Fasting serum insulin levels were significantly lower at 18 months (14.4 ± 2.1 mU/L) as compared to day 2 (20.2 ± 3.5 mU/L), $p = 0.045$. HOMA-IR was sig-

nificantly lower at 18 months (2.2 ± 0.3) as compared to day 2 (3.4 ± 0.4), $p = 0.019$, whereas HOMA- β did not significantly change between day 2 and 18 months. Serum C-peptide levels, another indirect measure for β -cell function, also did not change significantly between day 0 and 18 months (1.1 ± 0.1 ng/mL on day 0 to 1.0 ± 0.1 ng/mL at 18 months).

At 18 months follow-up both systolic and diastolic blood pressure were significantly lower than before the start of the diet. Although total cholesterol and triglyceride concentrations had increased between day 30 and 18 months, they were still significantly lower at 18 months as compared to day 0. HDL-cholesterol and the total cholesterol/HDL ratio were also significantly improved at 18 months follow-up (Table 1).

Surprisingly, the 8 patients who had gained more than 5 kg body weight still had a significantly lower systolic (183 ± 10 mmHg on day 0 to 152 ± 8 mmHg at 18 months, $p = 0.004$) and diastolic blood pressure (99 ± 5 mmHg on day 0 to 80 ± 4 mmHg at 18 months, $p = 0.013$), lower triglycerides (4.4 ± 0.8 mmol/L on day 0 and 3.1 ± 0.3 mmol/L at 18 months, $p = 0.025$) and a higher HDL-cholesterol (0.9 ± 0.08 mmol/L on day 0 to 1.2 ± 0.1 mmol/L at 18 months, $p = 0.005$) as compared to the start of the study. In addition, although not significant, FPG levels (14.1 ± 1.6 mmol/L on day 0 to 12.5 ± 1.6 mmol/L at 18 months) and HbA_{1c} levels ($9.1 \pm 0.6\%$ on day 0 to $8.1 \pm 0.6\%$) were also lower at 18 months follow up, as compared to before the dietary intervention.

Factors discriminating the patients on insulin therapy from those not on insulin therapy, at 18 months follow-up.

The 6 patients on insulin therapy at 18 months all had regained body-weight to prediet levels. They also had a longer duration of type 2 diabetes (10.7 ± 1.9 versus 6.2 ± 1.0 years, $p = 0.04$) with lower serum insulin (12.2 ± 3.7 versus 22.0 ± 2.7 mU/L, NS) and C-peptide levels (0.8 ± 0.1 versus 1.19 ± 0.16 ng/mL, NS) at the start of the study as compared to patients who were not restarted on insulin therapy.

The long-term influence of a once-only 30-day VLCD on the Framingham and UKPDS risk score for coronary heart disease

10 year coronary heart disease risk (CHD) risk estimates according to the Framingham Risk Tables declined from 11.3 ± 2.2 to $8.0 \pm 1.5\%$, $p = 0.007$. CHD risk estimates according to the UKPDS risk engine were higher than Framingham risk estimates but were also lower at 18 months follow-up (23.8 ± 4.0 to $17.8 \pm 3.0\%$, $p = 0.002$).

DISCUSSION

This study demonstrates that a 30-day VLCD in severely obese, mostly insulin-treated, type 2 diabetic patients is well tolerated and that the simultaneous discontinuation of all blood

glucose-lowering agents is safe. The diet resulted in a considerable loss of weight and waist circumference. Glycaemic control improved, as did cardiovascular risk factors such as blood pressure and plasma lipid levels.

During the 18 months regular follow-up in an outpatient setting, weight loss and the decrease in waist circumference were maintained for the whole group. Glycaemic control deteriorated to some extent but remained considerably better than before the VLCD whereas patients used less blood glucose-lowering medication, especially insulin (see Table 3 and below). Blood pressure and serum lipid levels also remained lower than before the dietary intervention while patients used fewer antihypertensive and lipid-lowering agents at 18 months follow-up.

Six of the 22 patients were started on insulin therapy (5 already had insulin therapy before the VLCD was instituted, 1 patient used insulin for the first time) during the 18 months follow-up. All these patients had regained body weight to pre-intervention levels. In addition, they had a longer duration of type 2 diabetes and lower serum insulin and C-peptide levels at the start of the study, underscoring our previous observation that remaining endogenous insulin secretion is important as well¹⁵. Nevertheless, even the patients who gained more than 5 kg body weight (n=8) still had better glycaemic control and improved lipid levels and blood pressure as compared to before the dietary intervention. We do not have a good explanation for this, other than that at least for some period of time between day 0 and 18 months follow-up, their body-weight has been lower.

Few studies have addressed the long-term effect of a VLCD in obese type 2 diabetic patients and most used the VLCD for a much longer period of time than we did (8-20 weeks)²¹⁻²³ or also included a behaviour therapy programme²⁴. The results of these other studies are also less favourable, resulting from an increase in weight to no increase in weight but deterioration of glycaemic control 1 year after the VLCD. One study²² also extended follow-up to 1.5 years, but found a deterioration in glycaemic control in most of the patients. One of the reasons that our results are so impressive might be that most patients did not want to be restarted on insulin therapy and, hence, were very motivated to maintain their weight loss. In addition, a normal diet was reintroduced very slowly once the 30-day VLCD had been completed. Finally, regular counselling (every week during the diet, once every 3 months thereafter) seems to be an important factor.

Whether the lower HbA_{1c} levels, blood pressure, triglyceride and total cholesterol levels, along with the increased HDL-cholesterol level, at 18 months follow-up will lead to a lower risk for cardiovascular disease in our patients, remains to be elucidated. Most studies investigating the effects of lowering cardiovascular risk factors on morbidity and mortality from cardiovascular disease have follow-up periods of at least 3 years, whereas our group showed sustained improvement in cardiovascular risk factors for 18 months. Nevertheless, if our patients are able to sustain their weight loss and/or their improved cardiovascular risk profile, a reduction in risk for cardiovascular disease might be expected given the evidence of several

large trials, also in patients with diabetes, that lower(ing) blood pressure^{25,26}, total²⁷ and LDL-cholesterol²⁸⁻³⁰ and decreasing triglycide levels while increasing HDL-cholesterol³¹⁻³³ significantly reduces the risk for cardiovascular disease. Although not designed for this purpose, one might also estimate cardiovascular risk according to the Framingham risk score¹⁹ or the UKPDS risk engine²⁰. 10-year CHD risk estimates in our patients were lower at 18 months follow-up as compared to day 0, both according to the Framingham and the UKPDS risk score. Risk percentages calculated with the Framingham risk score were relatively low, probably because the original Framingham cohort contained only 237 patients with diabetes. Values obtained with the UKPDS risk engine are more likely to reflect the true cardiovascular risk in our group of middle-aged patients with type 2 diabetes, hypertension and dyslipidaemia (at least at the start of the study) and a duration of type 2 diabetes of 7.4 years.

Treatment goals for glycaemic regulation, blood pressure and serum lipids as set by the American Diabetes Association (ADA)³⁴ were not reached for all parameters but came very close (HbA_{1c} $7.6 \pm 0.4\%$, total cholesterol 5.4 ± 0.2 mmol/L, triglycerides 2.5 ± 0.4 mmol/L, HDL cholesterol 1.3 ± 0.07 mmol/L, blood pressure 145 ± 4 mmHg / 81 ± 2 mmHg) and were substantially improved as compared to before the intervention (Table 1).

We are aware that the group of patients is relatively small, follow-up of limited duration and that a control group is lacking. Nevertheless, the observation in these 22 patients, that a once-only 30-day VLCD (with at the end a weight-maintaining advise, followed by regular outpatient clinic visits) has sustained beneficial metabolic effects that might extend over and beyond the weight loss/weight maintenance observed, is interesting and needs further investigation in a (randomised) controlled prospective study. We used a VLCD, to be able to discontinue all blood glucose-lowering medication at the start of the diet to avoid hypoglycaemia. Perhaps the same results can be obtained with a formula diet of greater energy content. In addition, varying the degree of calories with time (i.e. start with 450 kCal/day for 4 weeks, continue with 600 kCal/day and so on) or an intermittent VLCD might be as successful.

In conclusion, we show that a once-only 30-day VLCD in very obese, largely insulin-treated type 2 diabetic patients, leads to a sustained improvement in HbA_{1c} , total cholesterol, HDL-cholesterol, triglyceride levels and blood pressure at 18 months follow-up, even in patients who regained more than 5 kg body-weight. Although bariatric surgery is more effective in establishing sustained weight loss³⁵⁻³⁷, this is an invasive and costly procedure available for only a limited number of patients. VLCDs are cheap, safe, easy to use and can also lead to large weight losses³⁸. Given the enormous increase in obesity and type 2 diabetes, VLCDs can be an important therapeutic strategy.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-1053.
2. Type 2 diabetes in children and adolescents. American Diabetes Association. *Diabetes Care* 2000; 23(3):381-389.
3. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 2005; 146(5):693-700.
4. Prevalence of overweight and obesity among adults with diagnosed diabetes--United States, 1988-1994 and 1999-2002. *MMWR Morb Mortal Wkly Rep* 2004; 53(45):1066-1068.
5. Botero D, Wolfsdorf JL. Diabetes mellitus in children and adolescents. *Arch Med Res* 2005; 36(3):281-290.
6. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003; 46(1):3-19.
7. 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(5):1287-1293.
8. Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care* 1994; 17(1):30-36.
9. Henry RR, Scheaffer L, Olefsky JM. Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1985; 61(5):917-925.
10. Greco AV, Mingrone G, Giancaterini A, Manco M, Morroni M, Cinti S et al. Insulin resistance in morbid obesity: reversal with intramyocellular fat depletion. *Diabetes* 2002; 51(1):144-151.
11. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; 54(3):603-608.
12. Amatruda JM, Richeson JF, Welle SL, Brodows RG, Lockwood DH. The safety and efficacy of a controlled low-energy ('very-low-calorie') diet in the treatment of non-insulin-dependent diabetes and obesity. *Arch Intern Med* 1988; 148(4):873-877.
13. 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(1):2-8.
14. 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(4):354-362.
15. Jazet IM, Pijl H, Frolich M, Schoemaker RC, Meinders AE. Factors predicting the blood glucose lowering effect of a 30-day very low calorie diet in obese Type 2 diabetic patients. *Diabet Med* 2005; 22(1):52-55.
16. Jazet IM, Pijl H, Frolich M, Romijn JA, Meinders AE. Two days of a very low calorie diet reduces endogenous glucose production in obese type 2 diabetic patients despite the withdrawal of blood glucose-lowering therapies including insulin. *Metabolism* 2005; 54(6):705-712.

17. Andersson BL, Bjorntorp P, Seidell JC. Measuring Obesity-Classification and description of anthropometric data. Report on a WHO consultation on epidemiology of obesity. Copenhagen. Nutrition unit, WHO regional office for Europe; EUR/ICP/NUT. 125, 1-22. 1988.
18. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998; 21(12):2191-2192.
19. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97(18):1837-1847.
20. Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001; 101(6):671-679.
21. Dhindsa P, Scott AR, Donnelly R. Metabolic and cardiovascular effects of very-low-calorie diet therapy in obese patients with Type 2 diabetes in secondary failure: outcomes after 1 year. *Diabet Med* 2003; 20(4):319-324.
22. Bauman WA, Schwartz E, Rose HG, Eisenstein HN, Johnson DW. Early and long-term effects of acute caloric deprivation in obese diabetic patients. *Am J Med* 1988; 85(1):38-46.
23. Guare JC, Wing RR, Grant A. Comparison of obese NIDDM and nondiabetic women: short- and long-term weight loss. *Obes Res* 1995; 3(4):329-335.
24. Wing RR, Marcus MD, Salata R, Epstein LH, Miasiewicz S, Blair EH. Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Arch Intern Med* 1991; 151(7):1334-1340.
25. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; 317(7160):703-713.
26. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351(9118):1755-1762.
27. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16(2):434-444.
28. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 364(9435):685-696.
29. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361(9374):2005-2016.
30. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial-lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005; 28(5):1151-1157.
31. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260(5):641-651.
32. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cho-

- lesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; 341(6):410-418.
33. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001; 357(9260):905-910.
 34. Standards of medical care in diabetes. *Diabetes Care* 2004;27(S1):S15-35.
 35. Muscelli E, Mingrone G, Camastra S, Manco M, Pereira JA, Pareja JC et al. Differential effect of weight loss on insulin resistance in surgically treated obese patients. *Am J Med* 2005; 118(1):51-57.
 36. Greenway SE, Greenway FL, III, Klein S. Effects of obesity surgery on non-insulin-dependent diabetes mellitus. *Arch Surg* 2002; 137(10):1109-1117.
 37. Scopinaro N, Marinari GM, Camerini GB, Papadia FS, Adami GF. Specific effects of biliopancreatic diversion on the major components of metabolic syndrome. *Diabetes Care* 2005;28(10):2406-11.
 38. Anderson JW, Brinkman-Kaplan VL, Lee H, Wood CL. Relationship of weight loss to cardiovascular risk factors in morbidly obese individuals. *J Am Coll Nutr* 1994; 13(3):256-261.