# An Intensive Weight Loss Programme in Established Type 2 Diabetes and Controls: Effects on Weight and Atherosclerosis Risk Factors at 1 Year

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**The efficacy, safety, and effect on cardiovascular risk factors of two intensive weight loss programmes in overweight Type 2 diabetic subjects were studied. The patients were recruited from hospital diabetic clinics and control obese subjects from the community. Obese (BMI >30) patients with Type 2 diabetes mellitus and controls were offered intensive conventional diabetic advice or a very low calorie diet. Weekly 2 h sessions were conducted in two day-room areas of adjacent medical wards of Torbay Hospital. Non-diabetic and diabetic very low calorie diet groups reduced BMI by 6 and 5 kg $m^{-2}$, respectively, at 1 year. Waist–hip ratios (−0.06 and −0.05) were also reduced ($p = 0.04$ and $p = 0.01$), while HDL/total cholesterol ratios increased (+0.04 and +0.06, $p = <0.01$). Transient changes in blood pressure and antioxidant vitamin status occurred in the intensive conventional diet group. Fourteen of diabetic very low calorie diet subjects discontinued insulin and oral hypoglycaemic agents for the whole year, and psychological well-being transiently improved. Substantial weight loss and improvement in cardiovascular risk factors could be maintained for 1 year in Type 2 diabetic patients by the use of a very low calorie diet.** © 1998 John Wiley & Sons, Ltd.

*Diabet. Med.* 15: 73–79 (1998)

KEY WORDS type 2 diabetes; waist–hip ratio; HDL/cholesterol ratio; lipid peroxidation; serum antioxidant vitamins

Received 21 April 1997; revised 3 July 1997; accepted 23 July 1997

## Introduction

Type 2 diabetes mellitus is characterized by truncal obesity and is commonly accompanied by hypertension, dyslipidaemia, and hyperinsulinaemia.[1] Prognosis is relatively poor, with a doubling in cardiovascular mortality[2] which may be ameliorated by successful weight loss in the first year after diagnosis.[3] Massive weight loss is often sufficient to improve glycaemic control of diabetes and the associated cardiovascular risk factors.[4] Modest weight loss combined with exercise and dietary change has exceptionally been shown to have an equally striking effect.[5]

However there is a widespread clinical impression, borne out by the UK Prospective Study of Diabetes, that weight reduction is hard to achieve and sustain in obese patients.[6] Furthermore, there is concern that extensive weight loss, and more particularly rapid regain in weight, could destabilize coronary artery plaques and increase cardiovascular mortality,[7] although this has been contested.[8]

Recent studies have highlighted other factors involved in diabetes mellitus and cardiovascular disease, including psychosocial factors,[9] the importance of waist–hip ratio,[10–12] and the interrelationship between antioxidant vitamin status, lipid peroxidation, and vascular disease.[13–16] We have therefore studied changes in these variables as well as in standard anthropometric and biochemical data in a comparison of two dietary interventions in obese diabetic and non-diabetic subjects, intensive conventional dietary advice and a regimen including a commercial very low calorie diet (VLCD).

## Patients and Methods

The study was approved by the South Devon Health Care Trust Ethical Committee.

### *Patients*

Eighty-four subjects from primary care and hospital diabetic clinics were invited to attend discussions

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Sponsors: Torbay Hospital Special Medical Projects Grant Fund; BDA (Torbay Branch); University of Plymouth

CCC 0742–3071/98/010073–07$17.50

explaining the two treatment options. After obtaining written, informed consent, 49 subjects were recruited into their treatment preference group. Table 1 shows the resultant patient groups. All of them attended at least 50% of the weekly sessions in the first 4 months of the study, and all underwent clinical examination and provided blood tests at 0, 1, 3, 6, and 12 months. A group of obese non-diabetic subjects (see Table 1) were recruited from the community by advertisement as a control group for the very low calorie diet regimen. The present analysis was performed on the 12 month data but the study will continue for 3 years.

### *Study Protocol*

Parallel weekly sessions lasting 1.5 to 2 h took place in two medical ward day rooms. Body weight was recorded at each visit; blood pressure each month; quality of life assessment by questionnaire, waist–hip ratio, serum lipids and fructosamine, serum antioxidant vitamin levels, and serum malondialdehyde levels at baseline and then 3 monthly. In order to facilitate compliance blood samples were taken between 2 and 3 hours after breakfast.

### *Group Sessions*

Patients chose to enter either a programme of intensive conventional diet (ICD) or a regimen including a very low calorie diet (VLCD). All attended group sessions, which have been described in detail previously.[17] In the intensive conventional diet group, patients were encouraged to attend weekly from 10 am till 11.45 am for dietetic discussion, analysis of 5-day food records and lifestyle advice. A series of simple aerobic exercises were performed to music at each visit. Sessions were conducted by two dietitians with regular additional contact with a physician and physiotherapist. Attendance ranged from 50% to 60% throughout the year. The emphasis of dietetic management was to encourage low fat, low sugar, high fibre intake rather than prescriptive dietary therapy.

Subjects on the VLCD were advised to stop all antidiabetic medication and diuretics from day 1 of treatment. Mutually agreed goals were set and participants were encouraged to stay each week for a 1 hour discussion focusing on symptoms, and also on weight maintenance after stopping the formula. At each session patients were weighed, urine was tested for ketones, and blood pressure measured. Blood glucose and fructosamine levels were performed as clinically appropriate in addition to measurements required in the study protocol.

Failure to lose weight, and/or absence of ketonuria led to individual discussion of compliance. The first 2 weeks on the VLCD caused severe hunger pangs and headaches in some patients, but once ketosis had developed a feeling of well-being was induced. To prevent dehydration, all patients drank 4 pints of water per day. The VLCD was administered in the form of sachets of powder, one of which could be substituted for a flapjack each day (see Table 2).

Table 2. Constituents of the very low calorie diet

| | Men | Women |
|---|---|---|
| kcal day$^{-1}$ | 540–570 | 405–470 |
| Vitamin C day$^{-1}$ | 80 mg | 60 mg |
| Vitamin E day$^{-1}$ | 13.3 mg | 9.9 mg |
| Vitamin A day$^{-1}$ | 1.2 mg | 0.9 mg |

Table 1. Characteristics of patients recruited into the three groups studied for 12 months in an intensive weight loss programme

| Group | Number | M/F | Age (yr) | Medication | | Medical problems | |
|---|---|---|---|---|---|---|---|
| Very low calorie diet – non-diabetic | 19 | 6/13 | 50.3 ± 8.8 | Beta-blocker | 2 | Arthritis | 2 |
| | | | | Calcium antagonist | 2 | Hypertension | 3 |
| | | | | Diuretic | 4 | Hypothyroidism | 2 |
| | | | | Analgesics | 2 | Angina | 2 |
| | | | | Thyroxine | 2 | Multiple sclerosis | 1 |
| Very low calorie diet – diabetic | 15 | 7/8 | 52.9 ± 5.5 | Insulin | 6 | Hypertension | 8 |
| | | | | Sulphonylurea | 5 | Hyperlipidaemia | 7 |
| | | | | Metformin | 2 | Myocardial infarct | 1 |
| | | | | Diuretic | 3 | | |
| | | | | Beta-blocker | 2 | | |
| | | | | Bezafibrate | 1 | | |
| | | | | Calcium antagonist | 2 | | |
| Intensive conventional diet – diabetic | 15 | 3/12 | 55.4 ± 7.3 | Insulin | 6 | Hypertension | 7 |
| | | | | Sulphonylurea | 3 | Hyperlipidaemia | 6 |
| | | | | Metformin | 1 | Hypothyroidism | 1 |
| | | | | ACE inhibitor | 1 | Diabetic nephropathy | 1 |
| | | | | Bezafibrate | 1 | | |
| | | | | Beta-blocker | 2 | | |
| | | | | Thyroxine | 1 | | |



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Once an agreed target weight had been reached, in all but one case within 4 months of starting, patients were seen intensively to wean them back onto a low fat diet, and warned to expect a rapid 4–8 lb (2–4 kg) weight increase with repletion of muscle and liver glycogen stores. These sessions were run by two nurses and a counsellor. A commercially available, nutritionally complete formula was used (Lipotrim (Howard Foundation, Swaffham Bulbeck, Cambridge), and paid for by the patients—£24 per week for men and £18 per week for women. The calorie and vitamin constituents of the very low calorie diet are shown in Table 2.

### *Laboratory Methods*

Blood for analysis of antioxidant vitamins and lipid hydroperoxides was treated with EDTA as an anticoagulant.

Plasma glucose, serum fructosamine, cholesterol and triglyceride, hepatic and renal function tests, and uric acid were measured by standard laboratory techniques. Serum HDL cholesterol was measured after precipitation.

Plasma malondialdehyde (MDA) was measured after acid hydrolysis of lipid peroxides. The malondialdehyde released is reacted with TBA and following protein precipitation subjected to HPLC with fluorometric detection of the MDA–TBA adduct with excitation at 532 nM and emission at 553 nM.[18] Normal range 0.61–1.45 $\mu$mol $l^{-1}$.

Plasma ascorbic acid was measured by reversed phase HPLC with electrochemical detection, with an internal standard, using a mobile phase containing sodium acetate, sodium octane sulphonate, EDTA, and methanol at pH 4.0.[19] Normal range was 20–85 $\mu$mol $l^{-1}$.

Vitamins A and E were assayed, after extraction from plasma with hexane, by high pressure liquid chromatography (HPLC) with ultraviolet detection in subdued daylight at room temperature. A water/methanol/butanol mobile phase was used and the ultraviolet detector switched from 324 nM to 292 nM to enable both retinol and $\alpha$ tocopherol to be measured at their maximum wavelengths.[20] Normal ranges were 12–42 $\mu$mol $l^{-1}$ for vitamin E and 1.05–2.8 $\mu$mol $l^{-1}$ for vitamin A. All normal ranges expressed as mean ± 2 SD.

### *Statistical Analysis*

The VLCD and ICD groups of diabetic patients were not randomized, but selected their preferred treatment option. The baseline characteristics of the three groups were compared using analysis of variance. Changes within groups were assessed with paired *t*-test for normally distributed data and Wilcoxon Rank test for non-normally distributed data (serum triglycerides and quality of life scores).

## Results

Changes in anthropometric characteristics are shown in Figure 1 and Table 3. A substantial reduction in BMI was achieved by 3 months in the two very low calorie diet groups accompanied by a decrease in waist–hip ratio and this was maintained at 1 year, $p \leq 0.01$ in each case. The statistical significance was unaffected by re-analysing the data without the two extreme responders. There were accompanying decrements in systolic and diastolic blood pressure in non-diabetic, but not diabetic, subjects on the very low calorie diet. BMI and diastolic blood pressure were reduced in the intensive conventional diet diabetic group at 6 months but this was not sustained at 12 months.

Measures of diabetic control and lipid metabolism are shown in Figure 2 and Table 4. In the non-diabetic very low calorie diet group, significant reductions in serum cholesterol, serum triglyceride, and increases in HDL/total cholesterol ratio occurred by 3 months and were sustained at 6 and 12 months. In the diabetic very low calorie diet group, fructosamine levels fell by 1 month and remained significantly lower until 3 months. Serum cholesterol and triglycerides remained lower than at baseline for 6 months, the significance of the fall being

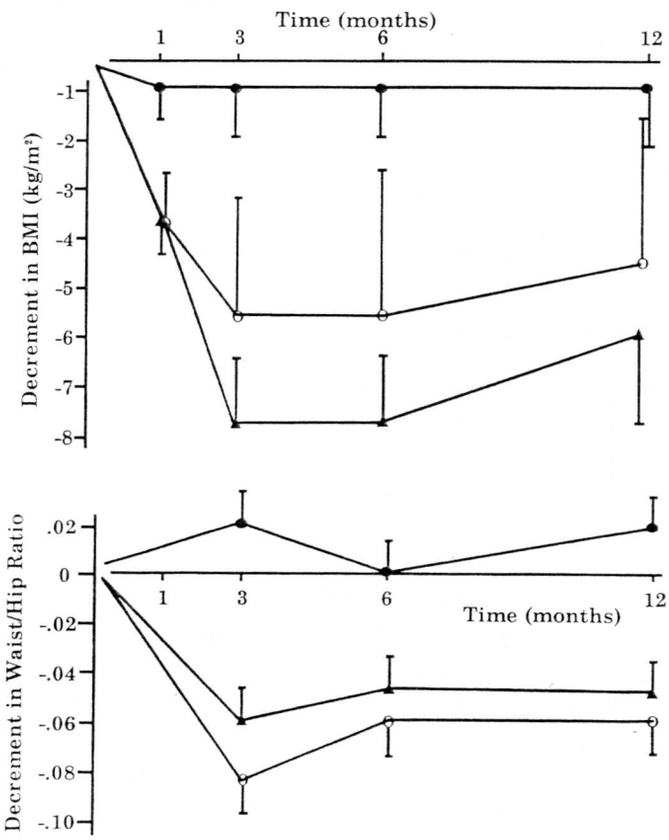


Figure 1. Decrement in BMI kg/m$^2$ and Waist–Hip ratio, mean ± SD, in 15 type 2 diabetic patients given VLCD (○), 15 type 2 diabetic patients during ICD treatment (●), and 19 non-diabetic subjects given VLCD (▲). VLCD = Very low calorie diet: ICD = Intensive conventional diet. For significances see text.

Table 3. Systolic and diastolic blood pressures during the first year of an intensive weight loss programme in all three groups

| | Systolic blood pressure (mmHg) | | | Diastolic blood pressure (mmHg) | | |
|---|---|---|---|---|---|---|
| | VLCD non-diabetic | VLCD diabetic | ICD diabetic | VLCD non-diabetic | VLCD diabetic | ICD diabetic |
| Baseline | 131 ± 21 | 140 ± 18 | 141 ± 20 | 82 ± 12 | 77 ± 11 | 85 ± 12 |
| 1 month | [a]115 ± 14 | 129 ± 14 | 137 ± 17 | [c]73 ± 11 | 74 ± 12 | [d]82 ± 11 |
| 3 months | [a]112 ± 11 | 134 ± 18 | 134 ± 19 | [c]69 ± 10 | 74 ± 11 | [d]78 ± 8 |
| 6 months | [b]120 ± 18 | 137 ± 17 | 134 ± 17 | [c]68 ± 8 | 78 ± 10 | [e]71 ± 9 |
| 12 months | [a]118 ± 17 | 143 ± 19 | 138 ± 19 | [c]72 ± 9 | 81 ± 11 | 78 ± 10 |

[a]$p < 0.01$; [b]$p = 0.03$; [c]$p < 0.01$; [d]$p = 0.04$; [e]$p < 0.001$.

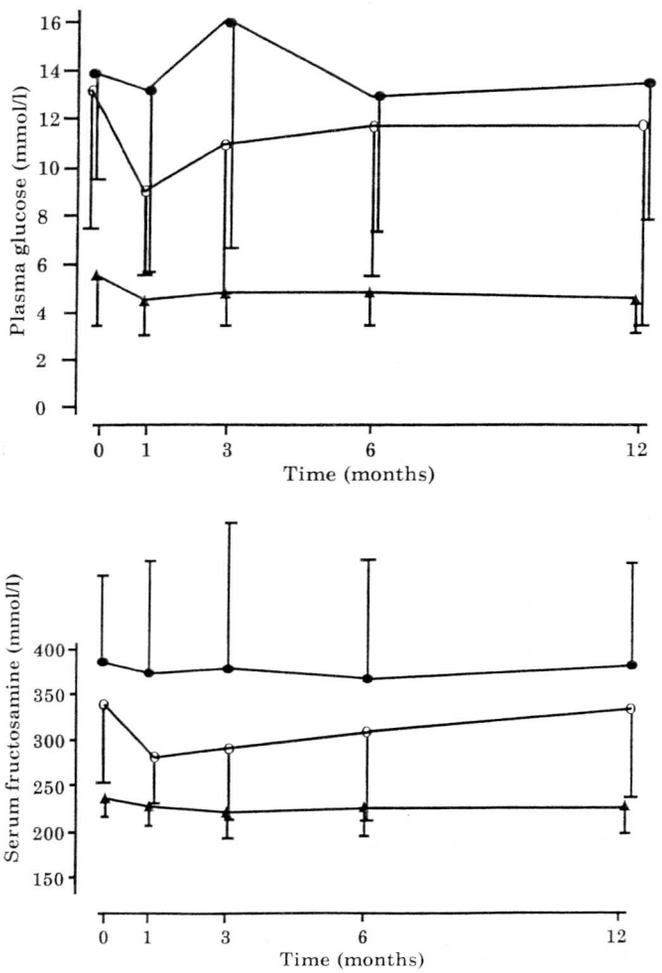


Figure 2. Plasma glucose and serum fructosamine levels, mean ± SD, in 15 type 2 diabetic patients given VLCD (○), 15 type 2 diabetic patients during ICD treatment (●), and 19 non-diabetic subjects given VLCD (▲). VLCD = Very low calorie diet: ICD = Intensive conventional diet. For significances see text.

lost at 6 months for the latter, and HDL/total cholesterol ratio increased after 6 months and remained elevated at 12 months.

Vitamin E ratios remained stable throughout in all three groups, except for a fall in the intensive conventional diet diabetic group at 12 months. Vitamin A levels decreased at 1 month in both very low calorie diet groups and at 3 months in the very low calorie diet non-diabetic subjects. There were no changes in the intensive conventional diet group. Vitamin C levels remained stable in both very low calorie diet groups, but increased significantly at 3 months in the intensive conventional diet group.

Serum malondialdehyde levels decreased at 1 month in both very low calorie diet groups and at 6 months in the non-diabetic very low calorie diet group only. Levels remained unchanged in the intensive conventional diet group (Table 5).

Although diabetic patients were not randomized, but self-selected into VLCD or intensive conventional diet groups, a comparison of treatment outcome is of interest. At 1 year, 14 of 15 patients in the VLCD group, but none of those in the conventional diet group, had remained off insulin and any oral hypoglycaemic medication, $\chi^2 = 26.25$, $p < 0.01$ at $\chi^2$ value of 6.635.

Psychological well-being score improved at 3 to 6 months in both very low calorie diet groups 73 ± 16 to 90 ± 11, $p = 0.0002$; 64 ± 24 to 78 ± 24, $p = 0.003$ in non-diabetic and diabetic groups, respectively. The 12 month scores were not significantly different from baseline and there were no changes in the intensive conventional diet group.

### *Adverse Effects*

All subjects remained at work throughout the study. However, one patient in each group suffered a non-fatal myocardial infarction. One VLCD diabetic patient experienced a severe hypoglycaemic attack.

## Discussion

A recent meta-analysis of weight loss strategies in subjects with Type 2 diabetes has indicated varying, but encouraging, measures of success for dietary, exercise, and psychotherapeutic interventions.[21] Most studies have only reported data up to 1 year after the intervention. The impetus for these studies has been the need to reduce the incidence of cardiovascular disorders in patients with Type 2 diabetes. Our feasibility and efficacy study was designed to measure the impact of very low

Table 4. Serum triglyceride (median and interquartile range) and HDL/cholesterol ratio (mean ± SD) during the first year of an intensive weight loss programme in all three groups

| | 2 h postprandial serum triglyceride mmol $l^{-1}$ (median and IQ range) | | | HDL/cholesterol ratio | | |
|---|---|---|---|---|---|---|
| | VLCD non-diabetic | VLCD diabetic | ICD diabetic | VLCD non-diabetic | VLCD diabetic | ICD diabetic |
| Baseline | 2.5 (2.1–3.7) | 2.7 (1.9–5.8) | 2.2 (1.5–3.7) | 0.18 ± 0.06 | 0.17 ± 0.06 | 0.21 ± 0.08 |
| 1 month | [a]1.3 (1.1–1.6) | [b]1.5 (1.1–1.8) | 1.9 (1.6–3.5) | [f]0.23 ± 0.06 | 0.2 ± 0.07 | 0.20 ± 0.08 |
| 3 months | [a]1.5 (1.1–1.8) | [c]1.6 (1.0–2.4) | 2.5 (1.7–3.4) | [e]0.22 ± 0.08 | 0.20 ± 0.07 | 0.21 ± 0.09 |
| 6 months | [a]1.5 (1.2–1.8) | [d]1.8 (1.1–3.4) | 2.1 (1.8–2.5) | [f]0.23 ± 0.07 | [g]0.21 ± 0.07 | 0.19 ± 0.06 |
| 12 months | [a]1.8 (1.5–2.1) | [d]1.8 (1.1–4.3) | 2.3 (1.6–4.7) | [f]0.22 ± 0.06 | [h]0.23 ± 0.08 | 0.20 ± 0.08 |

VLCD, very low calorie diet; ICD, intensive conventional diet.
[a]$p \leq 0.001$; [b]$p = < 0.01$; [c]$p = 0.03$; [d]$p = 0.055$; [e]$p = 0.027$; [f]$p = < 0.01$; [g]$p = 0.004$; [h]$p = 0.0003$.

Table 5. Serum vitamin A, serum vitamin E/lipid ratios, serum vitamin C, and serum malondialdehyde levels during the first year of an intensive weight loss study in all three groups

| | Baseline | 1 month | 3 months | 6 months | 12 months |
|---|---|---|---|---|---|
| Serum vitamin A levels ($\mu$mol $l^{-1}$) | | | | | |
| VLCD non-diabetic | 1.9 ± 0.4 | [a]1.3 ± 0.3 | [b]1.7 ± 0.5 | 2.0 ± 0.4 | 2.0 ± 0.5 |
| VLCD diabetic | 1.9 ± 0.5 | 1.6 ± 0.7 | 1.8 ± 0.8 | 2.1 ± 0.8 | 2.0 ± 0.8 |
| ICD diabetic | 2.2 ± 0.6 | 2.3 ± 0.8 | 2.1 ± 0.6 | 2.1 ± 0.6 | 2.1 ± 0.7 |
| Serum vitamin E/cholesterol and triglyceride ratio | | | | | |
| VLCD non-diabetic | 3.7 ± 1.2 | 3.7 ± 0.5 | 4.2 ± 1.1 | 3.9 ± 0.7 | 3.7 ± 0.9 |
| VLCD diabetic | 3.6 ± 0.7 | 4.0 ± 0.8 | 4.0 ± 0.9 | 4.0 ± 0.5 | 3.9 ± 1.1 |
| ICD diabetic | 3.8 ± 1.1 | 3.8 ± 1.0 | 3.6 ± 0.8 | 3.3 ± 0.9 | [c]3.2 ± 0.64 |
| Serum vitamin C level ($\mu$mol $l^{-1}$) | | | | | |
| VLCD non-diabetic | 44 ± 24 | 47 ± 16 | 37 ± 19 | 40 ± 20 | 50 ± 19 |
| VLCD diabetic | 36 ± 18 | 33 ± 17 | 39 ± 26 | 47 ± 20 | 45 ± 22 |
| ICD diabetic | 39 ± 20 | 44 ± 14 | [d]52 ± 19 | 39 ± 21 | 39 ± 19 |
| Serum malondialdehyde level ($\mu$mol $l^{-1}$) | | | | | |
| VLCD non-diabetic | 1.6 ± 0.4 | 1.4 ± 0.4 | 1.4 ± 0.3 | 1.3 ± 0.4 | 1.5 ± 0.3 |
| VLCD diabetic | 1.7 ± 0.4 | 1.4 ± 0.4 | 1.5 ± 0.4 | 1.5 ± 0.6 | 1.5 ± 0.4 |
| ICD diabetic | 1.7 ± 0.4 | 1.8 ± 0.5 | 1.8 ± 0.6 | 1.9 ± 0.7 | 1.9 ± 0.8 |

Mean ± SD; VLCD, very low calorie diet; ICD, intensive conventional diet.
[a]$p < 0.0001$; [b]$p = 0.003$; [c]$p = 0.05$; [d]$p = 0.03$.

calorie diet and intensive conventional diet with exercise advice on psychological well-being and other cardiovascular risk factors over 3 years and this report is based on the first year. The intensive interventions we have studied have proved safe, and variably effective in this group of established diabetic subjects. We have not corrected for multiple comparisons, so caution must be exercised in interpreting our findings. However, it seems clear that intensive conventional diet and group education/exercise sessions only produced a transient weight loss of 1 BMI unit to 6 months. An improvement in diastolic blood pressure was seen and there was a transient increase in serum vitamin C levels and a reduction in vitamin E/cholesterol and triglyceride ratio at 1 year, perhaps reflecting the consumption of more fruit and vegetables and less fat. In contrast, the very low calorie diet diabetic group attained a weight loss of 15 kg at 3 and 6 months, and 14 kg at 12 months, 6 and 5 BMI units, respectively. The success was variable, ranging from 1.5 to 27 BMI units, but occurred in all

subjects. This was accompanied by significant improvements in waist–hip ratio, serum triglycerides, and HDL total cholesterol ratio which were sustained at 12 months. Glycaemic control was maintained despite withdrawal of insulin and oral hypoglycaemic agents. There were no associated adverse changes in serum antioxidant vitamin levels, or malondialdehyde levels. Psychological well-being was unaffected in the long term.

The VLCD diabetic group showed similar changes to the VLCD non-diabetic group, except that blood pressure was very significantly reduced in those without diabetes. As the diabetic patients on intensive conventional diet attained lower diastolic blood pressure temporarily, this suggests a mechanism of hypertension in non-insulin-dependent diabetes different from that in non-diabetic subjects and more responsive to improvement in diet and gentle exercise.

Prolonged remission of Type 2 diabetes of recent onset has been clearly demonstrated in association with weight loss after gastric bypass surgery for obesity.[22] It is of interest in our study that all except one of the patients in the very low calorie diet diabetic group showed normalization of blood glucose and fructosamine levels, despite stopping all antidiabetic medication. This might be anticipated in the weight loss phase with depletion of liver and muscle glycogen stores and consequent increase in insulin sensitivity. However, it is noteworthy that the four people with recently diagnosed (<2 years) diabetes sustained this improvement for the whole year, despite refeeding.

Antioxidant vitamin status and lipid peroxidation have recently been studied before and after 2 months' dietary therapy in 20 newly diagnosed obese Type 2 diabetic patients.[23] Our data, showing decrease in serum malondialdehyde levels and an increase in serum ascorbate levels, are compatible with this earlier report.

Sustainable weight loss was apparently less successful in the intensive conventional diet group. However, two patients were judged clinically to require insulin treatment during the second 6 months of the study. As with the failure to withdraw other pharmacological therapy, this may be judged a treatment 'failure' but if the group is analysed without these two patients, then there is a significant fall in BMI from 35.4 to 34 at 1 year $p = 0.0017$, suggesting some efficacy of the dietary intervention. No other parameters alter in significance.

Further studies on both intensive conventional diet and exercise, and VLCDs are indicated in patients with Type 2 diabetes mellitus. Our data do suggest that the latter is safe and may be more effective than conventional dietary management. Our study groups, which could be accommodated in the scheme of diabetic follow-up in the UK by focusing them as group sessions, will continue for a further 2 years, to assess longer term results of the strategies employed.

**Acknowledgements**

We would like to thank the patients for their enthusiastic help with this study, and S. Wyse for secretarial assistance and co-ordination of clerical aspects of the study. We are also grateful to the Mayfield Medical Centre, Paignton, for stimulating this project. Funding was obtained from a local endocrine research fund, the Torbay Hospital Special Medical Projects Grant Fund, the Torbay Branch of the BDA, and the University of Plymouth for a PhD grant to IB.

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