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Research: Treatment

Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes

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Abstract

Aims To establish whether an 8-week very-low-calorie diet could improve glycaemic control in Type 2 diabetes of long duration.

Methods A total of 29 people with Type 2 diabetes [short-duration group (diabetes duration < 4 years), $n = 15$; long-duration group (diabetes duration > 8 years), $n = 14$] completed an 8-week very-low-calorie diet, with assessments of fasting anthropometry, blood tests and blood pressure at baseline and weeks 1, 4 and 8 of the diet.

Results Similar weight loss was achieved in the short- and long-duration groups (14.8 ± 0.8% and 14.4 ± 0.7% respectively; $P = 0.662$). The glucose response to acute calorie restriction was heterogeneous in the long-duration group with some responding similarly to those in the short-duration group, some responding, but only slowly, and others not responding at all. Overall, HbA_{1c} concentration in the short- vs. long-duration groups fell to 44 ± 2 vs. 64 ± 6 mmol/l (6.2 ± 0.2 vs. 8.0 ± 0.5%; $P = 0.002$). Fasting plasma glucose levels decreased to 5.8 ± 0.2 vs. 8.4 ± 1.1 mmol/l ($P = 0.024$) respectively. A total of 87% of the short-duration group and 50% of the long-duration group achieved non-diabetic fasting plasma glucose levels at week 8. Clinically significant improvements in blood pressure and lipid profile were seen regardless of diabetes duration.

Conclusion In people with Type 2 diabetes of > 8 years' duration, a therapeutic trial of a very-low-calorie diet may be undertaken with a 50% chance of achieving non-diabetic fasting glucose levels off all antidiabetic therapies.

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Introduction

The inevitably progressive nature of Type 2 diabetes has been widely accepted since the UK Prospective Diabetes Study was carried out, which showed that glucose control steadily worsened towards requirement for insulin treatment despite best possible therapy [1]. The approach to management has developed around this concept of Type 2 diabetes and guidelines lay out the sequential addition of therapies [2]. The Counterpoint Study, however, showed that a hypocaloric diet could reverse the twin pathophysiological defects of Type 2 diabetes: impaired β-cell function and decreased liver insulin sensitivity [3]. That study involved only people with Type 2 diabetes of < 4 years' duration.

Although very-low-calorie diets were first used in clinical practice many years ago to achieve significant weight loss [4], recent observations have stimulated worldwide interest from people with Type 2 diabetes and healthcare practitioners in the therapeutic potential of such diets to normalize blood glucose levels [5]. It is now essential to evaluate the wider applicability of a very-low-calorie diet as a treatment strategy in Type 2 diabetes.

The aim of the present study was to establish how effectively a very-low-calorie diet could improve glycaemic control in long-duration Type 2 diabetes.

Participants and methods

Participants

People with Type 2 diabetes were identified in response to local advertisement; a total of 15 people with short-duration disease (< 4 years) and 15 people with long-duration disease (> 8 years) were recruited. Inclusion criteria were age 25–80 years; Type 2 diabetes treated by diet, metformin, sulphonylureas, dipeptidyl peptidase-4 inhibitors and/or

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What's new?

- We examined the glucose response to a very-low-calorie diet in long-duration Type 2 diabetes. This has not previously been investigated.
- The data extend the previous demonstration of normalization of fasting glucose levels using a very-low-calorie diet in people with short-duration diabetes, to now include a significant proportion (50%) of those with long-duration diabetes.
- These insights carry important implications for the management of longer-duration Type 2 diabetes in everyday clinical practice.

insulin; and BMI 27–45 kg/m^2. Exclusion criteria were loss of > 5 kg body weight in the preceding 6 months, treatment with thiazolidinediones, glucagon-like peptide-1 agonists, steroids or atypical antipsychotic medications, untreated thyroid disease, renal dysfunction (serum creatinine > 150 μmol/l) or hepatic dysfunction (alanine aminotransferase > 2.5 times the upper limit of normal), and alcohol consumption > 3 units per day for women and > 4 units per day for men. The history of the diagnosis of diabetes was taken by a diabetes physician to clinically exclude diagnoses other than Type 2 diabetes. The baseline characteristics for the participants who completed the very-low-calorie diet are shown in Table 1. Date of diagnosis of Type 2 diabetes was confirmed from medical records. Participants were asked to remain on their usual dose of lipid-lowering treatment throughout the study. Anti-hypertensive medications were decreased as necessary throughout the study. The study protocol was approved by Newcastle and North Tyneside 2 Ethics Committee (REC 12/NE/0208) and all participants gave informed written consent. Participants were asked to discontinue all antidiabetic therapy before the baseline study: metformin and sulphonylureas for 72 h; dipeptidyl peptidase-4 inhibitors for 2 weeks; long-acting insulin for > 36 h and short-acting insulin for > 12 h. Dietary adherence was assessed using capillary blood ketones. As in an earlier study, participants were excluded if they were unable to achieve weight loss targets of 3.8% body weight at week 1 of the very-low-calorie diet and 9.3% at week 4 [3]. Only one participant in the long-duration group did not meet the weight loss target and left the study after week 1. Hence the final numbers were 15 in the short-duration group and 14 in the long-duration group.

Table 1 Baseline participant characteristics

	Short-duration (n = 15)	Long-duration (n = 14)	*P*
Gender: male/female	7/8	8/6	
Age, years	52.1 ± 2.6	61.6 ± 2.0	0.007
Weight, kg	99.0 ± 3.7	96.9 ± 3.8	0.683
BMI, kg/m^2	34.2 ± 0.8	34.3 ± 1.2	0.905
Diabetes duration, years	2.3 ± 0.3	12.7 ± 1.2	< 0.001
Fasting plasma glucose, mmol/l	9.6 ± 0.7	13.4 ± 0.8	0.001
HbA_{1c}, mmol/mol	55 ± 2	70 ± 4	0.004
HbA_{1c}, %	7.2 ± 0.2	8.6 ± 0.4	
Diabetes treatment, *n*			
Diet	4	3	
Metformin	11	10	
Sulphonylurea	3	8	
Insulin	0	3	
Anti-hypertensives, *n*	6	11	
Statins, *n*	9	10	

Data are mean ± SEM unless otherwise indicated.

Experimental protocol

Participants were asked to continue their habitual pattern of eating until the start of the study. Assessments of anthropometry, fasting blood tests and blood pressure were made at baseline, and then at weeks 1, 4 and 8 of the very-low-calorie diet. Immediately after the baseline measurements, participants started the hypocaloric diet. This was provided using a meal replacement liquid diet formula [43% carbohydrate, 34% protein and 19.5% fat; vitamins, minerals and trace elements; 2.6 MJ/day (624 kcal/day); Optifast; Nestlé Nutrition, Croydon, UK]. In addition, participants were asked to consume up to 240 g of non-starchy vegetables per day, such that the total energy intake per day was 624–700 kcal. Participants were provided with detailed information on vegetable and recipe ideas. They were also encouraged to drink at least 2 l of calorie-free beverages per day and to maintain their habitual level of physical activity. In order to maximize adherence to the protocol, one-to-one support was provided weekly by telephone, e-mail, text or face-to-face contact. Additional face-to-face contact was provided if requested, but this was rare and similar between the study groups. Participants were asked to fast overnight for 10 h before all study visits.

Anthropometry

A standard non-distensible tape measure was used for all waist and hip measurements, which were taken with the participants standing in a relaxed posture. Waist circumference was taken at the mid-point between the anterior superior iliac spine and the lower edge of the rib cage, and hip circumference at the level of the greater trochanter. All measurements were made throughout the study period by a single observer (S.S.).

Body weight was measured to the nearest 0.1 kg (wearing light indoor clothing only after removal of footwear) using a calibrated upright pedestal digital scale (Seca

Ltd., Birmingham, UK). Height was measured to the nearest 0.5 cm using a stadiometer (Seca Ltd.). BMI was determined as weight (kg)/ height^2 (m).

Analytical procedures

Immediate measurements of glucose and 3-hydroxybutyrate were made using a Yellow Springs glucose analyser (YSI 2300 STAT Plus; Yellow Springs Inc., Yellow Springs, OH, USA) and an Optium Xceed ketone meter (Abbott Diabetes Care, Witney, UK) respectively. HbA_{1c}, liver function tests and lipids were measured at a Clinical Pathology Accredited laboratory (Department of Clinical Biochemistry, Newcastle upon Tyne Hospital NHS Foundation Trust).

Statistics

Statistical analyses were performed using MINITAB 16 statistical software (www.Minitab.com). Data are presented as mean ± SEM. Statistical comparisons between the short- and long-duration groups were performed using the two-tailed Student's *t*-test, while within-group differences before and after the very-low-calorie diet were determined using a two-tailed Student's paired *t*-test or Wilcoxon rank test if non-parametric. Correlations were examined using the Spearman rank test. A P value < 0.05 was taken to indicate statistical significance.

Results

Weight loss

At baseline, the groups were well matched for weight and BMI (Table 1). Weight loss during the first week for the short-duration vs. the long-duration group was 4.0 ± 0.2% vs. 3.7 ± 0.2% and at week 4 was 9.0 ± 0.5% vs. 8.4 ± 0.4%. The mean weight loss over the 8-week diet period was very similar in the two groups at 14.8 ± 0.8% and 14.4 ± 0.7%, respectively (P = 0.662). BMI decreased from 34.1 ± 0.8 to 29.1 ± 0.9 kg/m^2 in the short-duration group (P < 0.001) and from 34.3 ± 1.2 to 29.4 ± 1.1 kg/m^2 in the long-duration group (P = 0.001).

The changes in waist and hip circumference, waist–hip ratio and fasting ketones were similar in the two groups (Table 2). Overall, the conditions were established to allow direct comparison of the glucose response to weight loss in short- and long-duration Type 2 diabetes.

Glucose control

Over the course of the 8-week very-low-calorie diet, fasting plasma glucose decreased from 9.6 ± 0.7 to 5.8 ± 0.2 mmol/l in the short-duration group (P < 0.001) and from 13.4 ± 0.8 to 8.4 ± 1.1 mmol/l in the long-duration group (P < 0.001). The glucose response to acute calorie restriction was strikingly heterogeneous in long-duration diabetes (Fig. 1b), with some responding within 1 week, just as in the short-duration group (Fig. 1a), and some not at all. In 3/14 people (21%) in the long-duration group, a slow, steady return to non-diabetic fasting plasma glucose levels occurred and this was not observed in any of the short-duration group. This was reflected in the difference in the fall in fasting glucose levels between weeks 1 and 8 of the very-low-calorie diet between the groups; being significantly greater in the long-duration group compared with the short-duration group: 2.6 ± 0.6 vs. 1.1 ± 0.3 mmol/l (P = 0.039). In the short-duration group, 87% of people achieved non-diabetic fasting plasma glucose levels at week 8 compared with 50% in the long-duration group.

Diabetes duration correlated with fasting plasma glucose at week 8 (Spearman rank = 0.501; P = 0.006; Fig. 2). If diabetes duration was < 4 years, the mean fasting plasma

Table 2 Change in anthropometry and fasting ketones over the 8-week very-low-calorie diet in both the short and long-duration groups

	Baseline	Week 1	Week 4	Week 8
Weight, kg				
Short-duration	99.0 ± 3.7	95.1 ± 3.6	90.2 ± 3.6	84.5 ± 3.5
Long-duration	96.9 ± 3.8	93.2 ± 3.6	88.6 ± 3.4	83.0 ± 3.2
Waist circumference, cm				
Short-duration	110.0 ± 2.3	107.6 ± 2.2	102.9 ± 2.4	98.0 ± 2.5
Long-duration	113.8 ± 3.0	112.3 ± 2.9	107.0 ± 2.9	101.4 ± 2.9
Hip circumference, cm				
Short-duration	115.7 ± 2.4	114.3 ± 2.5	112.2 ± 2.5	107.9 ± 2.4
Long-duration	117.3 ± 3.0	115.8 ± 3.1	113.1 ± 3.2	109.9 ± 3.1
Waist–hip ratio				
Short-duration	0.95 ± 0.02	0.94 ± 0.02	0.93 ± 0.02	0.91 ± 0.02
Long-duration	0.97 ± 0.02	0.97 ± 0.02	0.95 ± 0.02	0.92 ± 0.02
Fasting ketones, mmol/l				
Short-duration	0.15 ± 0.02	1.15 ± 0.16	0.97 ± 0.16	1.16 ± 0.29
Long-duration	0.24 ± 0.07	1.66 ± 0.45	1.81 ± 0.44	1.66 ± 0.38

Data are mean ± SEM.

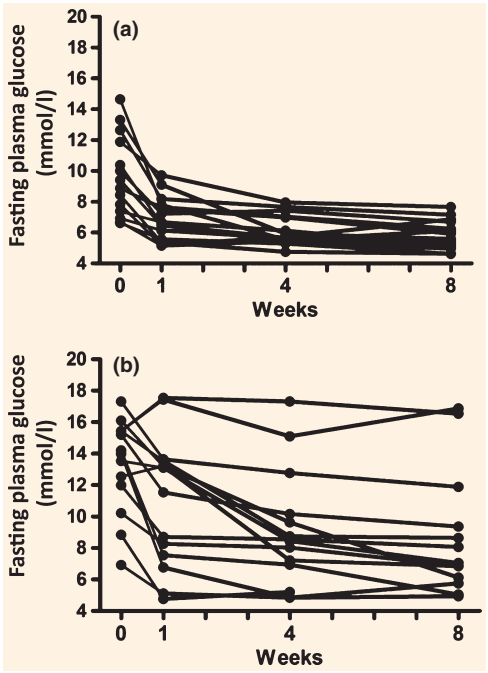

FIGURE 1 Change in fasting plasma glucose levels over the 8-week very-low-calorie diet for each person with (a) short-duration Type 2 diabetes and (b) long-duration Type 2 diabetes.

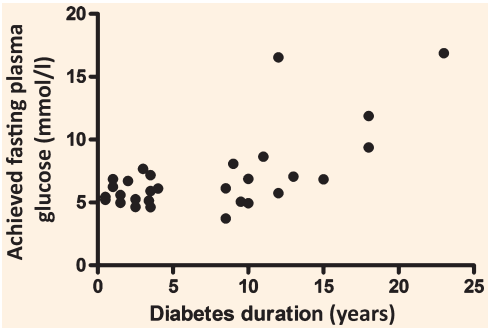

FIGURE 2 Fasting plasma glucose levels achieved at the end of the 8-week very-low-calorie diet were significantly correlated with diabetes duration (Spearman rank 0.501; $P = 0.006$).

glucose level achieved at week 8 of the very-low-calorie diet was 5.8 ± 0.2 mmol/l; for diabetes duration 8–12 years: 6.2 ± 0.7 mmol/l; and for diabetes duration ≥ 12 years: 10.6 ± 1.7 mmol/l.

Those who responded tended to be younger, have a shorter diabetes duration and lower baseline fasting glucose and required less treatment, compared with those who did not (Table 3). There was no effect of weight on degree of response.

Mean HbA_{1c} concentration decreased from 55 ± 2 mmol/mol (7.2 ± 0.2%) to 44 ± 2 mmol/mol (6.1 ± 0.2%) in the short-duration group ($P < 0.001$) and from 70 ± 4 mmol/mol (8.6 ± 0.4%) to 64 ± 6 mmol/mol (8.0 ± 0.5%) in the long-duration group ($P = 0.276$). Although the HbA_{1c} levels would not completely reflect change over the relatively short period of the study, non-diabetic levels (< 43 mmol/mol or < 6.1%) were achieved at week 8 in 6/15 (40%) of the short-duration group and 2/14 (14%) of the long-duration group.

Table 3 Baseline participant characteristics according to glucose response

	Responders (n = 20)	Non-responders (n = 9)	*P*
Gender: male/female	9/11	6/3	
Age, years	53.2 ± 2.2	64.4 ± 1.2	< 0.001
Weight, kg	96.4 ± 3.1	101.6 ± 4.8	0.374
BMI, kg/m^2	33.9 ± 0.7	34.9 ± 1.8	0.607
Diabetes duration, years	5.1 ± 1.0	12.3 ± 2.2	0.013
HbA1c			
mmol/mol	59 ± 3	69 ± 0.5	0.089
%	7.6 ± 0.3	8.5 ± 0.4	
Fasting plasma glucose, mmol/l	10.1 ± 0.7	14.3 ± 0.6	< 0.001
Diabetes treatment			
Insulin	0	3	
Diet	7	0	
Metformin only	8	1	
Metformin + sulphonylurea only	5	6	
Fasting triglycerides, mmol/l	1.7 ± 0.2	2.3 ± 0.8	0.466
Fasting total cholesterol, mmol/l	4.7 ± 0.2	4.7 ± 0.5	0.983
Fasting alanine aminotransferase, U/l	43.4 ± 7.9	26.0 ± 4.4	0.068

Responders were defined as achieving a fasting plasma glucose of < 7 mmol/l at week 8 of the very-low-calorie diet.

Blood pressure control

Blood pressure improved markedly and similarly in both groups: systolic: 144 ± 5 to 125 ± 5 mmHg ($P = 0.003$) vs. 160 ± 7 to 133 ± 6 mmHg ($P < 0.001$); diastolic: 91 ± 2 to 82 ± 3 mmHg ($P = 0.007$) vs. 90 ± 2 to 80 ± 3 mmHg ($P = 0.003$) in the short- vs. the long-duration groups, respectively. This improvement was sufficient to allow anti-hypertensive medication dose reduction in 1/6 (17%) and 7/11 (64%) people in the short- and long-duration groups, respectively, who were on anti-hypertensive medication at baseline.

Serum lipids

Total cholesterol improved from 4.6 ± 0.2 to 3.6 ± 0.2 mmol/l ($P = 0.004$) and from 4.8 ± 0.3 to 3.7 ± 0.3 mmol/l ($P < 0.001$) in the short- and long-duration groups, respectively. Triglycerides improved from 2.2 ± 0.5 to 1.0 ± 0.1 mmol/l ($P = 0.02$) and 1.5 ± 0.2 to 1.0 ± 0.1 mmol/l ($P = 0.001$), respectively; as did non-HDL cholesterol, improving from 3.5 ± 0.2 to 2.5 ± 0.2 mmol/l ($P = 0.004$) and 3.4 ± 0.3 to 2.4 ± 0.3 mmol/l ($P < 0.001$),

respectively. There was no change in HDL cholesterol in the short- and long-duration groups: 1.1 ± 0.1 to 1.1 ± 0.1 mmol/l ($P = 0.322$) and 1.4 ± 0.1 to 1.3 ± 0.1 mmol/l ($P = 0.187$), respectively. There was no correlation between decrease in fasting triglycerides and glucose response in either the short-duration (Pearson 0.371; $P = 0.174$) or long-duration groups (Pearson 0.077; $P = 0.793$).

Discussion

During the 8-week very-low-calorie diet, 50% of people with long-duration Type 2 diabetes and 87% with short-duration diabetes returned to non-diabetic fasting glucose levels despite withdrawal of all anti-diabetic therapies. The glucose response to acute calorie restriction in long-duration diabetes was heterogeneous, in contrast to the uniformly early fall in plasma glucose levels seen in short-duration diabetes. Important improvements in blood pressure and lipid profiles occurred irrespective of diabetes duration.

The steady loss of β-cell function observed during the UK Prospective Diabetes Study reinforced the view of Type 2 diabetes as an irreversible, inevitably progressive condition [1]; however, these observations were made during the usual clinical scenario of progressive weight gain. Reports of normalization of blood glucose control after bariatric surgery raised the possibility that negative calorie balance could restore normal physiology, but this was widely assumed to be surgery-specific and related to change in gut hormone profiles [6–8]. Direct comparison of gastric bypass with negative calorie balance alone has shown that the latter is entirely responsible for the improvement in glucose handling [9,10]. The Counterpoint study was designed to test the hypothesis that negative calorie balance would decrease fat levels in the liver and pancreas and that this would normalize liver insulin sensitivity and β-cell insulin secretion [3]. A return to normal in both variables was observed in step with a fall in intra-organ fat levels, with complete normalization of liver within 7 days and return of β-cell function gradually over 8 weeks. That study had been designed to examine the pathophysiological mechanisms underlying the reversibility of Type 2 diabetes, however, and, to ensure a homogenous study group, all were selected to have diabetes duration of < 4 years. The clinical question of whether the observations may have more widespread applicability was raised immediately on publication [11]. The present therapeutic study was therefore carried out to determine how people with longer-term Type 2 diabetes would respond to a very-low-calorie diet.

In the present study, a rapid fall in fasting plasma glucose concentration was observed in all the people with short-duration Type 2 diabetes, but the response in the long-duration group varied from rapid normalization to no decrease in fasting plasma glucose (Fig. 1). Some people with long-duration diabetes showed a distinct, intermediate response of a slow, steady decrease in glucose levels, which ultimately entered the normal range. At baseline, fasting plasma glucose concentration reflected the preceding withdrawal of therapy, and this would have had a greater impact in the long-duration group; however, baseline HbA_{1c} concentration would have been almost entirely unaffected by this. In the whole study group, those with the highest initial fasting plasma glucose, the longest duration of diabetes, the most treatment, and older age responded less well. The demonstration of potential for reversal in approximately half of those with long-standing diabetes is in line with observations made after bariatric surgery. A study of 110 people with Type 2 diabetes undergoing Roux-en-Y gastric bypass noted a remission rate of 44% for those with a diabetes duration of > 8 years [12].

Although a very-low-calorie diet strategy has been incorporated into the National Institute for Health and Care Excellence guidelines on obesity, this has not yet been widely taken up despite demonstration of efficacy and durability when applied in routine primary care [13,14]. This caution in using a very-low-calorie diet may relate to perceived low adherence, concerns about sustainability of effects and theoretical concerns about detrimental effects on lipid profile [15]. The present study provides clear information on acceptability and metabolic state. Compliance with the very-low-calorie diet is high, at least in motivated people, as judged by the hard endpoint of substantial weight loss, with only one of 30 participants unable to complete the study. Follow-up of the Counterpoint Study at 3 months after completing the very-low-calorie diet showed that seven of the 11 participants did not have diabetes on oral glucose tolerance testing, despite weight gain of 4 kg [3]. That study had not been designed as a therapeutic study and no follow-up support had been provided. It is intended that the presently reported cohort will be followed up to quantify the durability of the effect on both weight and glucose control.

The overall health benefits were both striking and appreciated by all participants. These included lower blood pressure, improvement in lipid profile, improved general wellbeing, increased mobility and better sleep quality. The 19–27 mmHg improvement in systolic blood pressure and 9–10 mmHg improvement in diastolic blood pressure was similar to that seen with the addition of two anti-hypertensive agents at usual dose [16]. The improvement in total cholesterol observed in the present study was similar to that observed with full-dose statin therapy, with likely major reduction in cardiovascular events in people with diabetes [17]. After publication of the Counterpoint Study, the extent of the enthusiasm of some people with Type 2 diabetes to take major steps to escape from diabetes became clear in the very large-scale email feedback [5]. The email feedback from those who lost weight and returned to normal glucose tolerance, showed that duration of normal glucose control in some now approaches 3 years [18]. Provided that weight loss is maintained, diabetes does not return, at least over several years.

The limitations of the present study must be considered. Diabetes duration is an imprecise entity and some individuals may have a prolonged period of unrecognized hyperglycaemia preceding a diagnosis. The best information suggests that fasting glucose levels rise only gradually over many years preceding a diagnosis, but in the final 12–24 months increase rapidly [19,20]. In the present study, the date of diagnosis reported by participants was verified from medical records and any subclinical period would be equally likely in each group. Secondly, the diagnosis of Type 2 diabetes itself depends upon exclusion of other possible diagnoses. Subjects were recruited if diabetes was detected through a routine test and excluded if diagnosis was precipitated by severe osmotic symptoms. Thorough history-taking was used to exclude those with clinical features suggestive of latent autoimmune diabetes of adulthood or maturity-onset diabetes of the young. Thirdly, the baseline levels of fasting plasma glucose were necessarily different in the groups defined by duration of Type 2 diabetes. Additional matching for glycaemic control or treatment for diabetes would have resulted in an atypical group as defined by duration of diabetes. Finally, the proportion of the research participants achieving reversal of Type 2 diabetes cannot be extrapolated to the general population with the condition. The participants in the study were highly motivated to succeed in losing weight and a selection bias will have operated; however, even if only a modest proportion of the affected population was able to follow this treatment, the impact upon health service budgets would be substantial. These considerations do not impinge on the purpose of the study: to understand the therapeutic potential of a very-low-calorie diet on glucose levels in long- compared with short-duration Type 2 diabetes.

In conclusion, in people with Type 2 diabetes of > 8 years' duration, a therapeutic trial of a very-low-calorie diet may be undertaken with a 50% chance of achieving non-diabetic fasting plasma glucose levels, without any other antidiabetic therapies. For those who do not achieve non-diabetic plasma glucose levels, general health, blood pressure and lipids will be considerably improved. These insights highlight the potential for use of a very-low-calorie diet in long-duration Type 2 diabetes and carry implications for everyday clinical practice. The genetic and metabolic factors that underlie the heterogeneity of response now need to be investigated. Further work is under way on the durability of the effect of the very-low-calorie diet and the impact of this therapeutic strategy when undertaken in a primary care setting in a larger cohort of individuals with Type 2 diabetes.

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Competing interests

None to declare.

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