The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial

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Abstract

Aims/hypothesis Short-term dietary studies suggest that high-protein diets can enhance weight loss and improve glycaemic control in people with type 2 diabetes. However, the long-term effects of such diets are unknown. The aim of this study was to determine whether high-protein diets are superior to high-carbohydrate diets for improving glycaemic control in individuals with type 2 diabetes.

Methods Overweight/obese individuals (BMI 27–40 kg/m²) with type 2 diabetes (HbA_{1c} 6.5–10%) were recruited for a 12 month, parallel design, dietary intervention trial conducted at a diabetes specialist clinic (Melbourne, VIC, Australia). Of the 108 initially randomised, 99 received advice to follow low-fat (30% total energy) diets that were either high in protein (30% total energy, *n*=53) or high in carbohydrate (55% total energy, *n*=46). Dietary assignment was done by a third party using computer-generated random numbers. The primary endpoint was change in HbA_{1c}. Secondary endpoints included changes in weight, lipids,

blood pressure, renal function and calcium loss. Study endpoints were assessed blinded to the diet group, but the statistical analysis was performed unblinded. This study used an intention-to-treat model for all participants who received dietary advice. Follow-up visits were encouraged regardless of dietary adherence and last measurements were carried forward for study non-completers.

Results Ninety-nine individuals were included in the analysis (53 in high protein group, 46 in high carbohydrate group). HbA_{1c} decreased in both groups over time, with no significant difference between groups (mean difference of the change at 12 months; 0.04 [95% CI −0.37, 0.46]; *p*=0.44). Both groups also demonstrated decreases over time in weight, serum triacylglycerol and total cholesterol, and increases in HDL-cholesterol. No differences in blood pressure, renal function or calcium loss were seen.

Conclusions/interpretation These results suggest that there is no superior long-term metabolic benefit of a high-protein diet over a high-carbohydrate in the management of type 2 diabetes.

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Keywords Dietary intervention · High-carbohydrate diet · High-protein diet · Type 2 diabetes

Abbreviations

ANCOVA	Analysis of covariance
eGFR	estimated GFR
HC	High-carbohydrate diet group
HP	High-protein diet group

Introduction

Although it is widely recognised that energy restriction is the dietary intervention most needed in type 2 diabetes, there remains considerable debate over the optimal macronutrient composition of the diet. Consensus-based nutritional guidelines currently recommend diets that are high in carbohydrates (45–65% of total daily energy intake) and low in fat (<30% of energy intake) [1]. However, this approach is regularly challenged as high-carbohydrate diets may exacerbate hyperglycaemia and dyslipidaemia [2, 3]. Furthermore, the long-term efficacy of this dietary approach remains uncertain.

There is emerging evidence from short-term dietary trials to suggest that high-protein, low-carbohydrate diets may be more favourable for weight loss than traditional high-carbohydrate, low-fat diets [4, 5]. Evidence supports an effect of protein on appetite suppression [6], increased thermogenesis [7], and preservation of lean body mass during weight loss [8]. High-protein diets may also improve glycaemic control and insulin sensitivity in people with type 2 diabetes [9–13], independent of changes in weight [9], and might even reduce the risk of developing type 2 diabetes [14]. Although high-protein, low-carbohydrate diets may offer modest short-term metabolic advantages, the long-term efficacy of this dietary approach is poorly understood. Furthermore, there are also concerns that high-protein diets are associated with an accelerated decline in renal function [15], increased calcium loss leading to osteoporosis and renal stones [16], and dyslipidaemia due to concomitant increases in fat intake [17]. Consequently, the aim of the present study was to investigate the long-term health effects of two energy-reduced, low-fat diets differing in the protein to carbohydrate ratio in overweight and obese individuals with type 2 diabetes.

Methods

Participants Participants with type 2 diabetes were recruited by study personnel from a diabetes clinic and from local community advertisements. Participants were aged 30–75 years, with a BMI of 27–40 kg/m² and HbA_{1c} levels of 6.5–10%, and were excluded if they had significant heart disease (unstable angina, cardiac failure, or recent myocardial infarction or coronary intervention), stroke within the previous 3 months, renal disease (proteinuria or serum creatinine >0.13 mmol/l), liver disease, or malignancy. Informed consent was obtained from all participants and the study was approved by the International Diabetes Institute's Human Ethics committee.

Study design This single-centre, randomised controlled trial was conducted at the Baker IDI Heart and Diabetes Institute

(Melbourne, Australia) between May 2005 and December 2006. Participants were randomised in a 1:1 ratio to either a high-protein (HP group) or high-carbohydrate (HC group) diet for a period of 12 months. Randomisation was carried out by a third party using computer-generated random numbers (using block randomisation and random block sizes) and stratified according to diabetes treatment (diet alone, oral medication, or insulin; see Table 1). Study personnel who enrolled participants were blinded to the sequence allocation. Dietary assignment was performed by a third party on the day of the initial dietary counselling visit.

The trial involved visits every 3 months to assess study outcomes. The primary endpoint of the study was change in HbA_{1c}. Predefined secondary endpoints included changes in weight, waist circumference, lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerol), blood pressure (systolic and diastolic), renal function (estimated GFR [eGFR] and albumin excretion rate) and calcium loss. It was calculated that 46 participants per group would provide 80% power (at the two-sided 5% level) to detect a difference of 0.5% in the HbA_{1c} levels between groups, assuming a standard deviation of 0.85%. To compensate for participant withdrawal, 108 participants were recruited.

This study was carried out using an intention-to-treat model following delivery of dietary advice. Participants who were randomised but withdrew consent before receiving dietary instruction were not included in the intention-to-treat analysis. To maintain the intention-to-treat integrity of the study design and to minimise the amount of missing data, study staff encouraged all participants to return for follow-up assessments of primary and secondary outcomes, regardless of dietary adherence.

Interventions A qualified dietitian administered the diet-specific advice to each study participant. The study consisted of two dietary periods: a 3 month energy restrictive period (~6,400 kJ/day or 30% energy restriction), followed by 9 months of energy balance. The HP diet consisted of 30% energy intake from protein (a combination of lean meat, chicken and fish) and 40% energy intake from carbohydrate. The HC diet consisted of 15% energy intake from protein and 55% energy intake from carbohydrate. The diets were matched for total fat (30% of energy) and the fatty acid profile (7% saturated fat, 10% polyunsaturated fat, 13% monounsaturated fat). Consistent with current guidelines [18], both diets recommended carbohydrates of low glycaemic index. In addition to regular face-to-face dietary counselling appointments, written materials were supplied to both groups containing information on the key nutrition intervention messages, prescriptive fixed menu plans and food choice lists.

Table 1 Participant characteristics at baseline

Characteristic	HP (n=53)	HC (n=46)
Demographics		
Age (years)	59.6 (57.5, 61.8)	58.8 (55.8, 61.7)
Duration of diabetes (years)	8.7 (6.8, 10.5)	8.6 (6.6, 10.6)
Male, n (%)	30 (57)	18 (39)
Diabetes treatment, n (%)		
None	5 (9)	5 (11)
Insulin	10 (19)	7 (15)
Tablets	38 (72)	34 (74)
Anthropometry		
Body weight (kg)	94.6 (90.5, 98.8)	95.5 (91.5, 99.6)
Waist circumference (cm)	110.2 (107.2, 113.1)	110.1 (107.5, 112.8)
HbA _{1c} (%)	7.89 (7.63, 8.15)	7.78 (7.50, 8.05)
Cardiovascular disease risk factors		
Total cholesterol (mmol/l)	4.73 (4.50, 4.96)	4.71 (4.40, 5.01)
LDL-cholesterol (mmol/l)	2.49 (2.28, 2.70)	2.42 (2.16, 2.68)
HDL-cholesterol (mmol/l)	1.19 (1.11, 1.24)	1.20 (1.12, 1.28)
Triacylglycerol (mmol/l)	2.39 (2.01, 2.76)	2.37 (1.85, 2.90)
Systolic blood pressure (mmHg)	131.8 (128.8, 134.8)	127.4 (124.5, 130.2)
Diastolic blood pressure (mmHg)	81.5 (79.5, 83.6)	81.5 (78.8, 84.2)
Renal variables		
Albumin excretion rate (µg/min)	30.0 (14.5, 45.6)	26.2 (11.0, 41.5)
eGFR (ml min ⁻¹ 1.73 m ⁻²)	70.2 (67.0, 73.4)	72.6 (68.5, 76.7)
Calcium excretion rate (µg/min)	120.7 (97.8, 143.6)	93.1 (71.1, 115.1)

Data are expressed as means (95% CI) or number (%) where specified

Dietary intakes were calculated from weighed/measured food records collected at baseline (5 days) and every 3 months during the intervention period (1 day/month) using Australia-specific dietary analysis software (Foodworks; Xyris Software, Highgate Hill, QLD, Australia). Dietary compliance was monitored by self-reported food intakes and 24-h urine samples for an assessment of urea excretion as a marker of protein intake. At 12 months, participants were asked to rate their dietary self-management on a Likert scale. This was the first section of a validated diabetes-specific questionnaire relating to dietary satisfaction and quality of life. Details regarding the questionnaire are described elsewhere [19].

Behavioural therapy and physical activity recommendations

Both groups were offered the same level of behavioural therapy and physical activity recommendations. The behavioural therapy consisted of individual appointments that were designed to monitor the participant's progress and provide individualised feedback to the participants. This consisted of four visits during the 3 month energy restrictive period (totalling 2.5 contact hours), and five visits during the 9 months of energy balance (totalling 2.5 contact hours). In addition, group meetings were held every 3 months to help reinforce the principles of the dietary programmes (total

contact time 3.3 h). Group topic modules included healthy cooking, goal setting and problem solving, physical activity, and supportive counselling. Physical activity was encouraged as a strategy to increase energy expenditure for those without limitations or complications, and the recommendations were consistent with public health guidelines. Physical activity was measured using the validated Active Australia survey [20].

Standard therapy At all visits, study personnel recorded information regarding concomitant medications (drug name, frequency and dosage). All medication changes were made independently of the study personnel by the treating physician.

Outcome measures

Baseline assessments of study outcomes were done at the initial informed consent appointment, approximately 1 week before randomisation/dietary counselling. Weight and waist circumference were measured every 3 months following dietary counselling. All participants were weighed in light clothes and weight was used to calculate BMI. At 6 and 12 months, a trained assessor, who was blinded to the dietary assignment of the individual, measured and recorded weight and waist circumference. Blood pressure was measured at baseline, 3, 6, 9 and 12 months with a mercury sphygmomanometer.

Fasting blood samples and 24-h urine specimens were collected at baseline, 3, 6, 9 and 12 months for the assessment of HbA_{1c}, lipids, eGFR, urinary albumin and urinary calcium. All biochemical analyses were performed by an independent laboratory. HbA_{1c} was determined using immunoturbidimetric spectrophotometry with the Roche Integra 800 analyser (Roche Diagnostics, Castle Hill, NSW, Australia). Urinary albumin was measured by nephelometry with the Beckman Coulter Image system (Beckman Coulter Instruments, Gladsville, NSW, Australia). Serum creatinine (for eGFR), urinary calcium and lipids were measured by spectrophotometric methods on the Roche Modular Analyser (Roche Diagnostics).

Statistical analysis This study used the single imputation method of last measurement carried forward for missing data for primary and secondary outcomes. This method was chosen because of the high rate of follow-up at each time point (see Fig. 1) and as this method was thought to provide a close approximation to the unobserved value.

All statistical analyses were performed using SPSS 17.0 for Windows. Dietary data and study outcomes were analysed by repeated measures ANOVA incorporating data from all time points to explore the effects of time, dietary group allocation and the time course between groups (time $\times$ group interaction). Triacylglycerol, HbA_{1c}, HDL-cholesterol and urinary albumin were log_e-transformed as the data were log_e-normally distributed. Blood pressure and medication changes were analysed using non-parametric tests to test for differences between groups. Post hoc analyses (multifactorial repeated measures ANOVA and repeated measures analysis of covariance [ANCOVA]) were performed to also account for differences between sexes and medication changes. To ensure that any observed changes were not the result of multiple comparisons, exploratory within- and between-group comparisons were performed at the end of the weight loss and weight maintenance phases and interpreted with the use of the Bonferroni adjustment. A critical α value of $p < 0.0025$ was used for the evaluation of the 20 dietary comparisons (Table 2) and $p < 0.0019$ for the 26 study outcome comparisons (Tables 3 and 4).

As this study involved changes to a number of dietary variables (i.e. intakes of calories, protein and carbohydrate), subsidiary correlation analyses were performed to identify whether study endpoints were a function of the change in specific dietary variables. The regression analysis was performed for the per protocol population after pooling data from both groups. These tests were interpreted marginally as there was no formal adjustment of the overall type 1 error rate and the p values serve principally to generate hypotheses for validation in future studies.

Results

Participant characteristics The baseline characteristics for the intention-to-treat population were well-matched at baseline (Table 1), although non-significant differences were apparent in calcium excretion rate, systolic blood pressure and the proportion of men. Compared with men, women had a lower mean baseline weight (mean difference -12.4 kg [95% CI -17.6 , -7.2]), waist circumference (mean difference -7.2 cm [95% CI -10.9 , -3.5]) and higher HDL-cholesterol (mean difference 0.28 mmol/l [95% CI 0.18 , 0.38]).

Attrition and protocol compliance In the intention-to-treat model, 18.9% (10/53) of HP participants and 19.6% (9/46) of HC participants discontinued the diet, but returned for follow-up assessments (Fig. 1). The proportion of individuals who were lost to follow-up was slightly higher in the HP group (9.2% vs 4.2%). However, 6 month data were collected for three of the five HP participants who were lost to follow-up.

Twenty-five per cent of the HP group and 37% of the HC group attended all nine individual appointments, while 21% and 26%, respectively, missed just one visit. Attendance at group education sessions was similar in the two groups, and ranged from 26% to 37% per session for each group. This study also found no significant group difference in self-reported time spent in physical activity.

Dietary intake and adherence Dietary intakes according to 3-day diet records are shown in Table 2. Repeated measures analysis that incorporated data from all time points indicated that energy intake decreased over time and there was no significant difference between groups. However, we found significant group differences with repeated measures analysis in the quantities of carbohydrate, protein and cholesterol in the two diets. Exploratory analyses, which adjusted for multiple comparisons, confirmed that the quantity of carbohydrate was significantly lower, and quantities of protein and cholesterol were significantly higher, in the HP group at the completion of the weight-loss and weight maintenance phases. The difference in reported protein intake was substantiated by significantly higher 24 h urea excretion in the HP group at 3 months (mean difference 114 mmol/24 h [95% CI 49 , 178], $p = 0.001$) and, although urea excretion remained higher in the HP group at 12 months, significance was lost following conservative statistical correction (mean difference 122 mmol/24 h [95% CI 40 , 203], $p = 0.004$).

In addition to self-reported dietary intakes, participants were also asked to rate their ability to self-manage their prescribed diet. After 12 months of following the prescribed diet, there was no significant difference between groups in median dietary self-management scores (median [interquartile range]; 4 [3, 4] for HP vs 4 [3, 4] for HC, $p = 0.85$).

Fig. 1 Participant flow diagram.
LOCF, last observation carried
forward

Glycaemic control and medication use Repeated measures analysis showed that HbA_{1c} fell significantly during the study, with levels decreasing sharply during weight loss and then rising to a similar extent in both groups during weight maintenance. Exploratory analysis revealed that the reduction in HbA_{1c} at 1 year for all study participants remained significant following Bonferroni correction.

Although we found no effect of diet composition on HbA_{1c}, we observed a trend for a reduction in the

requirement for hypoglycaemic medications in the HP group (Table 4). Reductions in insulin and sulfonylurea therapies were the main contributors to the per cent reduction in medications in the HP group. However, after adjusting for changes in medication, the between-group difference in HbA_{1c} remained non-significant.

Weight and body composition We found that body weight decreased during the initial weight loss period and

Table 2 Self-reported dietary composition at baseline, 3 and 12 months

Variable	Group				Difference between groups	<i>p</i> value ^a		
	HP	<i>n</i>	HC	<i>n</i>		Group	Time	Group×time interaction
Energy (kJ)						0.85	<0.001	0.22
Baseline	8,897	50	9,175	45	−179 (−1,939, 1,581)			
3 months	6,449	46	6,029	39	420 (−154, 994)			
12 months	6,664	30	6,628	33	35 (−780, 851)			
Carbohydrate (% of total energy)						<0.001	0.17	<0.001
Baseline	44.3	50	45.5	45	−1.2 (−4.2, 1.9)			
3 months	40.4	46	49.0	39	−8.6 (−11.0, −6.2) ^b			
12 months	41.8	30	48.2	33	−6.4 (−9.5, −3.3) ^b			
Protein (% of total energy)						<0.001	<0.001	<0.001
Baseline	21.3	50	20.3	45	1.0 (−0.7, 2.7)			
3 months	28.2	46	20.8	39	7.4 (6.0, 8.8) ^b			
12 months	26.5	30	18.9	33	7.6 (5.9, 9.3) ^b			
Fat (% of total energy)						0.98	0.004	0.47
Baseline	32.2	50	32.8	45	−0.6 (−3.1, 1.9)			
3 months	30.1	46	29.3	39	0.83 (−1.5, 3.1)			
12 months	30.7	30	32.0	33	−1.3 (−4.2, 1.6)			
Monounsaturated fat, % of total fat						0.09	0.02	0.72
Baseline	40.5	50	40.7	45	−0.18 (−1.73, 1.37)			
3 months	42.1	46	40.3	39	1.85 (0.17, 3.53)			
12 months	42.6	30	41.6	33	1.06 (−0.68, 2.81)			
Polyunsaturated fat (% of total fat)						0.72	0.66	0.11
Baseline	17.7	50	18.2	45	−0.5 (−2.5, 1.5)			
3 months	17.4	46	18.9	39	−1.5 (−3.7, 0.6)			
12 months	18.1	30	18.6	33	−0.5 (−2.7, 1.7)			
Saturated fat (% of total fat)						0.42	0.31	0.09
Baseline	41.8	50	41.1	45	0.7 (−1.8, 3.1)			
3 months	40.2	46	40.5	39	−0.3 (−3.0, 2.4)			
12 months	39.3	30	39.8	33	−0.5 (−3.2, 2.2)			
Fibre (mg/day)						0.34	0.001	0.62
Baseline	26.0	50	26.8	45	−0.8 (−4.2, 2.7)			
3 months	22.5	46	23.4	39	−1.0 (−3.5, 1.6)			
12 months	21.7	30	23.9	33	−2.2 (−5.6, 1.1)			
Cholesterol (mg/day)						<0.001	0.001	0.04
Baseline	357	50	298	45	59 (−3, 121)			
3 months	309	46	170	39	139 (98, 180) ^b			
12 months	320	30	208	33	111 (46, 177) ^b			

Data are expressed as group means or mean difference between groups (95% CI) with missing values excluded

^a Repeated-measures ANOVA incorporating data from all time points (0, 3, 6, 9 and 12 months) was used to test for overall differences between dietary groups (main effect of group), changes over time (main effect of time) and differences in the time course between groups (group×time interaction)

^b Testing for equality of means using independent *t* test revealed significant between-group ($p<0.004$) difference following Bonferroni adjustment for multiple comparisons

rebounded slightly during the weight maintenance phase (Table 2). There was no effect of diet type on mean changes in weight and waist circumference. Furthermore, we found no significant sex differences for changes in

weight (mean difference at 1 year 0.87 kg [95% CI −1.00, 2.74], $p=0.11$) and waist circumference (mean difference at 1 year 1.28 cm [95% CI −0.30, 2.86], $p=0.36$). Regression models that adjusted for sex differences

Table 3 Change in study outcomes at 3 and 12 months

Variable	Group				Difference between groups	<i>p</i> value ^a		
	HP	<i>n</i>	HC	<i>n</i>		Group	Time	Group×time interaction
HbA _{1c} (%)						0.50	<0.001	0.88
3 months	−0.52	53	−0.49	46	−0.03 (−0.28, 0.23)			
12 months	−0.23	53	−0.28	46	0.04 (−0.37, 0.46)			
Weight (kg)						0.78	<0.001	0.90
3 months	−2.79	53	−3.08	46	0.29 (−1.03, 1.61)			
12 months	−2.23	53	−2.17	46	−0.07 (−1.67, 1.54)			
Waist circumference (cm)						0.97	<0.001	0.75
3 months	−3.06	53	−2.72	46	−0.34 (−1.86, 1.19)			
12 months	−3.54	53	−3.35	46	−0.19 (−2.08, 1.69)			
Total cholesterol (mmol/l)						0.75	0.002	0.32
3 months	−0.23	53	−0.31	46	0.08 (−0.16, 0.33)			
12 months	−0.15	53	0.01	46	−0.16 (−0.51, 0.18)			
LDL cholesterol (mmol/l)						0.76	0.42	0.30
3 months	−0.04	53	−0.11	46	0.07 (−0.09, 0.24)			
12 months	−0.05	53	0.04	46	−0.10 (−0.37, 0.17)			
HDL cholesterol (mmol/l)						0.62	0.008	0.84
3 months	0.00	53	0.00	46	−0.00 (−0.05, 0.05)			
12 months	0.08	53	0.08	46	0.01 (−0.10, 0.11)			
Triacylglycerol (mmol/l)						0.75	<0.001	0.34
3 months	−0.50	53	−0.45	46	−0.05 (−0.54, 0.44)			
12 months	−0.47	53	−0.30	46	−0.17 (−0.65, 0.32)			
eGFR (ml min ^{−1} 1.73 m ^{−2})						0.32	0.001	0.64
3 months	−0.01	53	1.21	46	−1.21 (−4.43, 2.01)			
12 months	3.20	53	1.98	46	1.21 (−2.22, 4.63)			
Albumin excretion rate (μg/min)						0.78	0.18	0.45
3 months	−9.55	44	−1.97	37	−7.6 (−22.5, 7.4)			
12 months	−4.51	44	−4.65	37	0.14 (−18.8, 19.1)			
Calcium excretion rate (μg/min)						0.03	0.001	0.80
3 months	−5.6	51	−7.6	46	2.0 (−20.9, 24.9)			
12 months	22.6	51	11.6	46	11.0 (−13.5, 35.4)			

Data are expressed as means or the between-group difference (95% CI) of the change in study outcomes

^a Repeated-measures ANOVA was performed incorporating data from all time points (0, 3, 6, 9 and 12 months) on absolute or log-transformed data to explore differences in time, diet group and the time course between groups (group×time interaction)

demonstrated no interactive effects of sex and diet type on study outcomes.

Correlates of change in study endpoints Combining the two study groups, change in energy intake over 1 year was associated with changes in HbA_{1c} ($r=0.31$, $p=0.01$) and waist circumference ($r=0.34$, $p=0.008$) (see Electronic supplementary material [ESM] Fig. 1). Weight loss and the improvement in HbA_{1c} at 1 year were also associated with the self-management score (see ESM Fig. 2). Participants with the highest self-management score at 1 year lost an average of 5.5 kg of body weight and demonstrated a 0.87% reduction in their mean HbA_{1c}, whereas participants with the

lowest self-management score demonstrated a 0.03 kg weight change and a 0.03% change in HbA_{1c} levels.

Risk factors for chronic disease states (cardiovascular disease, kidney disease and osteoporosis) Total cholesterol, HDL-cholesterol and serum triacylglycerol improved significantly in both groups over time, but with no significant differences between the groups (Table 3). Adjustment for multiple testing was able to confirm significant within-group changes in HDL-cholesterol and serum triacylglycerol at 12 months. However, the reduction in total cholesterol was only significant at 3 months with Bonferroni correction. During the trial, three individuals increased

Table 4 Change in blood pressure and diabetes medication at 3 and 12 months

Variable	Group				Difference between groups	<i>p</i> value ^a
	HP	<i>n</i>	HC	<i>n</i>		
Systolic blood pressure (mmHg)						
3 months	−3.09	53	−0.06	46	−3.03 (−6.00, −0.05)	0.04
12 months	−5.03	53	−0.76	46	−4.26 (−8.80, 0.27)	0.05
Diastolic blood pressure (mmHg)						
3 months	2.24	53	1.63	46	0.62 (−2.32, 3.55)	0.43
12 months	0.21	53	0.65	46	−0.44 (−4.95, 4.06)	0.70
Weighted per cent change in diabetes medications ^b						
3 months	−8.71	48	0.68	41	−9.38 (−17.85, −0.92)	0.03
12 months	−8.17	48	4.56	41	−12.72 (−28.18, 2.73)	0.05

Data are expressed as means or the between-group difference (95% CI) of the change in study outcomes

^a Between-group analysis was performed using the Mann–Whitney *U* test

^b Weighted per cent change in medications calculated as: $\Sigma[\text{percentage dosage change for each diabetes medication}] \div \text{no. of different diabetes medications } (n)$

and three decreased hypolipidaemic therapy (dosage or number of medications) in the HP group; while two individuals increased and one decreased lipid treatment in the HC group. This study found no main effect of medication changes or an interaction effect of diet and medications on lipid variables.

In the HP group, there was a trend for reduction in systolic blood pressure. However, the difference between groups did not meet significance at 3 or 12 months following Bonferroni adjustment (Table 4). In the HC group, five individuals increased and three decreased antihypertensive medications (dosage or number of medications); while two individuals increased blood pressure therapy in the HP arm. Removing those with changes to medications from the analysis did not affect blood pressure outcomes.

There were no differences between the two diets with regards to changes in renal function (eGFR and albumin excretion rate). Furthermore, there were no associations between the change in protein intake (g/day) and the change in eGFR ($r=0.08$, $p=0.49$) or in urinary albumin excretion ($r=0.17$, $p=0.16$). Repeated measures analysis indicated that the calcium excretion rate changed in both groups over time and there was a significant difference between groups. However, exploratory analyses revealed that these effects were lost following adjustment for multiple statistical testing.

Discussion

In this randomised controlled trial, we found that a weight-reducing, high-protein diet was no more effective than a weight-reducing, high carbohydrate diet in improving

glycaemic control in type 2 diabetes. We found only modest reductions in weight and HbA_{1c} after 12 months of applying the recommended diets under real-world conditions.

Strengths of our study relative to past trials include longer study duration, the use of an intention-to-treat model and the measurement of dietary compliance. Attrition rates typically range from 30% to 50% in weight loss trials [21] and in dietary studies in type 2 diabetes [22]. This study followed up 94% of all participants who received dietary advice and relied on the last measurement carried forward for the small number of individuals who discontinued the study. Although this relies on the assumption that participants remain unchanged from the point of discontinuation, we believe this method to be appropriate as the individuals who dropped out immediately after receiving dietary advice were unlikely to show improvements in weight or HbA_{1c}, and as information collected at 6 and 9 months provides a reasonable approximation of the unobserved data at 12 months. This study also had several limitations. As both groups demonstrated improvements over time, it is possible that the improvements may reflect other behavioural aspects of the study design (i.e. physical activity and supportive counselling) rather than the changes in dietary composition per se. Second, we were not able to blind participants or the study personnel involved in dietary counselling. Furthermore, the statistical analysis was performed unblinded to the treatment allocation. However, key study endpoints (anthropometrics and laboratory variables) were measured by personnel who were blinded to group allocation. Other limitations of the study include problems associated self-reported dietary intakes, multiple medication use, and a predominantly female high-carbohydrate group.

Previous studies have demonstrated greater [9, 23, 24] or equivalent [12, 13, 25] improvements in glycaemic control when comparing high-protein diets with high-carbohydrate diets. However, it is important to distinguish trials performed under controlled feeding conditions from those that use standard dietary counselling to modulate dietary intakes. High-protein diets have been shown to lower glycaemic variables in controlled feeding studies [9, 24], where participants were provided with, and consumed food according to, exact specifications. Although these studies enable the measurement of the true short-term biological effect of such diets, they are unable to test to what extent people can adhere to these diets on their own. Under real-world conditions, variations in food selection and discrepancies in dietary adherence are likely to attenuate the effect previously demonstrated in controlled feeding studies. While the desired dietary compositions were not strictly met in our study, both groups demonstrated dietary changes towards recommended targets and we were able to confirm significant differences in dietary composition from urinary biomarkers. However, despite achieving a significant group difference in 24 h urea excretion at 3 months, the difference was not significant at 12 months. However, this may be partly due to the conservative nature of the statistical adjustment; we may not have obtained a sufficient difference between the groups to demonstrate a significant effect. A major problem of long-term dietary interventions is that compliance deteriorates over time and therefore a lack of a significant effect could be the result of inadequate difference between the diets.

The significance of the trend for a reduction in anti-diabetic medication in the HP is unclear. Although this would imply a trend for improved glycaemic control in this arm, statistical adjustment for the change in medications did not modify the outcome for the change in HbA_{1c}. Although we did not ask our participants to report on the frequency of hypoglycaemic episodes, this was a commonly cited reason for decreasing medication dosage. This suggests that diabetes medications, particularly insulin and sulfonylurea therapies, should be frequently reviewed when implementing a high-protein, low-carbohydrate diet in order to avoid hypoglycaemia.

One interesting finding from this study was that the degree of energy reduction, not the composition of the diet, was related to the long-term improvement in glycaemic control. Although these results should be interpreted marginally in light of the multiple testing, this finding suggests that dietary approaches should focus more on limiting energy intake rather than modifying the consumption of specific macronutrients. The notion that a variety of approaches may be useful for inducing weight loss and promoting metabolic control in type 2 diabetes has also been reflected in recent guidelines [26]. Greater liberalisation of dietary approaches means that diets can be better tailored to the individual, which may enhance dietary self-

management and clinical outcomes. In this study, we observed that the dietary self-management score at 1 year was associated with greater weight maintenance and improvements in glycaemic control. As dietary self-management involves the active and voluntary participation of the patient, it would seem reasonable that the patient should have the freedom to choose a course of behaviour, allowing for both patient and healthcare provider to mutually establish appropriate treatment goals and the dietary regimen. Future trials are therefore required to validate this hypothesis and to help establish an integrative approach to the patient's clinical management.

An appropriate diet for patients with type 2 diabetes should also focus on the prevention or the delay in the onset of developing chronic complications, particularly cardiovascular disease. In our study, both groups demonstrated reductions in cardiovascular risk factors in the form of decreasing triacylglycerol and total cholesterol during active weight loss and increasing HDL-cholesterol during weight stabilisation. Furthermore, we found no effect of increased protein consumption on markers of renal function or bone turnover. Calcium excretion rate and eGFR increased over time in both groups, suggesting that these changes may be more a function of weight loss than dietary composition. These results should, however, be viewed with some caution, as this study may not have been sufficiently powered to demonstrate differences in secondary outcomes.

This study suggests that a high-protein diet is no better or worse than a high-carbohydrate diet for managing type 2 diabetes. We recommend that future trials should focus on developing relevant skills to improve dietary adherence and self-management rather than modifying dietary composition.

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