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Protein and carbohydrate distribution among the meals: effect on metabolic parameters of patients with type 2 diabetes: a single-blinded randomised controlled trial

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Abstract

Studies have revealed that the timing of macronutrient ingestion may influence body weight and glucose tolerance. We aimed to examine the effect of high protein *v.* high carbohydrate intake at the evening meal on metabolic parameters of patients with type 2 diabetes. This is a single-blinded, parallel, randomised controlled trial. Ninety-six patients with type 2 diabetes, aged 32–65 years with a mean BMI of 28·5 (SD 3·4) kg/m^2, were randomly assigned into one of these three groups: standard evening meal (ST), high-carbohydrate evening meal (HC) and high-protein evening meal (HP). Then, the patients were followed for 10 weeks. HbA_1c, fasting blood glucose, fasting insulin, insulin resistance, TAG, LDL-cholesterol, VLDL-cholesterol, diastolic blood pressure, body weight, body fat percentage and waist circumference decreased significantly in all three groups ($P < 0·05$). HbA_1c showed more improvement in the ST compared with the HP group (–0·45 (SD 0·36) *v.* –0·26 (SD 0·36)). Reductions in BMI and body weight were significantly higher in the ST compared with the HP group ($P < 0·05$). Reductions in total cholesterol, non-HDL-cholesterol and systolic blood pressure were significant in all groups, except for the HP group. Non-HDL-cholesterol:HDL-cholesterol remained unchanged in all groups. The results of the present study revealed that even distribution of carbohydrates and protein among meals compared with reducing carbohydrates and increasing protein at dinner may have a more beneficial effect on glycaemic control of patients with type 2 diabetes.

Key words: **Type 2 diabetes: Carbohydrates: Protein: Evening meal: Glycaemic control**

Diabetes mellitus is a metabolic disorder characterised by chronic hyperglycaemia and is caused by either impaired insulin secretion or impaired insulin function or both[1]. The prevalence of diabetes is increasing rapidly throughout the world, partially as a result of obesity and a sedentary lifestyle[2]. It is estimated that in 2013, 382 million people had diabetes worldwide and this number will increase to 592 million by 2030[3]. Type 2 diabetes accounts for 90–95 % of all diabetes cases and results from relative insulin deficiency in the presence of insulin resistance[4].

Medical nutrition therapy is a cornerstone of diabetes prevention and management and may improve body weight, glycaemia, blood pressure and lipid profile[5]. Results of some studies have shown that in addition to total energy intake and food composition, the timing of meals and specific macronutrient ingestion has implications for metabolic health and influences appetite, body weight, insulin secretion and glucose tolerance[6–14]. The mechanism by which these dietary approaches may exert their effect is not completely known, but it seems that diurnal variation in secretion and activity of metabolic hormones and enzymes like insulin, glucagon-like peptide 1, adiponectin, leptin and ghrelin may be responsible[13,15,16].

Although the importance of diet therapy in diabetes management is well established, the appropriate macronutrient composition of dietary meals is not specified. In other words, studies in this area are limited and there is controversy in the study results. To the best of our knowledge, this is the first study that investigated the effect of protein and carbohydrate distribution throughout the day on metabolic parameters of patients with type 2 diabetes. The objective of the present study was to examine the effect of high protein *v.* high carbohydrate intake at the evening meal on anthropometric measurements, glycaemic control, lipid profile and blood pressure in patients with type 2 diabetes.

Abbreviations: FBG, fasting blood glucose; HC, high-carbohydrate evening meal; HOMA-IR, homoeostasis model assessment of insulin resistance; HP, high-protein evening meal; ITT, intention-to-treat; PP, per-protocol; ST, standard evening meal; TC, total cholesterol.

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Materials and methods

Subjects

Patients with type 2 diabetes were recruited primarily by local advertisements. Ninety-six subjects participated in the study (Fig. 1). Inclusion criteria were type 2 diabetes, age 30–65 years, diabetes duration of ≤15 years, $HbA_1c \leq 8\,\%$, BMI ≥22 and <35 kg/m^2, not taking insulin or α-glucosidase inhibitors, stable weight (±3 kg) during the past 3 months and not being on weight-loss or vegan diet. Subjects with hepatic, cardiac, renal, thyroid, respiratory, gastrointestinal and eating disorders were not included. Exclusion criteria were poor compliance to the prescribed diet or change in medications use throughout the study.

Study design and procedure

This is a 10-week single-blinded, parallel, randomised controlled trial with dietary intervention. The primary outcome of the current study was glycated Hb (HbA_1c), while the secondary outcomes were fasting blood glucose (FBG), insulin resistance, lipid profile, anthropometric measurements and blood pressure. The study procedure was described to all volunteers. However, the participants were not aware of the type of diet they were assigned to and the differences between them (single-blinded). A questionnaire with demographic questions was completed. The participants' dietary habits and their medical history were also recorded. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Ethics Committee of Shiraz University of Medical Sciences (no. IR.SUMS.REC.1396.7) and registered in the Iranian Registry of Clinical Trials (no. IRCT2017042733666N1). Written informed consent was obtained from all participants.

There was a 2-week run-in period at the beginning of the study (weeks –2 to 0). Throughout this period, the participants were advised to maintain their usual diet and physical activity and refrain from unusual physical activity or diet such as fasting. They were also asked to keep a 3-d food record (two weekdays and one weekend day). After the run-in period, applying block randomisation, the participants were randomly assigned to either of the following three groups: standard evening meal (ST), high-carbohydrate evening meal (HC) and high-protein evening meal (HP). The participants were followed for 10 weeks, during which they visited the specially designated clinic at weeks 2, 5 and 10. Anthropometric indices and blood pressure were monitored at weeks 0, 5 and 10, except for body weight that was measured at all sessions. Blood tests were performed at the beginning and the end of the study, except for FBG which was also measured at weeks 2 (optional) and 5. Physical activity was measured using a validated International Physical Activity Questionnaire[17,18]. Patients were advised not to change their physical activity level and smoking habits throughout the study and were not advised to keep on smoking throughout this period.

Diets

All participants received a balanced diet including 15–20 % protein, 50–55 % carbohydrate and 25–30 % fat. Total energy expenditure of each subject was calculated using the Institute of Medicine equations[19]. Exchange lists for Meal Planning[20] were provided for all subjects, and they were instructed how to substitute foods in their diets according to the exchange lists. Furthermore, they received dietary recommendations according to the American Diabetes Association guidelines (online Supplementary material)[21]. The only difference between the three prescribed diets was the distribution of protein and carbohydrate among meals. In the ST group, protein and carbohydrate were rather evenly distributed among the meals. In the HC group, 40–45 % of the total carbohydrate intake was provided at dinner and evening snack. In the HP group, 40–45 % of the total protein intake was at dinner and evening snack (online Supplementary material). It is worth noticing that in Iranian dietary culture, lunch is the main meal of the day and dinner is predominantly light. One of our major concerns about experimenting carbohydrate–protein redistribution diet was the rate of compliance and durability of the diet. In other words, more extreme changes in the proportions of carbohydrate or protein in the evening would probably reduce the participants' compliance dramatically. Therefore, we designed diets with a practical proportion of macronutrients which could be willingly followed by the patients during the study and in the long-term if it turns out to be beneficial. In order to prevent high energy intake in the evening, we reduced the protein and fat intake in the HC dinner. For the same reason, carbohydrate and fat intake in the HP dinner was decreased.

All dietary interventions were made by the nutritionist. At each visit, dietary consultation was made and the subjects were persuaded to follow their prescribed diet. In addition, phone calls were made if necessary. Participants were asked to fill 3-d food records (two weekdays and one weekend day) at weeks 2, 5 and 10. Nutritionist IV software (version 3.5.2 1994; N-Squared Computing) was used to assess dietary intake and compliance. At each visit, the participants were asked to rate their compliance to the diet in the preceding weeks from 1 to 5, with one meaning non-compliance to the diet and five meaning complete compliance to the diet. At the final visit, the participants were asked to rate their satisfaction with their prescribed diet from 1 to 5, with one meaning completely unsatisfied and five meaning completely satisfied.

Anthropometric and blood pressure measurements

Height was measured without shoes by means of a wall-mounted stadiometer to the nearest 0·5 cm. Body weight and body composition (percentage body fat mass, soft lean mass) were measured by a body composition analyzer (Easy Body 205, Jawon Medical). Weight was measured in light clothing without shoes to the nearest 100 g. BMI was calculated dividing weight (kg) by height (m) squared. Body composition was assessed using the bioelectrical impedance analysis technique. Since dehydration affects the accuracy of body composition analysis, participants were asked to drink enough water and avoid high-caffeine foods or beverages the days before the measurement. In addition, they were asked to refrain from physical activity 12 h and food consumption 2 h before the analysis.

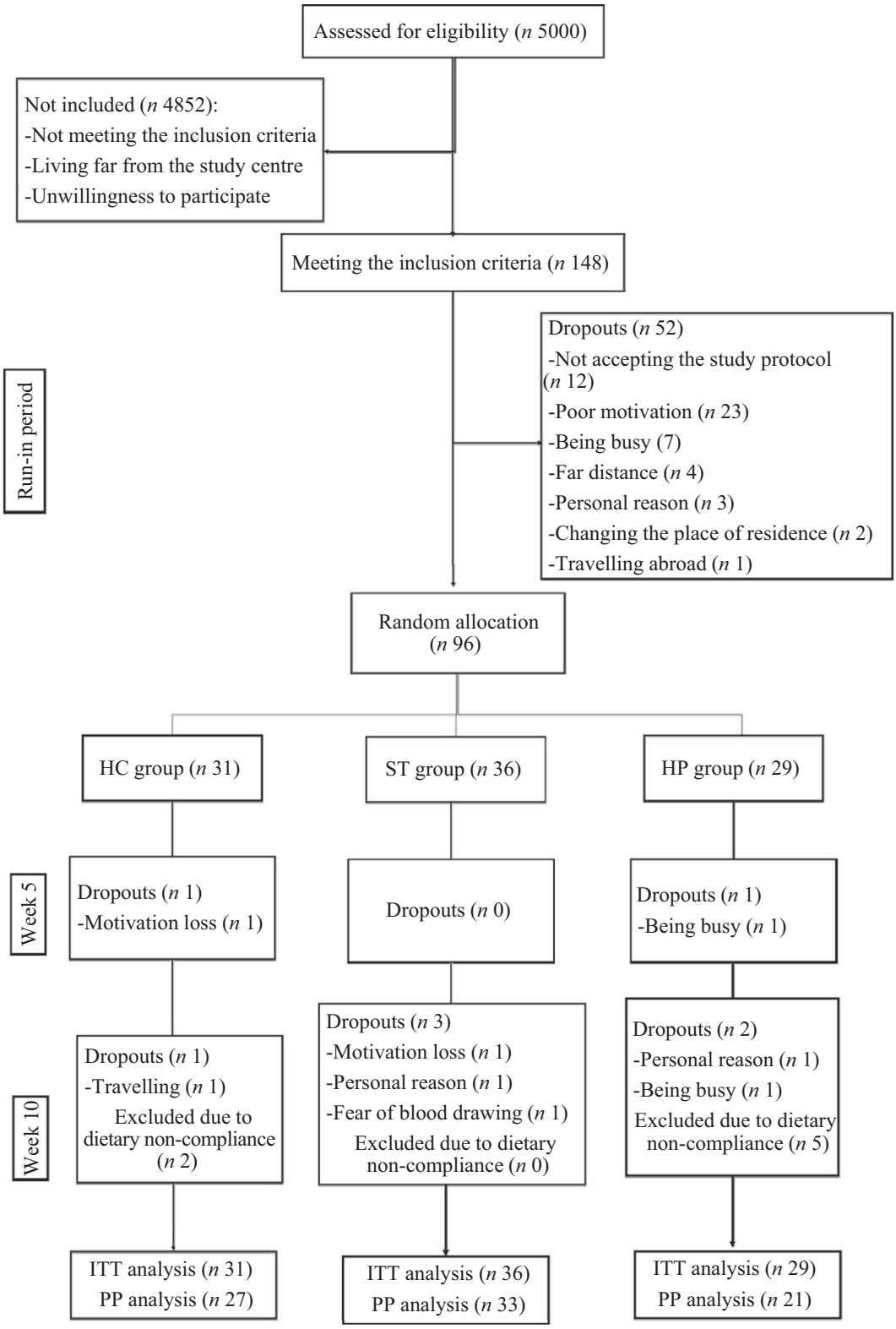

Fig. 1. Flow chart of the study participants. HC, high-carbohydrate evening meal; ST, standard evening meal; HP, high-protein evening meal; ITT, intention-to-treat; PP, per-protocol.

Measurement was performed with minimal clothes without socks, jewellery, belt and watch and after emptying the bladder. Waist circumference was measured by a non-stretch fibre glass tape measure to the nearest 0·1 cm at the top of the iliac crest. Blood pressure was obtained in the right arm after at least 5 min of rest using a mercury sphygmomanometer (ALPK2) in

a sitting position. Blood pressure was measured twice with at least 1 min interval, and the average of the two measurements was used for analysis.

Laboratory measurements

Blood samples were drawn after 12-h fasting. HbA_1c was measured by the boronate affinity HPLC method. Blood samples were centrifuged. FBG, TAG, total cholesterol (TC), HDL-cholesterol and LDL-cholesterol were measured by the enzymatic colorimetric method using assay kits (Pars Azmun) on autoanalyzer BT 1500 (Biotecnica Instruments S.p.A.). VLDL-cholesterol was calculated using Friedewald equation. Non-HDL-cholesterol and non-HDL-cholesterol:HDL-cholesterol were also computed. Insulin was measured by ELISA kit (Monobind Inc.). Homoeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were calculated by Matthews *et al.*'s formula as follows:

$$\text{HOMA-IR} = \text{fasting glucose(mg/dl)} \times \text{fasting insulin } (\mu\text{U/ml})/405$$

$$\text{HOMA-}\beta = 360 \times \text{fasting insulin}/(\text{fasting glucose (mg/dl)} - 63)$$

Statistical analysis

With regard to the distribution of the primary outcome (HbA_1c) in the study population which was determined by reading routine test results of diabetic patients at the time of registration (mean 6·50, SD 0·79), and the Clinically Meaningful Effect Size of 0·60 unit reduction in the level of HbA_1c determined by a consultant endocrinologist and setting α value at 0·05 and statistical power at 80 %, a sample size of twenty-eight in each group was estimated to be adequate (calculated using G*Power software). More participants were allocated to the reference category (the group with standard diet, n 36) to increase the power of statistical tests. In addition, thirty-one participants were allocated to each of the HC and HP groups. In the HP group, two participants withdrew before starting the diet (n 29). Results were expressed as mean and standard deviation or number (percentages). Baseline characteristics of the study participants were compared using either a one-way ANOVA for quantitative variables or χ^2 for qualitative variables. Paired t test was used for testing within-group changes. Due to a marginally significant difference in age between the study groups, generalised linear (GLM repeated measures) models were fitted using age and change in energy intake due to the interventions, and the study groups as independent variables and the values of outcome variables as the dependent variable. In case of significant difference among the intervention groups, Tukey's multiple comparison test was used to define the effects of which diets are different. A test with P value <0·05 was considered statistically significant. SPSS version 19 (SPSS Inc.) was used for analysis. The analysis was conducted using the intention-to-treat (ITT) approach. In that regard, the latest values of the outcome variables of the dropout participants were used for analysis. We also performed the per-protocol (PP) analysis to see what potential differences are between these two approaches of analysis.

Results

Participants and baseline characteristics

By the end of the study, eight out of ninety-six participants left the study. Moreover, seven participants had poor compliance to their diet (two in the HC group and five in the HP group) (Fig. 1). As a result, ninety-six and eighty-one participants were included in the ITT and PP analyses, respectively. Baseline characteristics of the study participants are shown in Tables 1 and 2. The age range of the study participants was 32–65 years. There were no statistically significant differences between the groups at baseline ($P > 0·05$). Baseline dietary intake of the participants is shown in Table 3. There were no significant differences between the groups ($P > 0·05$).

Intakes after dietary intervention

The energy and nutrient intake of the study participants is shown in Table 4. The energy and carbohydrate intake of the participants decreased significantly in all three groups ($P < 0·01$). Changes in dietary intakes during the study did not differ between the groups ($P > 0·05$). The energy intake of the participants at each meal is provided in online Supplementary Table S1. There were no significant differences between the groups in energy intake at baseline and its changes throughout the study ($P > 0·05$).

Dietary compliance

Compliance with the diets was assessed comparing the total energy intake of the participants with the energy of the prescribed diets. The participants consumed on average slightly lower energy than their prescribed diets ($P < 0·05$). However, daily energy intake of the participants had a significant correlation with the energy of the prescribed diets in each group ($P < 0·001$). Furthermore, in the HC group, 42·3 % of daily carbohydrate intake and, in the HP group, 41·9 % of daily protein intake were consumed in the evening.

The macronutrient composition of the meals consumed by the study participants in each group is shown in Table 5. The macronutrient composition of the breakfast did not differ significantly between the three groups. However, the composition of macronutrients at lunch and dinner was significantly different among the groups. Self-reported compliance with diet, according to a score from 1 to 5, was 4·1, 4·0 and 3·8 in the ST, HC and HP groups, respectively, which did not differ significantly among the groups ($P > 0·05$).

Mean satisfaction with diets of the study participants, according to a score from 1 to 5, was 4·6, 4·3 and 4·2 in the ST, HC and HP groups, respectively, which was significantly different among the groups ($P = 0·032$). In other words, participants in the ST group had significantly higher satisfaction with their diets compared with other groups. No adverse events related to the diets were reported by the study participants.

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Table 1. Demographic characteristics, anthropometries and blood pressure of the participants at baseline (Mean values and standard deviations†; numbers and percentages‡)

	Overall (*n* 96)		ST (*n* 36)		HC (*n* 31)		HP (*n* 29)		
	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %	*P**
Sex‡									
Male	46	47·9	16	44·4	16	51·6	14	48·3	0·84
Female	50	52·1	20	55·6	15	48·4	15	51·7	
Age (years)†	53·8	7·6	56·1	7·2	54·0	6·3	51·7	8·2	0·06
Marital status‡									
Married	90	93·8	33	91·7	30	96·8	27	93·1	0·77
Single/widowed	6	6·3	3	8·3	1	3·2	2	6·9	
Diabetes duration (years)†	5·6	4·1	5·8	4·3	5·3	4·3	5·5	3·5	0·86
Familial history (+)‡	71	74·0	25	69·4	24	77·4	22	75·9	0·73
Smoking (+)‡	6	6·3	1	2·8	2	6·5	3	10·3	0·43
Weight (kg)†	76·5	10·7	74·7	9·6	78·8	12·3	76·1	10·3	0·30
BMI (kg/m^2)†	28·5	3·4	27·8	2·8	29·1	4·4	28·6	2·9	0·30
WC (cm)†	99·8	8·5	99·3	6·7	101·1	10·3	99·0	8·4	0·58
BFP†	31·8	6·5	31·8	6·0	31·5	7·1	32·0	6·6	0·95
SLM (kg)†	47·7	7·8	46·8	8·1	49·1	7·5	47·3	7·9	0·47
SBP (mmHg)†	126·0	14·7	126·4	15·5	125·0	12·4	126·6	16·3	0·90
DBP (mmHg)†	79·8	9·9	77·3	9·8	80·2	9·2	82·4	10·4	0·11

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal; WC, waist circumference; BFP, body fat percentage; SLM, soft lean mass; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* Differences between groups using one-way ANOVA.
† Continuous variables.
‡ Categorical variables.

Table 2. Biochemical measurements and physical activity level of the participants at baseline (Mean values and standard deviations)

	Overall (*n* 96)		ST (*n* 36)		HC (*n* 31)		HP (*n* 29)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P**
HbA_1c (%)	6·61	0·81	6·61	0·76	6·58	0·81	6·64	0·90	0·96
FBG (mg/dl)†	134·1	29·2	131·7	28·2	134·2	29·4	137·0	30·8	0·77
TAG (mg/dl)†	168·3	79·2	164·6	75·8	176·9	65·6	163·9	96·7	0·77
TC (mg/dl)†	181·7	39·8	176·5	37·5	185·2	39·7	184·3	43·1	0·62
LDL-cholesterol (mg/dl)†	95·7	26·0	91·5	24·9	98·4	28·0	98·0	25·0	0·48
HDL-cholesterol (mg/dl)†	47·9	10·8	46·2	10·1	47·6	10·5	50·2	11·9	0·33
VLDL-cholesterol (mg/dl)†	33·7	15·8	32·9	15·2	35·4	13·1	32·8	19·3	0·77
Non-HDL-cholesterol (mg/dl)†	133·8	36·0	130·3	34·7	137·6	34·6	134·1	39·8	0·28
Non-HDL-cholesterol:HDL-cholesterol	2·90	0·91	2·95	0·99	2·96	0·75	2·78	0·99	0·84
Insulin (μU/ml)	8·6	4·6	8·6	3·9	9·5	6·4	7·5	2·7	0·25
HOMA-IR	2·84	1·58	2·77	1·26	3·11	2·09	2·62	1·31	0·46
HOMA-β	51·2	38·3	54·5	41·9	56·2	44·3	41·7	23·5	0·28
IPAQ score	1130	1369	1296	1313	1083	1677	975	1060	0·63

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal; FBG, fasting blood glucose; TC, total cholesterol; HOMA-IR, homoeostasis model assessment of insulin resistance; HOMA-β, homoeostasis model assessment of β-cell function; IPAQ, International Physical Activity Questionnaire.
* Differences between groups using one-way ANOVA.
† To convert FBG from mg/dl to mmol/l, multiply by 0·0555. To convert TAG from mg/dl to mmol/l, multiply by 0·0113. To convert cholesterol from mg/dl to mmol/l, multiply by 0·0259.

Anthropometric, blood pressure and physical activity measurements

The effect of diets on anthropometric and blood pressure measurements of the study participants is shown in Table 6. Body weight, BMI, waist circumference, body fat percentage and diastolic blood pressure decreased significantly in all three groups ($P < 0·05$). Systolic blood pressure reduction was significant in all groups, except for the HP group. Soft lean mass did not change significantly throughout the study. Changes in body composition, waist circumference and blood pressure measurements did not differ between the groups using both ITT and PP approaches ($P > 0·05$). In the ITT analysis, weight and BMI reductions were significantly higher in the ST compared with the HP group. Whereas, in the PP analysis, no significant difference between the intervention groups was observed for weight and BMI ($P = 0·24$ and $P = 0·19$, respectively). However, at the end of the study, there was a lower weight and BMI in the ST compared with the HP group. Physical activity of the study participants did not change significantly throughout the study ($P > 0·05$).

Biochemical measurements

The effect of diets on biochemical measurements of the study participants is shown in Table 7. HbA_1c, FBG, TAG, LDL-cholesterol, VLDL-cholesterol, insulin and HOMA-IR decreased significantly in all three groups. HbA_1c reduction was significantly higher in the ST compared with the HP group. Reductions in TC and non-

Table 3. Dietary intake of the participants at baseline (Mean values and standard deviations)

	Overall (*n* 96)		ST (*n* 36)		HC (*n* 31)		HP (*n* 29)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P**
Energy (kcal)†	1977	601	1902	562	2057	589	1983	665	0·59
Carbohydrate (g)	292·3	92·0	287·8	91·6	306·2	94·5	282·9	91·4	0·59
Carbohydrate (% of energy)	59·2	7·2	60·5	5·6	59·5	7·5	57·4	8·5	0·22
Protein (g)	70·7	23·5	65·8	20·1	73·6	21·8	73·7	28·5	0·29
Protein (% of energy)	14·4	2·1	14·0	2·2	14·4	1·6	14·9	2·5	0·19
Fat (g)	61·5	24·0	57·1	20·3	63·0	23·7	65·4	28·1	0·35
Fat (% of energy)	27·9	5·7	26·9	5·0	27·6	6·1	29·3	6·1	0·23
SFA (g)	16·5	7·4	15·2	6·4	17·4	8·9	17·2	7·0	0·4
SFA (% of energy)	7·4	2·1	7·1	1·8	7·5	2·2	7·8	2·5	0·48
MUFA (g)	22·3	9·7	20·9	8·8	21·9	9·8	24·4	12·4	0·34
MUFA (% of energy)	10·1	2·7	9·9	2·7	9·6	2·8	10·9	2·4	0·12
PUFA (g)	15·7	6·4	14·1	5·3	16·5	6·2	16·7	7·5	0·18
PUFA (% of energy)	7·1	1·9	6·7	1·7	7·4	2·4	7·5	1·6	0·15
Fibre (g)	18·0	8·0	15·9	5·2	19·4	10·0	19·0	8·3	0·14

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal.
* Differences between groups using one-way ANOVA.
† To convert energy values from kcal to kJ, multiply by 4·184.

Table 4. Changes in dietary intakes from weeks 0 to 10 (Mean values and standard deviations)

	ST (*n* 36)		HC (*n* 31)		HP (*n* 29)		
	Mean	SD	Mean	SD	Mean	SD	*P*†
Energy (kcal)‡	–219**	337	–283***	383	–297**	463	0·70
Carbohydrate (g)	–42·6***	54·5	–48·2***	66·9	–44·7***	62·8	0·93
Carbohydrate (% of energy)	–2·4**	5·1	–1·0	6·2	–0·6	6·1	0·40
Protein (g)	–0·8	15·1	–1·1	16·7	–2·3	19·3	0·93
Protein (% of energy)	1·5***	2·2	2·3***	2·6	1·9***	2·2	0·77
Fat (g)	–5·3*	15·5	–9·2*	20·3	–12·9*	25·0	0·28
Fat (% of energy)	1·0	4·5	0·3	5·7	0·9	5·1	0·85
SFA (g)	–0·3	5·8	–2·2	7·5	–1·9	7·1	0·42
SFA (% of energy)	0·9*	2·1	0·4	2·0	1·2	2·3	0·40
MUFA (g)	–2·0	6·6	–2·7	8·7	–5·6**	10·1	0·17
MUFA (% of energy)	0·2	2·3	0·4	2·9	–0·2*	2·1	0·67
PUFA (g)	–1·8*	4·8	–3·4**	6·3	–4·3**	7·3	0·20
PUFA (% of energy)	–0·02	1·7	–0·7	2·3	–0·9**	1·8	0·14
Fibre (g)	1·0	4·9	0·8	7·8	–1·6	9·8	0·29

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal.
* $P < 0·05$, ** $P < 0·01$, *** $P < 0·001$.
† Difference between groups using one-way ANOVA.
‡ To convert energy values from kcal to kJ, multiply by 4·184.

Table 5. Macronutrient composition of the meals in the three groups (Mean values and standard deviations)

	ST (*n* 36)		HC (*n* 31)		HP (*n* 29)		
	Mean	SD	Mean	SD	Mean	SD	*P**
Breakfast and morning snack							
% of energy from protein	13·5	1·5	13·9	1·7	13·0	1·7	0·16
% of energy from carbohydrate	58·7	5·3	57·6	7·0	59·0	5·7	0·66
% of energy from fat	27·6	4·4	28·3	5·8	27·8	4·8	0·87
Lunch and afternoon snack							
% of energy from protein	16·9	3·2	20·0	4·1	16·1	2·3	<0·001
% of energy from carbohydrate	55·5	5·0	50·4	4·7	58·6	6·2	<0·001
% of energy from fat	27·4	4·6	29·4	4·3	25·1	5·6	0·008
Dinner and evening snack							
% of energy from protein	15·2	2·2	13·7	2·1	20·8	3·3	<0·001
% of energy from carbohydrate	58·2	5·8	63·9	4·4	50·0	6·8	<0·001
% of energy from fat	26·6	5·0	22·2	4·0	29·1	6·2	<0·001

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal.
* Difference between groups using one-way ANOVA.

Table 6. Changes in anthropometric and blood pressure measurements throughout the study (Mean values and standard deviations)

	ST (*n* 36)							HC (*n* 31)							HP (*n* 29)							
	Week 0		Week 10		Difference			Week 0		Week 10		Difference			Week 0		Week 10		Difference			
	Mean	SD	Mean	SD	Mean	SD	*P*†	Mean	SD	Mean	SD	Mean	SD	*P*†	Mean	SD	Mean	SD	Mean	SD	*P*†	*P*‡
Weight (kg)	74·7	9·6	72·6	8·8	–2·1	2·1	<0·001	78·8	12·3	76·9	11·9	–1·9	1·8	<0·001	76·1	10·3	74·9	10·4	–1·3	1·2	<0·001*	0·046
BMI (kg/m^2)	27·8	2·8	27·1	2·6	–0·76	0·74	<0·001	29·1	4·4	28·4	4·2	–0·69	0·65	<0·001	28·6	2·9	28·1	2·9	–0·48	0·47	<0·001*	0·040
WC (cm)	99·3	6·7	96·3	6·1	–3·0	3·1	<0·001	101·1	10·3	97·4	9·6	–3·8	2·4	<0·001	99·0	8·4	96·3	8·6	–2·8	2·3	<0·001	0·41
BFP	31·8	6·0	29·6	7·3	–2·2	2·9	<0·001	31·5	7·1	30·2	7·4	–1·3	1·6	<0·001	32·0	6·6	30·6	7·0	–1·4	1·8	<0·001	0·21
SLM (kg)	46·8	8·1	74·0	8·9	0·24	2·37	0·54	49·1	7·5	49·0	7·2	–0·09	1·14	0·68	47·3	7·9	47·8	8·3	0·48	1·45	0·09	0·43
SBP (mmHg)	126·4	15·5	123·3	16·8	–3·1	8·9	0·04	125·0	12·4	120·6	9·9	–4·5	9·8	0·02	126·6	16·3	122·9	13·8	–3·8	10·1	0·054	0·74
DBP (mmHg)	77·3	9·8	73·7	10·1	–3·5	6·9	0·004	80·2	9·2	73·7	8·0	–6·5	6·9	<0·001	82·4	10·4	79·2	9·6	–3·3	7·7	0·03	0·071

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal; WC, waist circumference; BFP, body fat percentage; SLM, soft lean mass; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*Significantly different from the ST group using Tukey multiple comparison test.
† Changes from week 0 to week 10 using paired *t* test.
‡ Difference from ST group using generalised linear model (GLM) repeated measures model with age, change in energy intake and diet as covariates.

Table 7. Changes in biochemical measurements throughout the study (Mean values and standard deviations)

	ST (*n* 36)							HC (*n* 31)							HP (*n* 29)							
	Week 0		Week 10		Difference			Week 0		Week 10		Difference			Week 0		Week 10		Difference			
	Mean	SD	Mean	SDSD	Mean	SD	*P*†	Mean	SD	Mean	SD	Mean	SD	*P*†	Mean	SD	Mean	SD	Mean	SD	*P*†	*P*‡
HbA_1c (%)	6·61	0·81	6·16	0·63	–0·45	0·36	<0·001	6·58	0·81	6·26	0·71	–0·34	0·06	<0·001	6·64	0·90	6·39	0·87	–0·26	0·36	0·001*	0·019
FBG (mg/dl)§	134·1	29·2	110·8	25·0	–20·9	20·7	<0·001	134·2	29·4	118·4	24·0	–15·7	15·5	<0·001	137·0	30·8	125·1	38·0	–11·9	29·6	0·04	0·097
TAG (mg/dl)§	168·3	79·2	136·0	55·9	–29·1	31·8	<0·001	176·9	65·6	151·0	57·2	–25·9	46·1	0·004	163·8	96·7	148·7	96·0	–15·1	32·5	0·02	0·27
TC (mg/dl)§	181·7	39·8	62·5	32·9	–14·1	27·9	0·01	185·2	39·7	174·3	36·9	–11·0	25·5	0·02	184·3	43·1	177·3	36·6	–7·1	18·8	0·053	0·23
LDL-cholesterol (mg/dl)§	95·7	26·0	81·9	21·7	–9·6	17·2	0·002	98·4	28·0	89·2	27·3	–9·3	18·8	0·01	98·0	25·0	90·7	21·0	–7·3	11·6	0·002	0·55
HDL-cholesterol (mg/dl)§	47·9	10·8	44·4	9·0	–1·8	3·9	0·01	47·6	10·5	45·1	7·9	–2·5	7·0	0·06	50·2	11·9	47·8	11·8	–2·4	3·7	0·001	0·88
VLDL-cholesterol (mg/dl)§	33·7	15·8	27·1	11·1	–5·9	6·3	<0·001	35·4	13·1	30·2	11·4	–5·2	9·2	0·004	32·8	19·3	29·7	19·2	–3·0	6·5	0·02	0·26
Non-HDL-cholesterol (mg/dl)§	133·8	36·0	118·1	31·4	–12·3	26·0	0·01	137·6	34·6	129·1	33·8	–8·5	21·0	0·03	134·1	39·8	130·0	34·4	–4·6	16·6	0·14	0·22
Non-HDL-cholesterol: HDL-cholesterol	2·90	0·91	2·78	0·88	–0·17	0·53	0·06	2·96	0·75	2·91	0·79	–0·05	0·36	0·41	2·78	0·99	2·86	0·99	0·08	0·36	0·26	0·12
Insulin (μU/ml)	8·6	4·6	6·7	2·9	–1·9	3·9	0·01	9·5	6·4	6·7	2·3	–2·8	5·6	0·01	7·5	2·7	6·0	2·2	–1·5	2·3	0·001	0·74
HOMA-IR	2·84	1·58	1·88	1·00	–0·89	1·20	<0·001	3·11	2·09	1·97	0·82	–1·1	1·8	0·01	2·62	1·31	1·89	0·98	–0·73	1·1	0·001	0·96
HOMA-β	54·5	41·9	83·7	102·6	29·2	90·3	0·06	56·2	44·3	50·3	24·1	–5·9	36·6	0·34	41·8	23·5	55·3	81·2	13·5	69·0	0·30	0·15

ST, standard evening meal; HC, high-carbohydrate evening meal; HP, high-protein evening meal; HbA_1c, glycated Hb; FBG, fasting blood glucose; TC, total cholesterol; HOMA-IR, homoeostasis model assessment of insulin resistance; HOMA-β, homoeostasis model assessment of β-cell function.
* Significantly different from the ST group using Tukey multiple comparison test.
† Changes from week 0 to week 10 using paired *t* test.
‡ Difference from ST group using generalised linear model (GLM) repeated measures model with age, change in energy intake and diet as covariates.
§ To convert FBG from mg/dl to mmol/l, multiply by 0·0555. To convert TAG from mg/dl to mmol/l, multiply by 0·0113. To convert cholesterol from mg/dl to mmol/l, multiply by 0·0259.

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HDL-cholesterol were significant in the ST and HC groups, but not in the HP group. Reduction in HDL-cholesterol was not significant in all groups, except for the HC group. Non-HDL-cholesterol: HDL-cholesterol and HOMA-β did not change significantly throughout the study. Differences among the groups were not significant for other biochemical measurements. The PP analysis revealed similar results with only one marginal exception as HbA_1c was significantly lower in the ST compared with the HC and HP groups ($P = 0{\cdot}034$).

Discussion

Glycaemic control

To the best of our knowledge, this is the first randomised controlled trial comparing the effect of carbohydrate and protein distribution among meals on the metabolic profile of patients with type 2 diabetes. Results of this study indicated a significant reduction in HbA_1c, FBG, insulin and HOMA-IR following all three diets, regardless of the macronutrient distribution among meals. Insulin resistance improvement in the present study may be due to reduction in body weight and adipose tissue. Reduced energy and carbohydrate intake and weight loss may have contributed to better glycaemic control[21].

In a similar study, Alves *et al.*[22] compared the effect of two hypoenergetic diets in which protein or carbohydrate was eaten mostly at lunch or dinner with a control diet on metabolic markers of overweight or obese men. The participants received either a Diurnal Carbohydrate/Nocturnal Protein diet or Nocturnal Carbohydrate/Diurnal Protein or a control diet with a balanced distribution of protein and carbohydrate between dinner and lunch. In Alves *et al.*'s[22] study, a significant increase in fasting glucose, insulin and HOMA-IR was observed in the Diurnal Carbohydrate/Nocturnal Protein group. In a somewhat similar manner, our ITT analysis showed that the HP group tended to have the least improvement in fasting glucose, possibly as a result of lower BMI reduction in this group[21]. In contrast to Alves *et al.*'s[22] study, we did not observe any significant differences between the diets regarding fasting insulin and HOMA-IR. Some of the differences between the results of our study and that of Alves *et al.* may be due to smaller differences between the diets in our study.

In another study by Sofer *et al.*[15] on obese men and women, following a low-energy diet with carbohydrate eaten mostly at dinner resulted in a significant reduction in insulin compared with a control diet. Similar to our trial, Sofer *et al.* noticed a significant reduction in fasting glucose following both diets, but there was no significant difference between the groups. Moreover, a significant reduction in HOMA-IR was found in the intervention compared with the control group after 3 months of the study, but not after 6 months. In an epidemiological study, Berryman *et al.*[23] examined the relationship between the timing of protein intake and metabolic parameters. They found a positive association between higher intake of protein at dinner and HOMA-IR, but it was not associated with the insulin level.

Some studies demonstrated that glucose tolerance may vary throughout the day[24–29]. A limited number of studies that have been performed in the short-term aimed to compare glucose response following different meals in patients with type 2 diabetes. The results of these studies were controversial, and it is not obvious which meal of the day would be followed by the least increase in blood glucose[30–32]. For a conclusive decision, more long-term studies are required.

Finally, studies have shown that protein ingestion does not affect the glucose response significantly in patients with type 2 diabetes, and it is the carbohydrate intake at each meal that mostly determines the postprandial glycaemia[21]. Therefore, even distribution of carbohydrates among the meals may have better effects on glycaemic control. Evidence of this claim is the significant improvement in HbA_1c of the ST diet compared with others in our PP analysis. However, in the ITT analysis, this effect was diluted and the difference between the ST and the HC group was not statistically significant.

Lipid profile

TAG, LDL-cholesterol and VLDL-cholesterol concentrations decreased significantly in the three groups. Reduction in TC and non-HDL-cholesterol was not significant in the HP group. Positive effects of diets on lipid profile may be partly due to reduced intake of carbohydrates and weight reduction[21]. Non-HDL-cholesterol to HDL-cholesterol had no change in the three groups. Reduction in HDL-cholesterol was significant in all groups, except for the HC group. There were no significant differences among the groups for all measurements. Failure to observe a significant reduction in non-HDL-cholesterol to HDL-cholesterol in the present study may be due to dietary changes throughout the study. Overall, dietary fat intake of the study participants decreased significantly through the study, and it was due to reduction in PUFA intake rather than SFA. This dietary change may have prevented non-HDL-cholesterol:HDL-cholesterol ratio to be declined[33]. Consistent with our results, Alves *et al.*[22] did not observe any significant differences between lipid profiles of the participants following three studied diets. In a cross-sectional study, Chen *et al.* could not find any association between the timing of protein and carbohydrate intake with TC and LDL-cholesterol levels[34]. In Berryman *et al.*'s[23] study, higher intake of protein at breakfast and snacks was positively associated with HDL-cholesterol level, but not with TC, LDL-cholesterol and TAG.

Anthropometric measurements

All anthropometric indices in the present study decreased significantly in all groups except for soft lean mass which remained unchanged throughout the study. Reduced energy intake resulted in decreased body weight, body fat percentage and waist circumference. In the ITT analysis, there were no significant differences among the groups, except for the BMI and body weight which reduced significantly in the ST compared with the HP group. In the PP analysis, there were no significant differences among the groups for neither of the indices. This difference in the results can be explained by lower compliance with the diet in dropout participants of the HP group. We observed that individuals who were not satisfied with their diet had low motivation to follow their prescribed diet. They discontinued the diet or had poor compliance with the diet.

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In a similar study, Alves *et al.*[22] did not observe any significant differences among three mentioned diets. In Sofer *et al.*'s[15] study, weight reduction was higher in a group that ate carbohydrates mostly at dinner, but other anthropometric indices were not significantly different among the groups. They observed that the pattern of carbohydrate distribution throughout the day may affect satiety, leptin and adiponectin concentrations. Totally, it seems that reducing carbohydrate and increasing protein at dinner do not have any beneficial effect on anthropometric measurements of patients with type 2 diabetes. It is not clear which one, either the concentration of carbohydrate at dinner or even distribution of it among meals, may be better.

Blood pressure

In the present study, a significant reduction in the diastolic blood pressure was observed in all three groups. This blood pressure reduction was probably the result of weight loss[21]. Reduction in systolic blood pressure was not significant in the HP group, which may be due to lower BMI reduction in this group. There were no significant differences among the groups. In Alves *et al.*'s[22] study, no significant change in the systolic and diastolic blood pressure was observed following the three mentioned diets, with no difference among the groups.

Study limitations

One of the limitations of present study was that we could not measure postprandial and pre-meal (before lunch and dinner) glucose, mainly due to possible discomfort for the participants. In addition, compliance with diet was lower in the HP group mainly because of the incompatibility of the allocated diet with eating habits of Iranian people that eat more protein foods at lunch rather than dinner. For the same reason, we had a limited choice to make a big difference between the distributions of macronutrients among designed diets. However, the prescribed diets have no major deviation from the dietary habits of the population, making them more realistic and acceptable.

Conclusion

A balanced diet, regardless of the pattern of protein and carbohydrate distribution among the meals, may improve glycaemic control, lipid profile, blood pressure and anthropometric measurements in patients with type 2 diabetes. However, consuming protein mainly at dinner may have fewer favourable effects compared with distributing macronutrients rather evenly among meals. In addition, the diet with even distribution of macronutrients among the meals was accompanied by higher satisfaction. Therefore, it could be the diet of choice for patients with type 2 diabetes.

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The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114520001944

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