Effect of a High-Protein, High–Monounsaturated Fat Weight Loss Diet on Glycemic Control and Lipid Levels in Type 2 Diabetes

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OBJECTIVE — To determine the effect of a high-protein (HP) weight loss diet compared with a lower-protein (LP) diet on fat and lean tissue and fasting and postprandial glucose and insulin concentrations.

RESEARCH DESIGN AND METHODS — Replacing dietary protein for carbohydrate (CHO) during energy restriction and weight loss has been effective in sparing lean mass and improving insulin sensitivity in obese subjects but has not been tested in subjects with type 2 diabetes. We compared an HP diet (28% protein, 42% CHO, 28% fat [8% saturated fatty acids, 12% monounsaturated fatty acids, 5% polyunsaturated fatty acids]) with an LP diet (16% protein, 55% CHO, 26% fat [8% saturated fatty acids, 11% monounsaturated fatty acids, 5% polyunsaturated fatty acids]) in 54 obese men and women with type 2 diabetes during 8 weeks of energy restriction (1,600 kcal) and 4 weeks of energy balance. Body composition was determined by dual-energy X-ray absorptiometry at weeks 0 and 12.

RESULTS — Overall, weight loss of 5.2 ± 1.8 kg was achieved independently of diet composition. However, women on the HP diet lost significantly more total (5.3 vs. 2.8 kg, $P = 0.009$) and abdominal (1.3 vs. 0.7 kg, $P = 0.006$) fat compared with the women on the LP diet, whereas, in men, there was no difference in fat loss between diets (3.9 vs. 5.1 kg). Total lean mass decreased in all subjects independently of diet composition. LDL cholesterol reduction was significantly greater on the HP diet (5.7%) than on the LP diet (2.7%) ($P < 0.01$).

CONCLUSIONS — Both dietary patterns resulted in improvements in the cardiovascular disease (CVD) risk profile as a consequence of weight loss. However, the greater reductions in total and abdominal fat mass in women and greater LDL cholesterol reduction observed in both sexes on the HP diet suggest that it is a valid diet choice for reducing CVD risk in type 2 diabetes.

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Type 2 diabetes is a major public health problem in the developed world (1). Although there is a strong genetic predisposition to the development of type 2 diabetes, lifestyle and dietary factors, particularly those that promote obesity, are contributors (2). Type 2 diabetes is characterized in most subjects by insulin resistance with inadequate insulin response to maintain normoglycemia (3). Insulin resistance occurs partly as a result of increased concentrations of circulating plasma free fatty acids, released from excess adipocytes in obesity, which compete with glucose for uptake in skeletal muscle (4). In addition, hormones such as resistin (5) and cytokines such as tumor necrosis factor-α (6) released from adipocytes may exacerbate insulin resistance. Because ~90% of people with type 2 diabetes are obese, weight loss is essential in management. The optimal diet for type 2 diabetes has been the focus of much research, and there remains no consensus on macronutrient composition apart from recommendations that saturated fats be kept low (7). Energy restriction alone significantly improves glucose control and the plasma lipid profile with subsequent weight loss contributing about half of the total change (8,9). A number of studies also suggest that macronutrient composition may be important, both in energy restriction and energy balance, in improving the glucose and lipid profile (10,11).

Furthermore, although weight loss improves insulin sensitivity (12), replacing carbohydrate (CHO) with protein may preserve lean body mass during weight loss and result in improved insulin-mediated glucose uptake in skeletal muscle (13). We have also observed an apparent increase in insulin sensitivity after weight loss in a small number of obese men with impaired glucose (14). In addition, a high-protein (HP) intake may enhance weight loss by increasing both satiation, leading to a reduced energy intake (15), and thermogenesis, which blunts the normal fall in energy expenditure seen in weight loss (16). A greater fat and weight loss has also been demonstrated on an HP diet when compared with a high-CHO diet over a 6-month period (17) in normal subjects. However, the effects of replacing CHO with protein have not been tested in subjects with type 2 diabetes.

Our aim was to evaluate the effects of an HP intake on insulin sensitivity and changes in body composition in subjects with type 2 diabetes in both energy restriction and energy balance after weight loss. We proposed that a HP diet will im-

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Abbreviations: CHO, carbohydrate; CV, coefficient of variation; DEXA, dual-energy X-ray absorptiometry; FPG, fasting plasma glucose; HP, high-protein; LDIGIT, low-dose glucose and insulin infusion test; LP, low-protein; SSPG, steady-state plasma glucose; SSPI, steady-state plasma insulin.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

prove insulin resistance in type 2 diabetes after weight loss and reduce fasting and postprandial glucose and insulin concentrations. We also proposed an improvement in insulin-mediated glucose uptake by preservation of lean mass on the HP diet when compared with the low-protein (LP) diet.

RESEARCH DESIGN AND METHODS

Subjects

A total of 66 subjects with type 2 diabetes and no proteinuria were recruited by public advertisement. Subjects attended detailed information sessions, and all gave written informed consent. No payment was provided for participation in the study. The study design was approved by the Human Ethics Committee of the CSIRO (Commonwealth Scientific and Industrial Research Organisation), Health Sciences and Nutrition. Of the subjects, 54 completed the study. Two subjects withdrew before commencement. A further 10 subjects (5 from each diet group) withdrew throughout the study. Of the 54 subjects (19 men, 35 women), 25 managed their diabetes by diet alone, 26 required oral hypoglycemic medications (19 on metformin, 15 sulfonylureas alone or combination), and 4 required insulin. Four subjects with fasting plasma glucose (FPG) of 4–6 mmol/l were asked to cease medications before commencement of the diet to allay possible hypoglycemic episodes with weight loss. Decreases in dosage occurred in eight subjects at weeks 4 and 8 (five from the HP diet and three from the LP diet). Subjects on antihypertensive or lipid-lowering medication were asked to maintain the same dose throughout the study. All subjects were asked to maintain exercise programs at levels established before the study.

Experimental design

Subjects were matched on the basis of FPG, BMI, age, sex, and medication and were randomly assigned to either the HP diet (30% protein, 40% CHO) or LP diet (15% protein, 60% CHO). The 12-week study was conducted on an outpatient basis and consisted of an 8-week energy restriction component (1,600 kcal) followed by a 4-week period of the same macronutrient composition but in energy balance. Subjects attended the clinic for venous blood samples on 2 consecutive days at weeks 0, 4, 8, and 12 after a 12-h fast. Weight was recorded in light clothing at each visit. At weeks 0, 8, and 12, all subjects underwent a 75-g 3-h oral glucose tolerance test (OGTT) with venous blood samples taken fasting and at 1, 2, and 3 h. Subjects collected 24 h urine samples for assessment of urea/creatinine ratio at weeks 0, 8 and 12.

Diets

The HP diet consisted of 30% energy from protein and 40% energy from CHO, and the LP diet consisted of 15% energy from protein and 60% energy from CHO. Diets were matched for fatty acid profile (8% saturated fatty acids, 12% monounsaturated fatty acids, 5% polyunsaturated fatty acids). The diets were prescriptive fixed menu plans, and subjects were supplied with key foods, which amounted to 60% of energy intake, to assist with dietary compliance. These included preweighed portions of beef and chicken suitable for six meals per week and shortbread biscuits plus low-fat cheese (3% fat), diet yogurt, and skim milk powder for the HP diet and rice for the LP diet. The other differences between the diets lay in the amount of meat and chicken (200 vs. 100 g), fruit (200 vs. 300 g), and whole-meal bread (3 vs. 4 slices). Alcohol was not permitted, and a list of free choice vegetables and salad (maximum 2.5 cups) was provided. During the stable weight phase, caloric intake was increased by ~30%, with a further 7 g protein in the LP diet and 21 g in the HP diet. Each subject completed weighed daily diet checklists of all foods and was assessed by the same dietitian at 2-week intervals. Group training was provided in the use of scales and keeping food records. Three consecutive days (1 weekend and 2 weekdays) of the checklist from each 2-week period were analyzed by Diet/1 Nutrient Calculation software (Xyris Software 1998, Highgate Hill, Australia). This program had no missing values for the nutrients of interest, and because the diet was very prescriptive, unusual foods were rarely encountered. Recipes were entered as proportions of the original ingredients. The database had been extensively modified by our group to add new foods and recipes.

Body composition

For assessment of body fat amount and distribution, all subjects underwent a dual-energy X-ray absorptiometry (DEXA; Norland, Fort Atkinson, WI) scan at weeks 0 and 12. Abdominal fat mass was measured from the area demarcated by the ribs at the upper portion and the ileac crests at the lower portion. DEXA calculates the percentage of lean and fat mass based on measured tissue density and the known density of the two tissue types. The CV of these measures was 3–4%.

Insulin sensitivity

At weeks 0 and 12, 25 subjects (8 men, 17 women), not on diabetes medication, underwent a continuous low-dose glucose and insulin infusion test (LDIGIT) for determination of steady-state plasma glucose (SSPG) and steady-state plasma insulin (SSPI) concentrations. The method, a refinement of the modified Harano test previously described (18), involved the insertion of a cannula into a forearm vein for infusion of a combination of 25 mU · kg^{-1} · h^{-1} insulin and 4 mg · kg^{-1} · min^{-1} glucose. From a cannula inserted into the opposite forearm, blood samples (under a warmed blanket) were taken at baseline and at 120, 130, 140, 145, and 150 min after commencement of the infusion. SSPG and SSPI concentrations were determined from the average of the samples taken between 120 and 150 min. Subjects were required to lie quietly in a supine position for the duration of the test.

Biochemical analysis

Fasting blood samples were collected in tubes containing either no additives for lipids and insulin or sodium fluoride/EDTA for glucose measurements. Plasma or serum was isolated by centrifugation at 600*g* for 10 min at 5°C (Beckman GS-6R centrifuge; Beckman, Fullerton, CA) and frozen at −20°C. Biochemical assays were performed in a single assay at the completion of the study, except LDIGIT glucose samples, which were analyzed after each test. Plasma glucose and serum total cholesterol and triacylglycerol concentrations were measured on a Cobas-Bio centrifugal analyzer (Roche, Basel) by using enzymatic kits (Roche) and control sera. Plasma HDL cholesterol concentrations were measured using a Cobas-Bio analyzer after precipitation of LDL and VLDL cholesterol with polyethylene glycol 6000 solution. A modified

Table 1—*Baseline characteristics*

	HP diet	LP diet
Men		
n	9	10
Age (years)	63.4 ± 1.7	64.2 ± 3.8
BMI (kg/m^2)	35.4 ± 2.0	33.4 ± 1.0
Weight (kg)	107.6 ± 5.8	101.2 ± 5.4
Glucose (mmol/l)	7.9 ± 0.9	7.4 ± 0.4
Insulin (mU/l)	18.7 ± 2.6	17.1 ± 3.0
sBP (mmHg)	151 ± 5	144 ± 6
dBP (mmHg)	90 ± 3	81 ± 3
Women		
n	17	18
Age (years)	58.7 ± 2.2	60.9 ± 2.3
BMI (kg/m^2)	34.5 ± 1.4	33.2 ± 1.4
Weight (kg)	93.2 ± 3.7	86.7 ± 4.1
Glucose (mmol/l)	7.5 ± 0.4	7.4 ± 0.3
Insulin (mU/l)	15.8 ± 2.0	16.1 ± 1.4
sBP (mmHg)	143 ± 3	137 ± 3
dBP (mmHg)	83 ± 3	78 ± 3

Data are means ± SEM, with no significant differences between variables. dBP, diastolic blood pressure; sBP, systolic blood pressure.

Friedewald equation was used to calculate LDL cholesterol (19). Insulin was determined in duplicate using a radioimmunoassay kit (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden). HbA_{1c} samples were frozen at −20°C and analyzed by high-performance liquid chromatography at the end of the study (20). Urine samples to assess compliance to the diet and albumin excretion were frozen, and urea and creatinine were measured in one run on a Hitachi autoanalyzer (Roche, Indianapolis, IN) at the end of the study.

Statistical analysis

Analysis was performed by repeated-measures ANOVA (with covariates of baseline weight and total fat mass in some analyses) with variables measured at weeks 0, 4, 8, and 12 using SPSS for Windows 10.0 statistical software (SPSS, Chicago). Diet and sex were between-subject factors. Data are expressed as means ± SEM. One-way ANOVA was used to exclude significant differences at baseline between diets and men and women. Inclusion of data from subjects with medication changes significantly affected the results for the OGTT; therefore, these eight subjects were excluded from analysis in this test. Significance was set at $P < 0.05$.

RESULTS

Baseline characteristics

Subjects were matched for BMI, age, sex, FPG, and medication. Baseline characteristics of subjects are shown in Table 1. There were no significant differences between the two groups for weight or blood pressure.

Diet composition and compliance

Energy intake in the 8-week energy restriction phase and the 4-week energy balance phase was not different between the two diets (Table 2). As planned, protein intake was higher and CHO intake lower in the HP diet than in the LP diet both in energy restriction and energy balance ($P < 0.001$), with no differences between phases. Saturated fat intake was not different between the diets or the phases, but dietary fiber and dietary cholesterol were significantly different between diets in both phases. Urine urea fell from 450 to 420 mmol/day on the HP diet and from 428 to 301 mmol/day on the LP diet ($P < 0.001$ for difference) during the weight loss phase and rose to 461 and 344 mmol/day, respectively, in the weight maintenance phase diet ($P < 0.001$ for difference). Urinary urea/creatinine ratio was significantly different between diets by repeated-measures ANOVA ($P < 0.001$). Urinary albumin excretion did not change with weight loss on either diet:

Table 2—*Diet composition determined by subjects' consecutive 3-day weighted dietary records every 2 week*

	HP diet (n = 26)		LP diet (n = 28)	
	Energy restriction	Energy balance	Energy restriction	Energy balance
Energy (kcal/day)	1,587 ± 36	2,029 ± 55	1,543 ± 44	1,785 ± 74
Protein (% E)	28.1 ± 0.3*	27.7 ± 0.3	16.4 ± 0.3	16.0 ± 0.3
CHO (% E)	42.1 ± 0.2*	42.6 ± 0.4	54.8 ± 0.4	55.0 ± 0
Total fat (% E)	27.8 ± 0.2	27.6 ± 0.3	26.3 ± 0.4	26.7 ± 0.5
Saturated (% E)	8.2 ± 0.1	8.2 ± 0.2	7.5 ± 0.1	7.6 ± 0.2
Monounsaturated (% E)	12.1 ± 0.1	12.2 ± 0.2	11.2 ± 0.2	11.6 ± 0.3
Polyunsaturated	4.9 ± 0.1	4.7 ± 0.1	4.9 ± 0.1	4.8 ± 0.1
Fiber (g/day)	24.3 ± 0.7*	29.3 ± 1.2†	28.3 ± 0.8	33.5 ± 1.3
Cholesterol (mg/day)	175.7 ± 6.1*	202.9 ± 8.5*	93.9 ± 5.6	98.6 ± 5.9

Data are means ± SEM. Subjects were required to complete daily weighed dietary records. The 3-day dietary records (1 weekend and 2 weekdays) were analyzed every 2 weeks in 8 weeks of energy restriction and 4 weeks of energy balance. E, energy, *$P < 0.001$, †$P < 0.05$ (difference between diets).

24.2 to 19.8 mg/l in the 12 subjects with microalbuminuria on the HP diet and 4.3 to 3.5 mg/l in the 7 subjects on the LP diet.

Weight and body composition

Both men and women lost weight on both diets; however, there was a weak sex by diet interaction ($P = 0.04$), such that men lost more weight on the LP diet (5.8 vs. 4.7 kg), whereas women lost more weight on the HP diet (6 vs. 4.2 kg). Similarly for total fat mass, men lost more on the LP diet (5.1 vs. 3.8 kg), whereas women lost more on the HP diet (5.3 vs. 2.8 kg), as reflected by a significant sex by diet interaction ($P = 0.01$). A significant sex by diet effect was also observed in the change in abdominal fat mass ($P < 0.02$), such that men lost more fat on the LP diet (1.7 vs. 1.4 kg), whereas women lost more on the HP diet (1.3 vs. 0.7 kg). Total lean mass was reduced significantly with both diets (1.35 kg on the LP diet and 0.52 kg on the HP diet) with no significant difference between them.

Table 3—*Weight and fat changes with energy-restricted diets*

Variable	Week 0	Week 8	Week 12
Weight (kg)			
HP diet	97.7 ± 17.4	93.2 ± 16.7	92.2 ± 16.8
LP diet	91.4 ± 18.2	86.9 ± 16.9	86.6 ± 16.8
Fat mass in men			
HP diet	38.7 ± 5.0	—	35.5 ± 2.6
LP diet	34.8 ± 5.2	—	30.4 ± 2.4
Fat mass in women			
HP diet	42.8 ± 2.6	—	37.5 ± 2.5
LP diet	39.9 ± 3.2	—	37.0 ± 3.1*
Fasting glucose			
HP diet	8.44 ± 0.41	7.30 ± 0.28	7.701 ± 0.31
LP diet	7.76 ± 0.24	7.02 ± 0.21	7.33 ± 0.30
Fasting insulin			
HP diet	16.3 ± 7.2	12.1 ± 6.5	13.3 ± 6.8
LP diet	16.5 ± 7.7	14.0 ± 10.8	14.8 ± 9.2
2 h glucose			
HP diet	8.4	7.3	7.7
LP diet	7.8	7.0	7.3
HbA_{1c}			
HP diet	6.42 ± 0.83	—	5.88 ± 0.78
LP diet	6.30 ± 0.77	—	5.79 ± 0.59

*$P < 0.05$ (difference between diets).

Glycemic control

Fasting and 1-, 2-, and 3-h plasma glucose concentrations were reduced by both dietary interventions ($P < 0.001$); however, no significant effects of diet or sex were observed (Table 3). Fasting and 2-h insulin concentrations were reduced at weeks 8 and 12 (both $P < 0.001$). The insulin.glucose product was reduced by 42% at 3 h at week 12. HbA_{1c} decreased by 9.4% between baseline and week 12 ($P < 0.001$). There were no significant differences observed for diet or sex.

Continuous low-dose insulin and glucose infusion (LDIGIT)

SSPG concentrations were significantly reduced ($P = 0.01$) from baseline to week 12 (12.1 to 10.7 mmol/l) with no difference between diets. Weight loss was the same in both groups. SSPI concentrations decreased significantly ($P = 0.003$) from 523 to 428 pmol/l with no effect of diet or sex.

Lipids

Total cholesterol concentrations decreased more on the HP diet than on the LP diet, as reflected by a diet by time interaction of $P = 0.009$. For all subjects, triacylglycerol concentrations decreased at week 12 ($P < 0.001$), and there was no diet or sex effect. There was no effect of time or diet for HDL cholesterol concentrations (Table 4). A significant time by diet effect was observed in the reduction of LDL cholesterol ($P = 0.009$), with a greater decrease in LDL cholesterol concentrations on the HP diet than on the LP diet.

Blood pressure

Systolic blood pressure fell significantly by 8 mmHg and diastolic blood pressure by 4 mmHg at week 8 ($P < 0.001$) with no differential effect of diet. During the weight stabilization period between weeks 8 and 12, systolic blood pressure rose by 3 mmHg and diastolic blood pressure by 1 mmHg ($P < 0.001$). This was also not affected by diet composition.

CONCLUSIONS — In this study, both HP and LP diets decreased weight, fasting glucose, and insulin concentrations as well as total and abdominal fat. However, in women, the HP diet was able to decrease total and abdominal fat differentially compared with the LP diet. In addition, the HP diet significantly decreased LDL cholesterol concentrations in both men and women compared with the LP diet. We were able to confirm good dietary compliance from both the urinary urea excretion data and the dietary data completed daily by each subject. To maintain energy balance in the last 4-week period, a higher energy intake was required on the HP diet. This finding is consistent with previous observations that an increase in energy expenditure, and a blunting in the normal fall in energy expenditure in weight loss, results from an HP intake (16). Weight loss was not different between the two diets. Our novel observation of a possible sex-specific effect of the HP diet on total and abdominal fat loss in women but not men requires confirmation. Although this result may reflect the small number of male subjects in both dietary interventions, there was no suggestion that the HP diet was advantageous in men. In our study, subjects lost an absolute 2.1% lean mass overall with no significant difference between the two diets. Greater energy restriction, (800 vs. 1,600 kcal), higher protein levels, and the inclusion of only glucose-tolerant women may have affected the disparity in outcomes between the study of Piatti et al. (13), who found that HP weight loss diets spared lean body mass, and our study. We used DEXA for estimating body composition in obese subjects with type 2 diabetes, whereas Piatti et al. (13) used anthropometry. DEXA is a more accurate method of determina-

Table 4—*Lipid changes with energy-restricted diets*

Variable	Week 0	Week 8	Week 12
Total cholesterol			
HP diet	5.16 ± 0.17	4.64 ± 0.18	4.81 ± 0.16*
LP diet	5.16 ± 0.25	4.82 ± 0.22	5.15 ± 0.25
Triglyceride			
HP diet	2.02 ± 0.15	1.56 ± 0.13	1.68 ± 0.14
LP diet	2.17 ± 0.21	1.76 ± 0.11	1.94 ± 0.16
LDL cholesterol			
HP diet	3.32 ± 0.16	3.02 ± 0.15	3.13 ± 0.15*
LP diet	3.23 ± 0.20	3.12 ± 0.20	3.32 ± 0.22
HDL cholesterol			
HP diet	0.93 ± 0.03	0.92 ± 0.03	0.92 ± 0.04
LP diet	0.95 ± 0.05	0.91 ± 0.04	0.96 ± 0.03

*$P < 0.01$, †$P < 0.05$ (difference between diets).

tion of body fat distribution when compared with traditional anthropometric methods, such as skinfold thickness measurements and waist-to-hip ratio. Thus, the effect of HP moderately energy-restricted diets in preserving lean body mass still remains unproven.

Despite greater fat loss, the women on the HP diet were apparently not more insulin sensitive than the men or women who lost less fat. A possible explanation for this may be the small differential fat loss (2.5 kg), which may not have been large enough to produce a significant change in insulin sensitivity, as assessed by the LDIGIT or OGTT. Longer-term studies with greater weight loss might reveal such differences. SSPG concentrations were significantly decreased at week 12, indicating that subjects became more insulin sensitive. SSPI concentrations were also significantly reduced at week 12, but this may reflect the decrease in infused insulin (due to a lower body weight) or an enhanced clearance and not necessarily a decrease in insulin secretion. We did not measure C-peptide concentrations, which would indicate whether endogenous insulin secretion had decreased. Fasting and post-load glucose and insulin concentrations were reduced during and after weight loss in all subjects after an OGTT regardless of diet. This outcome was probably largely the result of a decrease in substrate intake and reduced hepatic glucose production, although increased insulin sensitivity through reduced fat mass cannot be excluded. This finding is consistent with previous research that found that energy restriction and weight loss both corresponded with reductions in fasting glucose and insulin concentrations (8,9). In contrast, some acute studies (21,22) have found a significant effect of protein intake in stimulating insulin secretion and lowering glucose concentrations. However, whether this still occurs after repeated exposure to HP meals is not known. Our finding of a significant effect of the HP diet on lowering LDL cholesterol concentrations confirms the results from one other study (23). In their energy balance study, Wolfe and Giovanetti (23) contrasted an HP diet (23% energy) with an LP diet (11% energy) and randomly assigned free-living hypercholesterolemic subjects, in a crossover design, to both dietary interventions for 4–5 weeks. Both diets were low in saturated fat and cholesterol. In contrast to our findings, they found significant decreases in triglyceride concentrations as well as increases in HDL cholesterol concentrations on the HP diet. Although triglyceride concentrations were improved in our study, there was no difference between the diets. We found a significant decrease in LDL cholesterol at all time points from baseline in both men and women on the HP diet compared with the LP diet. There was no impact of body composition changes on this result. Because saturated fat intake was not different between the diets, this was not the cause of the differential LDL cholesterol reduction. The mechanism for the hypolipidemic effect of an HP intake on LDL cholesterol concentrations is unclear. Our observed decrease in LDL cholesterol concentrations of 5.7% on the HP diet may lead to a 10% decrease in the risk of CVD in these subjects. This result is relevant because in people with type 2 diabetes, the risk of CVD is increased two to four times that of the normal population (1). However, because this effect on LDL has not been observed before with HP weight loss diets, further confirmatory work is required.

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