

Weight-loss diets in people with type 2 diabetes and renal disease: a randomized controlled trial of the effect of different dietary protein amounts^{1–4}

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ABSTRACT

Background: Higher-protein weight-loss diets (defined as >25% of energy as protein) are not recommended for individuals with type 2 diabetes because of their potential adverse effect on renal function.

Objective: We aimed to examine the effect of such diets on renal function over 12 mo in people with type 2 diabetes and early renal disease.

Design: Overweight and obese people with type 2 diabetes were screened to identify those with an albumin:creatinine ratio from 3 to 30 mg/mmol. Seventy-six subjects were randomly assigned to either a moderate-protein weight-loss diet or a standard-protein weight-loss diet for 12 mo. The primary endpoint was the change in renal function as assessed by the isotope glomerular filtration rate (GFR), estimated GFR, and cystatin C. Forty-five subjects (moderate protein: $n = 21$; standard protein: $n = 24$) completed the study.

Results: The mean (\pm SE) weight loss was not different between diets at 9.7 ± 13.4 kg for the moderate-protein diet and 6.6 ± 7.1 kg for the standard-protein diet. There were no changes in renal function or albuminuria or blood pressure, although glycated hemoglobin was lowered with both diets. Changes in renal function were related to the baseline estimated GFR. Patients with stage 1–3 renal disease (<120 mL \cdot min⁻¹ \cdot 1.73 m⁻²; $n = 33$) had an improvement in renal function, whereas patients with hyperfiltration (>120 mL \cdot min⁻¹ \cdot 1.73 m⁻²; $n = 12$) had a decrease in the GFR. After adjustment for weight loss, the baseline GFR remained a significant predictor of outcomes with no effect of dietary treatment. An average difference in protein intake between diets of 19 ± 6 g/d was achieved.

Conclusion: Weight loss improved renal function, but differences in dietary protein had no effect. This trial was registered at the Australian and New Zealand Clinical Trial Register as ACTRN12608000045314. *Am J Clin Nutr* 2013;98:494–501.

INTRODUCTION

High-protein, lower-carbohydrate diets are frequently used for weight loss in obese people. There is some evidence that high-protein diets may spare lean body mass and increase fat loss (1, 2) as well as lower plasma triglycerides in both men and women (3). Although Gannon and Nuttal (4) have extensively documented the short-term effects of a lower-carbohydrate, higher-protein weight-stable diet on glucose control, there have been few longer-term high-protein weight-loss diets (5, 6). One concern frequently cited in dietary recommendations for type 2 diabetes is the potential for an increase in renal disease and the lack of data

for diets that contain >20% of energy as protein (7). This concern is based on the following 3 separate observations: 1) the beneficial effect of low-protein diets in rat partial nephrectomy models discussed in detail by Brenner et al (8), 2) a very-modest reduction in the rate of progression of renal disease with a low-protein diet in type 1 diabetes and, to a lesser extent, in type 2 diabetes (9, 10), and 3) data from the Nurses Health Studies that has shown that women with a baseline glomerular filtration rate (GFR)⁵ between 55 and 80 mL \cdot min⁻¹ \cdot 1.73 m⁻² showed a decline in GFR over 11 y of 7.7 mL \cdot min⁻¹ \cdot 10 g protein⁻¹ (11). No effects of protein were seen in subjects with normal renal function. To our knowledge, there are no data on the effect of protein intake on the change in renal function in individuals with type 2 diabetes and early renal disease manifested as microalbuminuria. Thus, the objectives were to examine the effect of 2 weight-loss diets that differed in protein amounts on renal function over 12 mo in a randomized parallel study.

SUBJECTS AND METHODS

Volunteer inclusion criteria

Volunteers with type 2 diabetes aged between 18–75 y with microalbuminuria (30–300 mg/24 h or an albumin-to-creatinine ratio of 3.0–30 mg/mmol) with an estimated GFR (eGFR) >40 mL \cdot min⁻¹ \cdot 1.73 m⁻² (12) and BMI (in kg/m²) >27 were

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⁵ Abbreviations used: DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; Hb A_{1c}, glycated hemoglobin; iGFR, isotope glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MP, moderate-protein diet; SP, standard-protein diet; ^{99m}Tc-DTPA, ^{99m}Tc-diethylenetriamine-pentaacetic acid.

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recruited. Type 2 diabetes was defined as a fasting blood glucose concentration >7.0 mmol/L, 2-h glucose concentration >11.1 mmol/L, or taking a drug treatment for type 2 diabetes. People with coronary artery disease or any other active disease of clinical significance were excluded. Volunteers provided written, informed consent, and the trial was approved by the Commonwealth Scientific and Industrial Research Organisation Human Ethics Committee. Random assignment was carried out before inclusion on the basis of a computer-generated random-number list. The allocation sequence was concealed in sealed envelopes from the researcher who enrolled and assessed participants. Volunteers were allocated one to one to the diets. The study was undertaken at the Commonwealth Scientific and Industrial Research Organisation in Adelaide, Australia, from 2007 to 2010. The primary endpoint was the change in renal function.

Screening

Volunteers were screened with a spot urine albumin:creatinine ratio as well as a 24-h albumin excretion, and if confirmed as positive in both measurements, entered the run-in phase in which lipid, blood pressure, and glucose treatment were optimized to ensure that renal function would change only with diet once the study commenced. If microalbuminuria was not reconfirmed at the baseline measurement, then volunteers were omitted from the trial. This exclusion occurred with 2 volunteers.

Design

After the run-in phase, volunteers were randomly assigned to either a moderate-protein or standard-protein weight-loss diet for 1 y. Volunteers attended a diet visit every 2 wk during the 16-wk weight-loss phase and monthly visits for the measurement of weight, blood pressure, and diet. Fasting blood tests were taken at baseline and after 1, 4, 8, and 12 mo. Spot urine albumin and creatinine samples as well as 24-h urine tests for urea, creatinine, albumin, protein, sodium, potassium, and phosphate were collected at these time points. Routine biochemistry for electrolytes, urea, and creatinine and liver-function tests were collected. Glycated hemoglobin (Hb A_{1c}), fasting lipids, glucose, and cystatin C were measured on all samples except the 1-mo sample. All tests apart from cystatin C were done in a certified commercial laboratory. Cystatin C was determined turbidimetrically at 546 nm with a latex-particle-enhanced immunoassay (Randox) on an autoanalyser (Hitachi 902).

GFR

GFR was measured directly with ^{99m}Tc-diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA) at baseline and at the end of the study. A dose of 50–60 MBq ^{99m}Tc-DTPA was injected, and blood samples were taken exactly 1 and 3 h later. Five milliliters of whole blood was collected in tubes that contained anticoagulant and was centrifuged at 3000 rpm. A total of 200 μ L plasma and 200 μ L of the standard together with 4 mL H₂O was added into a labeled tube and counted in a multi sample counter. The rate of clearance of ^{99m}Tc-DTPA corresponds with the GFR measured by using the clearance of iothalamate ($r = 0.966$) except in individuals with a GFR <20 mL/min (13). The GFR was also estimated at regular intervals by using an eGFR on the

basis of the Modification of Diet in Renal Disease (MDRD) equation (12):

$$\text{GFR} = 175 \times (\text{Serum creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \\ \times (0.742 \text{ if female}) \quad (1)$$

We have discussed the difficulty of assessing renal function in obesity in a recent publication (14). An additional estimate of renal function was made by using cystatin C, which is secreted from all cells and filtered unchanged by the kidney and is unrelated to fat or lean mass, and thus, it can be used without adjustments for age, sex, or weight (15).

Diet

A moderate-protein diet (MP) was compared with a standard-protein diet (SP). The target nutrient composition was 30%:30%:40% of energy from protein:fat:carbohydrate for the MP and 20%:30%:50% of energy from protein:fat:carbohydrate for the SP. The planned range of absolute protein intake was 90–120 g/d in the MP compared with 55–70 g/d in the SP, with a potential difference of 35–50 g/d. Thus, although the MP contained $>30\%$ of energy as protein, the absolute amount was only increased by a small amount from the free-living diet, whereas the protein amount in the SP was lower than usual. Nevertheless, there was a planned absolute 10% difference in energy from protein between the 2 diets. Alcohol was limited to 2 standard drinks/wk (4 g or 2% of energy). Fiber intake was high in both diet plans (31 g/d in the MP and 36 g/d in the SP). The energy content was 6000 kJ with an allowance to ≤ 7000 kJ for men. Diet-information booklets that specified foods needed for the 2 diets, and a food-selection guide for the different energy amounts were provided. A sample daily meal plan and a selection of diet-specific recipes were also included. A 3-d weighed food record was completed before random assignment at 4 and 8 mo and at the end of the study.

Body weight, height, and blood pressure

Body height without shoes was measured at baseline by using a stadiometer to the nearest 0.1 cm (Seca). Volunteers were weighed at all visits to the clinic, wearing light clothing without shoes, by using calibrated electronic digital scales to the nearest 0.05 kg (weight range: 0–220 kg, Mercury weighing scales, Thebarton, model, AMZ 14). Blood pressure was measured after volunteers were resting in a seated position for ≥ 5 min before measurement. An average of 3 measurements (Philips Healthcare SureSigns VS3 Patient Monitor) taken ≥ 2 min apart was used. Measurements had to be consistent so that systolic blood pressure was within 10 mm Hg, and diastolic blood pressure was within 5 mm Hg, and more measurements were taken if there was inconsistency. The first measurement was discarded.

Body composition

Body composition was assessed by using dual-energy X-ray absorptiometry (DXA) [Norland XR-800 DXA Bone Densitometer

Medical Systems (Siemens Medical)]. For the whole-body scan, a 6.5×13 -mm resolution was used together with a scan speed of 260 mm/s. The CV for total body fat was 1.4%.

Statistics

Significance was assessed by using a repeated-measures ANOVA with SPSS 18 software (IBM). Multiple regression was performed with the 12-mo change in the variable as the dependent variable and 3–4 baseline variables as independent variables. Pearson's correlation coefficients were also calculated. Significance was accepted with a 2-sided $P < 0.05$. With the SD of 13.7 mL/min from the Knight study (11) and 45 finishing, we had the power (80%; one-sided $P < 0.05$) to see an overall decrease in the GFR of 5.2 mL/min in the MP group per 10 g protein. At the beginning of the study with 76 people, we had 80% power ($P < 0.05$) to see a difference in the eGFR of $8.9 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$.

RESULTS

The recruitment of eligible volunteers was difficult and lasted 3 y. More than 15,000 study questionnaires were sent out, and 580 questionnaires were returned. A total of 380 people were assessed as eligible, and 362 individuals were screened. Seventy-six subjects (56 men and 20 women) were identified as having type 2 diabetes and microalbuminuria confirmed on repeated screening and commenced the study. A total of 45 people completed the study (35 men and 10 women), and thus, dropouts were equal in men and women despite disproportionate starting numbers. Twenty-one subjects completed the MP, and 24 subjects completed the normal-protein diet. Twenty people started the study and withdrew at various time points (13 subjects in the MP group; 7 subjects in the normal-protein group); one withdrawal was a result of the development of multiple sclerosis. Eleven people failed to commence the study after screening, 3 subjects of whom failed to have microalbuminuria reconfirmed at their first visit, and one person was excluded because it was discovered the

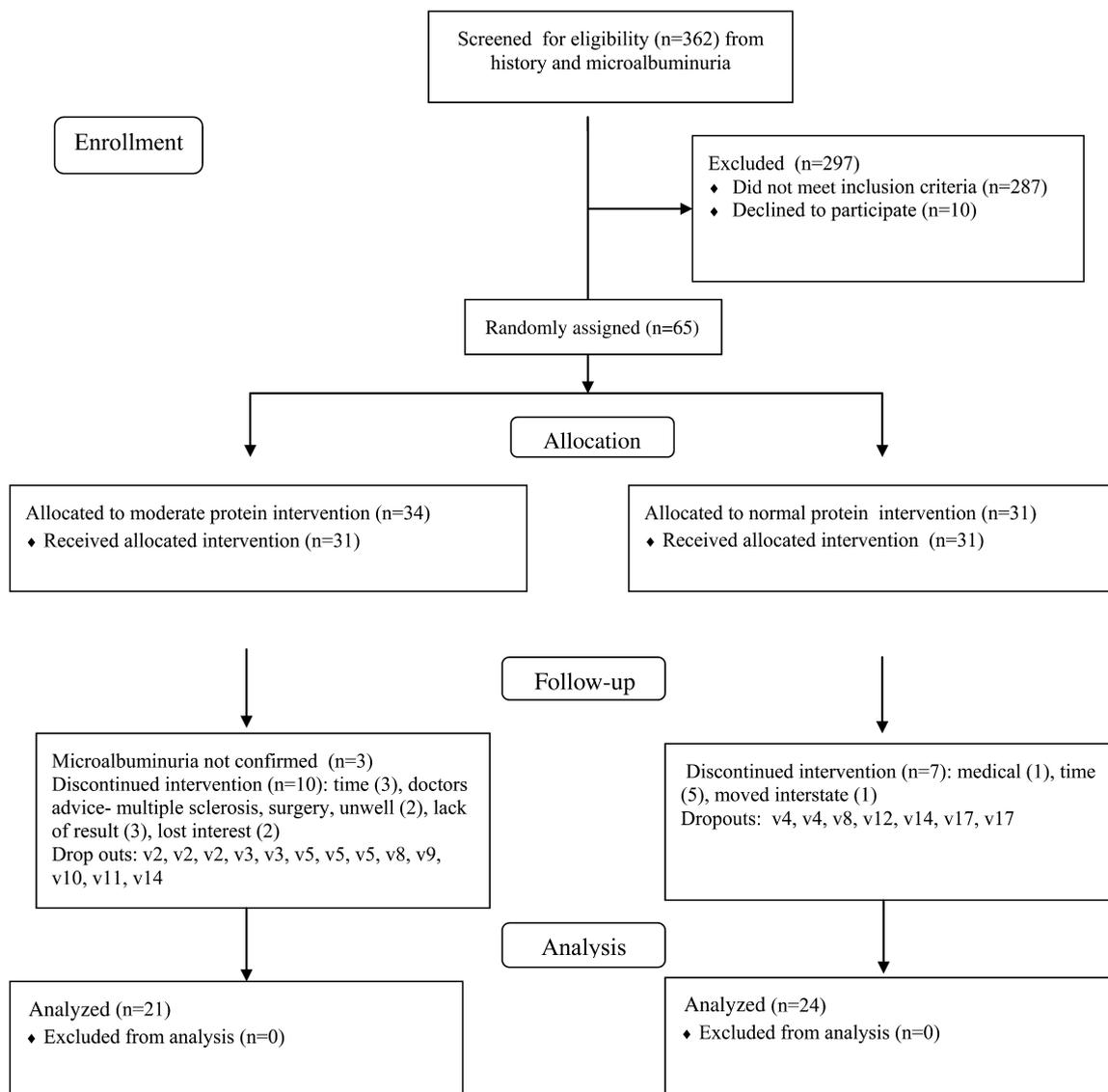


FIGURE 1. Consolidated Standards of Reporting Trials flow diagram.

TABLE 1
Baseline characteristics of all randomly assigned subjects¹

Groups and variables	MP	SP	P
Completers			
<i>n</i>	21	24	—
Sex (M/F)	15/6	20/4	0.44
Weight (kg)	108.1 ± 5.0 ²	104.7 ± 3.8	0.59
BMI (kg/m ²)	36.7	35.4	0.32
Hb A _{1c} [% (mmol/mol)]	7.5 ± 0.2 [54]	7.1 ± 0.2 [51]	0.35
Age at study start (y)	59.4 ± 2.2	62.4 ± 1.7	0.10
Diabetes duration (y)	12.4 ± 2.5	7.9 ± 1.0	0.03
iGFR (mL · min ⁻¹ · 1.73 m ⁻²)	114 ± 9	90 ± 6	0.43
eGFR (mL · min ⁻¹ · 1.73 m ⁻²) ³	98 ± 6	91 ± 6	0.02
AER (μg/min)	41 ± 11	82 ± 13	0.08
Alb:Cr spot urine (mg/mmol)	6.1 ± 1.4	11.4 ± 2.5	—
Dropouts			
<i>n</i>	13	7	—
Sex (M/F)	6/7	4/3	—
BMI (kg/m ²)	35.7	35.8	—
Hb A _{1c} (%)	7.4	7.3	—
Age at study start (y)	57.4	62.4	—
Diabetes duration (y)	8.3	9.8	—
iGFR (mL · min ⁻¹ · 1.73 m ⁻²)	95	101	—
eGFR (mL · min ⁻¹ · 1.73 m ⁻²) ³	102	103	—
AER (μg/min)	68	72	—
Alb:Cr spot urine (mg/mmol)	5.1	6.2	—

¹ AER, albumin excretion rate; Alb:Cr, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; iGFR, isotope glomerular filtration rate; MP, moderate-protein diet; SP, standard-protein diet.

² Mean ± SEM (all such values).

³ Estimated by using the Modification of Diet in Renal Disease Study formula.

subject had renal disease that was the result of glomerulonephritis (**Figure 1**). Of 31 dropouts, after random assignment, only 17 participants attended the baseline blood test for a creatinine concentration; 14 subjects had a second blood test at 1 mo, and 4 subjects had a second blood test at 4 mo. The change in the eGFR in dropouts over these time periods was exactly the same as in completers, and thus, dropouts did not influence the results.

Baseline characteristics of completers and dropouts are shown in **Table 1**. Twenty-three people had no record of the duration of their diabetes. The age of subjects varied from 39 to 75 y, whereas the diabetes duration varied from 1 to 54 y. BMI was similar in both groups, but there was a wide range from 27 to 54. Fifteen women were postmenopausal, and 4 women were taking hormone-replacement medication. There were no differences between diet groups except for diabetes duration.

Medication

In the 45 completers, medication use was as follows: no oral hypoglycemic medication: 5 subjects; metformin only: 15 subjects; metformin plus sulphonylureas: 10 subjects; metformin plus glitazones: 1 subject; metformin plus sulphonylureas and glitazones: 6 subjects; metformin plus insulin: 5 subjects; 2 oral hypoglycemic medications plus insulin: 1 subject; and insulin alone: 2 subjects. There were no differences in medication use between the 2 diets. Renin-angiotensin system blocking agents

were used by 76% of participants, whereas the remainder of subjects took other agents. There was no change in the use of these agents over 12 mo.

Medication changes

Eight drugs were stopped, including insulin by 2 people. Six new drugs were started, and metformin was increased in 6 subjects and reduced in 2 subjects. Insulin was started in one subject. Twenty people had no changes in medication.

Weight loss

Weight loss was not different between groups at 9.7 ± 13.4 kg for the MP group and 6.6 kg (±7.1) for the SP group. Seven people failed to lose weight or gained weight [2 subjects in the MP group (average weight gain of 4.6 kg) and 5 subjects in the SP group (average weight gain of 2.5 kg)]. Weight loss reached a plateau at ~6 mo and changed by ~1 kg thereafter. In subjects who had a DXA scan (*n* = 42), changes in fat mass were 6.2 ± 7.7 and 4.9 ± 5.1 kg, and changes in lean mass were 1.7 ± 2.7 and 1.8 ± 2.9 kg. When we examined only subjects who lost weight, fat mass changes were 6.6 ± 7.9 and 6.8 ± 4.3 kg, and lean mass changes 2.7 ± 2.8 and 2.7 ± 3.0 kg. Thus, there was no benefit of the MP on lean mass changes in either compliant or noncompliant subjects.

Compliance to diet

From baseline to 12 mo, the MP group increased protein intake from 106 ± 31 to 110 ± 38 g (1.22 g/kg), whereas the SP group decreased protein intake from 112 ± 33 to 97 ± 25 g/d (0.93 g/kg). Over the 12-mo period, the average difference between groups was 19 ± 6 g/d. At the 4-mo time point, the SP group had lowered their protein intake to as low as 81 g/d. These changes were calculated from the 24-h urinary urea excretion (**Figure 2**), which fell by >25% in the SP group (time-by-treatment effect: *P* < 0.05) and then rose after visit 3 (4 mo). Serum urea concentrations behaved in a similar way (time-by-treatment effect: *P* < 0.001), although the 1-mmol/L increase with the MP (**Figure 3**) was not reflected in a similar size change in urea excretion. On the basis of serum urea alone,

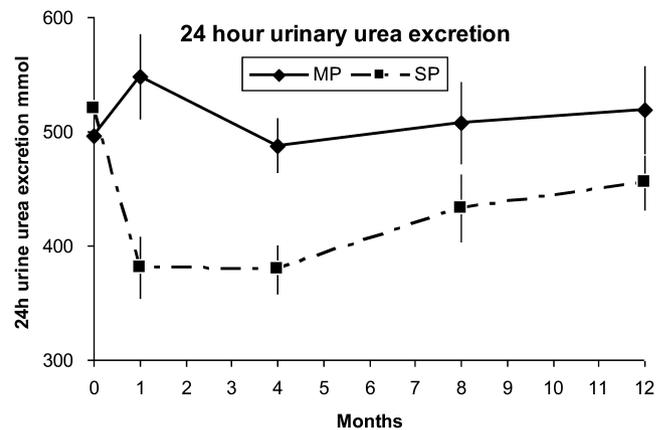


FIGURE 2. Mean (±SEM) 24-h urinary urea excretion (mmol). Time-by-diet interaction, *n* = 45 at baseline and 12 mo, *n* = 42 at 4 mo, and *n* = 34 at 8 mo. *P* < 0.05 (repeated-measures ANOVA). MP, moderate-protein diet; SP, standard-protein diet.

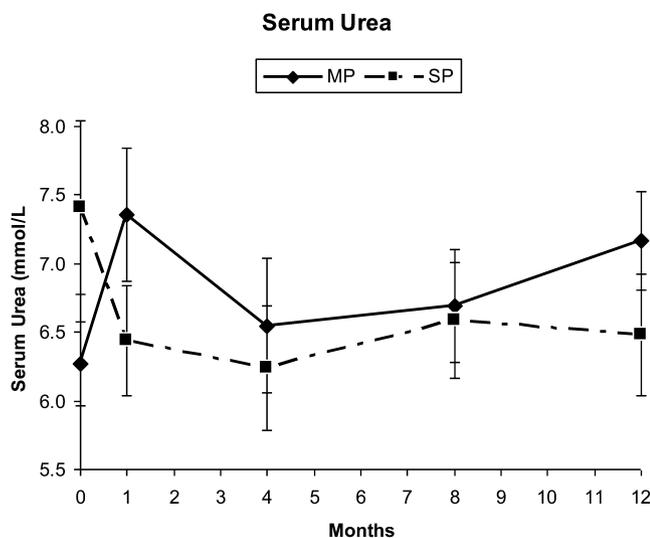


FIGURE 3. Mean (\pm SEM) serum urea (mmol/L). $n = 45$ at baseline and 4 and 12 mo, and $n = 36$ at 8 mo. Time-by-diet interaction, $P < 0.001$ (repeated-measures ANOVA). MP, moderate-protein diet; SP, standard-protein diet.

protein intake rose by an average of 10% over 12 mo in the MP group and fell by 16% in the SP group. Energy intakes were similar in both groups at 6500 ± 2400 kJ in the MP group and 6200 ± 1720 kJ in the SP group ($P = 0.4$). These amounts were reductions from baseline values of 2800 ± 2900 kJ in the MP group and 2200 ± 2048 kJ in the SP group ($P = 0.4$). Food records indicated a much greater difference in protein intake between the groups with the MP group eating 113 ± 45 g/d and the SP group eating 71 ± 18 g/d at 12 mo ($P < 0.001$). There was a 10% rise in serum creatinine at 1 mo in the MP group with a smaller rise in the SP group, which suggested that weight loss had acute effects on renal perfusion that resolved with time, whereas the 10% rise in protein intake at this time in the MP group (as assessed by the rise in serum urea) also increased serum creatinine. There was a time-by-treatment effect ($P = 0.006$), although both groups finished the study at 12 mo with almost the same serum creatinine as at the start of the study. Changes in creatinine were correlated with changes in lean mass ($r = 0.39$), and thus, part of the later fall in creatinine was related to the loss of lean mass.

Renal function

The GFR measured by iothalamate (Table 2) did not change with time or by diet, although there was a borderline ($P = 0.086$) reduction in the MP group, but this reduction was not confirmed by the eGFR or cystatin C. Changes in the eGFR were independently related to the baseline eGFR ($P < 0.001$). Because of this dependence on the baseline eGFR, data were analyzed by using an unplanned post hoc test according to the Foundation Kidney Disease Quality Outcome Initiative (16) stages of kidney disease (Table 3) as follows: stage 1: GFR >90 mL/min (plus urine abnormalities); stage 2: GFR from 60 to 89 mL/min; and stage 3: GFR from 30 to 59 mL/min. Hyperfiltration was defined as a GFT >120 mL/min (17).

Patients with stage 1, 2, or 3 renal disease (<120 mL/min; $n = 33$) had an improvement in renal function of 4 mL/min with weight loss ($P = 0.033$), whereas patients with hyperfiltration ($n = 12$) had a decrease in the eGFR of 15 mL/min ($P = 0.001$). Patients with stage 3 renal disease ($n = 5$) had an improvement in the eGFR, isotope glomerular filtration rate (iGFR), and cystatin C. Weight change was directly related to improvement in the eGFR ($r = 0.43$, $P = 0.013$) in stage 1–3 groups, but was not related to a change in the hyperfiltering group. After adjustment for weight loss ($P = 0.005$), the baseline eGFR remained a significant predictor of change ($P < 0.001$). Dietary treatment was unrelated to changes in the eGFR.

Changes in the eGFR and baseline cystatin C were correlated ($r = 0.53$). On multiple regression, changes in the eGFR were related to the baseline eGFR ($P = 0.001$), changes in cystatin C ($P = 0.023$), and changes in weight ($P = 0.034$), which accounted for 43% of the variance. When a decrease in lean mass rather than body weight was added to the regression, this decrease was related to a change in the eGFR ($P = 0.002$) along with changes in cystatin C ($P = 0.004$) and the baseline eGFR ($P = 0.014$), and the variance accounted for increases to 53%. Decreases in BP or Hb A_{1c} were unrelated to changes in renal function.

Although the changes in the iGFR were quantitatively similar to the eGFR, there were no overall relations with the baseline eGFR or changes in the eGFR or weight or cystatin C. However, the baseline iGFR predicted the change in the iGFR ($P < 0.001$).

In the group of 11 volunteers with an eGFR from 55 to 80 mL \cdot min⁻¹ \cdot 1.73 m⁻², subjects in the MP group ($n = 4$)

TABLE 2

GFR and cystatin C values at baseline and 12 mo for both diets¹

Variables	MP	SP	<i>P</i> -time	<i>P</i> -time-by-diet
<i>n</i>	21	24	—	—
iGFR at baseline (mL/min)	143 \pm 59	112 \pm 39	0.1	0.086
iGFR at end (mL/min)	129 \pm 49	113 \pm 40	—	—
Cystatin C at baseline (nmol/L)	61 \pm 11	69 \pm 20	0.9	0.7
Cystatin C at end ($n = 40$) (nmol/L)	61 \pm 10	69 \pm 20	—	—
Creatinine at baseline (μ mol/L)	75 \pm 25	84 \pm 21	0.6	0.8
Creatinine at end (μ mol/L)	74 \pm 25	84 \pm 15	—	—
eGFR at baseline (mL \cdot min ⁻¹ \cdot 1.73 m ⁻²) ²	98 \pm 28	91 \pm 30	0.6	0.9
eGFR at end (mL \cdot min ⁻¹ \cdot 1.73 m ⁻²) ²	97 \pm 20	90 \pm 28	—	—

¹ All values are means \pm SDs. *P* values were obtained by using a repeated-measures ANOVA with baseline and 12-mo values. eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; iGFR, isotope glomerular filtration rate; MP, moderate-protein diet; SP, standard-protein diet.

² Estimated by using the Modification of Diet in Renal Disease Study formula.

TABLE 3
Change in eGFR by baseline eGFR¹

eGFR	Change in eGFR ²	Change in iGFR	Change in cystatin C
	<i>mL · min⁻¹ · 1.73 m⁻²</i>	<i>mL · min⁻¹ · 1.73 m⁻²</i>	<i>nmol/L</i>
<60 mL · min ⁻¹ · 1.73 m ⁻² (n = 5)	5 ± 8	5 ± 10	-7 ± 10
60–89 mL · min ⁻¹ · 1.73 m ⁻² (n = 21)	3 ± 12	-1 ± 19	0 ± 5
90–120 mL · min ⁻¹ · 1.73 m ⁻² (n = 7)	6 ± 11	2 ± 23	2 ± 6
>120 mL · min ⁻¹ · 1.73 m ⁻² (n = 12)	-15 ± 12	-13 ± 26	1 ± 7
Total (n = 45)	-1 ± 14	-3 ± 21	0 ± 7

¹ All values are means ± SDs. Subjects with stage 1–3 renal disease (<120 mL/min; n = 33) had an improvement in renal function of 4 mL/min with weight loss (P = 0.033), whereas subjects with hyperfiltration (n = 12) had a decrease in the eGFR of 15 mL/min (P = 0.001) by using repeated-measures ANOVA. eGFR, estimated glomerular filtration rate; iGFR, isotope glomerular filtration rate.

² Estimated by using the Modification of Diet in Renal Disease Study formula both in mL · min⁻¹ · 1.73 m⁻² and nmol cystatin C/L.

had an increase in the eGFR of 7.4 ± 9.2 mL/min, whereas subjects in the SP group (n = 7) had a decrease in the eGFR of 2.5 ± 9.8 mL/min (P-difference between groups = 0.09). Parallel changes were seen in the iGFR (an increase of 11.1 ± 15.3 mL/min compared with a decrease of 0.8 ± 10.8 mL/min; P = 0.16) and cystatin C (a decrease of 8 ± 7 nmol/L compared with an increase of 2 ± 8 nmol/L; P = 0.067).

Protein excretion

There were no overall changes in albumin or total protein excretion either in a 24-h or spot sample (Figure 4). All protein measures were strongly correlated with each (r = 0.6–0.8). Changes in albumin excretion were related only to changes in diastolic blood pressure, which accounted for 35% of the variance (P < 0.001). There were strong time effects with a sharp drop in all protein measures at 1 mo with a slow return to baseline by 12 mo, which suggested an energy-restriction effect with no effect of weight loss or diet.

Blood pressure

There were no overall changes in systolic or diastolic blood pressure, but there was a time-by-treatment interaction (P < 0.05) for diastolic blood pressure, which was lower throughout the 12 mo that subjects consumed the MP (from 75 ± 7 to 72 ± 9 mm Hg in the MP group compared with 71 ± 9 to 75 ± 10 mm Hg in the SP group)

Glucose and Hb A_{1c}

Fasting glucose concentrations fell by 1.2 ± 2.0 mmol/L (P < 0.001), and Hb A_{1c} concentrations fell by 0.3 ± 1% or 2 mmol/mol (P = 0.05) with no diet effects.

DISCUSSION

In this study, we have shown that a moderate-protein weight-loss diet and a normal-protein weight-loss diet (or a low normal absolute-protein diet) have similar effects on renal function either in individuals with impaired function or a normal GFR. In subjects with an eGFR <120 mL, there was an overall rise in the GFR with weight loss on both diets, whereas in subjects with hyperfiltration, weight loss caused a substantial decline in the GFR. This result was true whether GFR was assessed by isotopic methods, MDRD, or cystatin C. The greatest improvement in the GFR was seen in the 5 men with a baseline eGFR <60 mL/min, in whom an improvement of ≥10% was seen. In the impaired renal function group as defined by Knight et al (11) (GFR: 55–80 mL/min), there was improvement in the MP group but not in the SP group, which was of borderline significance (P = 0.07 for cystatin C) and not accounted for by differences in weight loss. Thus, over a 1 y period, a moderate-protein weight-loss diet is not harmful and may even be beneficial if accompanied by weight loss. However, longer follow up is required to be sure of these effects. Although the eGFR is related to changes in lean body mass, these differences have been shown with all methods of assessment of GFR and persisted after adjustment for changes in weight or lean body mass.

Thus, with weight loss, we have blocked the expected decline in the GFR in individuals with a GFR <120 mL/min but more than doubled the expected decline in the hyperfiltering group. With the use of repeated iothalamate tests over 10 y, Fontserre et al (18) showed the rate of decline in renal function in hyperfiltering patients with type 2 diabetes was -4.8 ± 4.7 mL/min/y (3%) whereas in patients with normal renal function it

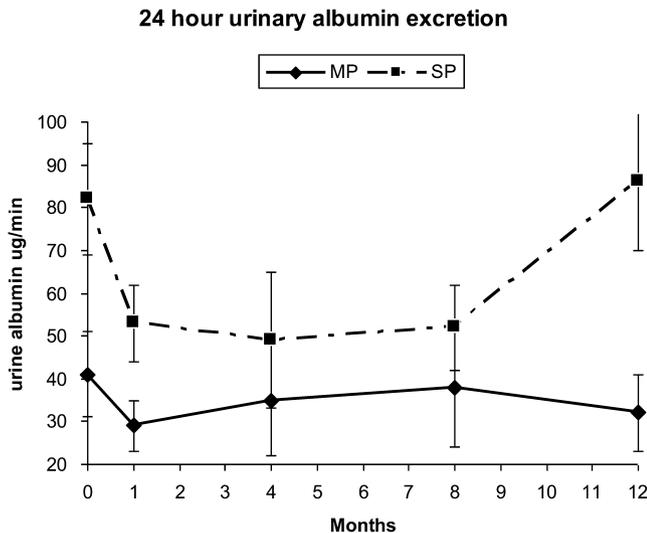


FIGURE 4. Mean (±SEM) 24-h urinary albumin excretion (µg/min). n = 45 at baseline and 4 and 12 mo, and n = 36 at 8 mo. P = NS (repeated-measures ANOVA). MP, moderate-protein diet; SP, standard-protein diet.

was $-3.0 \pm 2.3 \text{ mL} \cdot \text{min}^{-1} \cdot \text{y}^{-1}$ (3%). In patients with stage 2 and 3 chronic kidney disease, the decline was $-1.4 \pm 1.8 \text{ mL} \cdot \text{min}^{-1} \cdot \text{y}^{-1}$ (2–3%/y). Thus, it would appear that the rate of decline of renal function (expressed as a the percentage of change) was similar across all groups, and the hyperfiltering group did not differ from the normal group. In both groups with an eGFR $>90 \text{ mL/min}$, the use of the MDRD equation underestimated renal function and was not useful to assess changes (isotopic methods were required), whereas with chronic kidney disease stages 2 and 3, MDRD assessment did not differ from the isotopic method. Whether hyperfiltration predicts an early decline in the GFR, a faster rate of decline or a higher frequency of decline is not clear in either type 1 or type 2 diabetes (19). However, it has been observed in type 1 diabetes that individuals with hyperfiltration ($>120 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) had double the total mortality of those with an eGFR of 60–120 mL/min in subjects with and without albuminuria (20). Hyperfiltration does not appear to predict microalbuminuria in type 1 diabetes (21).

Obesity is known to increase risk of renal disease independently of other risk factors such as age, sex, ethnicity, smoking, alcohol, diabetes, dyslipidemia, and hypertension (22). BMI ≥ 25 was associated with increased risk of renal disease of 40%, whereas BMI >30 predicted 80% increased risk of renal disease. Similarly, Hsu et al (23) reported a 7-fold increase in the RR of end-stage renal disease between BMI ≤ 25 and ≥ 40 in 320,252 adults who participated in a multiphasic health checkup between 1964 and 1985. Thus, in this group, we would expect that, if their weight loss is maintained, then their future risk of more-severe renal disease should be reduced. Chagnac et al (24) showed that, in a group of 8 severely obese subjects (mean BMI: 48) a GFR measured by using 145mL inulin/min was reduced to 110 mL inulin/min (not adjusted for surface area) by a 32% weight loss. Albumin excretion was also reduced from 16 to 5 $\mu\text{g}/\text{min}$.

Caloric restriction attenuates renal damage regardless of the amount of dietary protein in unilaterally nephrectomized, spontaneously hypertensive rats (25). In randomized controlled intervention studies that investigated the effect of energy restriction on the change in urinary protein excretion in healthy overweight and obese volunteers (BMI ≥ 27), reductions in urinary protein excretion between 30% and 80% compared with at baseline have been reported after weight-loss in nondiabetic (26) and 30 type 2 diabetic participants (27). In 22 obese patients with diabetic nephropathy, the fall in protein excretion was related to weight change (28).

Despite the weight loss, there were no significant changes in this study at 12 mo in albumin or total protein excretion, although with all variables, there were strong time-related trends. During the first month in which weight loss occurred at the greatest rate, albumin excretion almost halved in both diets. Thereafter, albumin excretion increased with a greater increase in the SP group particularly in the last 3 mo. During this period, protein intake increased in the SP group, and Hb A_{1c} and blood pressure increased in both groups. During the first month, there was also a sharp increase in serum creatinine with both diets, and thus, it appeared to be related to energy restriction and weight loss per se rather than changes in protein intake. These changes disappeared over the next 11 mo, part of which was a result of a lowering of serum creatinine through a loss of lean mass.

In epidemiologic studies, there has been a very mixed picture of the relation between protein intake and presence of micro-

albuminuria or reduction of GFR. In a study of 150 patients with type 2 diabetes for >5 y, 75 cases of microalbuminuria were identified. No differences in protein intake from any source were seen between patients with and without microalbuminuria (29). The opposite effect was seen in an age-, sex-, and glucose-tolerance-tratified random sample of a 50- to 75-y-old general white population ($n = 680$). A $0.1\text{-g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ increment of protein intake was associated with increased risk of microalbuminuria risk ratio 1.20 (1.08–1.32) (30). However, another large study showed no relation between protein intake and microalbuminuria (31). As noted previously, Nurses' Health study investigators examined changes in serum creatinine over 11 y and related it to dietary protein intake (11). In a subgroup of women with an estimated creatinine clearance of 55–80 $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, a borderline significant reduction in creatinine clearance of 7.72 mL/min per 10-g increase in dietary protein was seen. Nondairy animal protein was more strongly associated with a reduction than were other proteins. The NHANES III showed no association between protein intake and microalbuminuria in participants without renal impairment, hypertension, or diabetes. However, in participants with both hypertension and diabetes, a high intake of protein was associated with an increased prevalence of microalbuminuria (32). In the more recent Prevention of Renal and Vascular End stage Disease study that investigated the effect of protein intake (which ranged between 0.3 and 3.33 $\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ as assessed by urinary urea excretion) on renal function in 8461 participants who did not have renal disease, no significant effect of protein was seen in the change in the GFR over a follow-up period of 7.2 y (33). In participants with renal impairment, there seems to be a U-shaped association between protein intake and deterioration of the GFR. A low protein intake [$<90\%$ of recommended intake (0.6–0.75 g/kg)] and a high protein intake ($\geq 110\%$ recommended intake) was associated with deterioration, whereas an intake in the recommended range had no deleterious effect. The same effect was seen in participants with a low energy intake (34).

In conclusion, weight loss improves renal function in individuals with impaired renal function, whereas it normalizes renal function in individuals with hyperfiltration with no different effects of an MD compared with a normal-protein diet. Although this study was relatively small and required a longer duration of follow-up, there was no evidence of harm from a moderate-protein weight-loss diet.

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