Animal Versus Plant Protein Meals in Individuals With Type 2 Diabetes and Microalbuminuria

Effects on renal, glycemic, and lipid parameters

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OBJECTIVE — To determine, for individuals with type 2 diabetes and microalbuminuria, the effects of 6 weeks of meals containing plant-based protein (PP) versus meals with predominantly animal-based protein (AP) on renal function and secondarily on glycemia, lipid levels, and blood pressure.

RESEARCH DESIGN AND METHODS — In a randomized crossover trial, we compared 6 weeks of meals containing only PP with meals containing primarily AP (60% animal, 40% plant) in 17 subjects with type 2 diabetes and microalbuminuria treated with diet and/or oral antidiabetic agents. Protein content was equivalent to the average American diet, and calories provided weight maintenance. Nutrients were equivalent between the two diets. Meals were prepared and packaged by a metabolic kitchen staff and were sent home weekly. At the beginning and end of each 6-week period, subjects were studied for 36 h on a metabolic unit.

RESULTS — There were no significant differences between diets for glomerular filtration rate, renal plasma flow, albumin excretion rate, total cholesterol, HDL cholesterol, triglyceride area under the curve (AUC), glucose and insulin AUC, HbA_{1c}, blood pressure, or serum amino acids. For both diets, at the end of the treatment periods as compared with baseline, total cholesterol was significantly lower (PP and AP: from 4.75 to 4.34 mmol/l, $P < 0.01$), HbA_{1c} had significantly improved (PP: from 8.1 to 7.5%, $P < 0.01$; AP: from 7.9 to 7.4%, $P < 0.01$), and diastolic blood pressure was significantly lower (PP: from 83 to 80 mmHg, $P < 0.02$; AP: from 82 to 78, $P < 0.02$).

CONCLUSIONS — There is no clear advantage for the recommendation of diets containing only PP rather than diets containing protein that is primarily animal-based for individuals with type 2 diabetes and microalbuminuria. There are, however, potential lipid, glycemic, and blood pressure benefits for following a carefully constructed, weight-maintaining, healthy diet, regardless of protein source.

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Abbreviations: AER, albumin excretion rate; AP, animal-based protein; AUC, area under the curve; CV, coefficient of variation; GCRC, General Clinical Research Center; GFR, glomerular filtration rate; PAH, paraminohippurate; PDCAAS, protein digestibility–corrected amino acid score; PP, plant-based protein; RPF, renal plasma flow.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial on p. 1474.

One of the risk factors in type 2 diabetes for progression to diabetic nephropathy, renal failure, and early cardiovascular morbidity and mortality (1–6) is microalbuminuria. Therapies that reverse or delay the progression of microalbuminuria include normalization of blood pressure with ACE inhibitors (7) and angiotensin II receptor blockers (8) and improved blood glucose control (9,10). More problematic is the effectiveness of reducing the amount of dietary protein to at least 0.8–1.0 g · kg body $wt^{-1} \cdot day^{-1}$ (11) or changing the type of protein. Studies performed in normoalbuminuric individuals with diabetes have suggested that changing the composition of the diet by altering the source of protein from animal to plant, either acutely in the setting of a standard test meal (12) or for up to 4 weeks (13), might produce beneficial renal effects. However, in another acute study, individuals with type 1 or type 2 diabetes and microalbuminuria showed no significant change in renal function when given plant-based protein (PP) versus animal-based protein (AP) (14).

In addition to having a possible renal benefit, plant-based diets (particularly those using soy) have been reported to reduce total and LDL cholesterol (15–17).

Our hypothesis was that a diet based on PP would have beneficial renal and lipid effects compared with a diet with a majority of its protein from animal sources. The mechanism, if these benefits could be confirmed, might be attributed to differences in the distribution of amino acids between diets. In addition, we compared the two diets for effects on glycemia and blood pressure. Efforts were made to design the study to be of sufficient duration to measure the end points of interest, to design diets that were nutritionally equivalent except for protein source, and to provide all food from a central research kitchen. To our knowledge, this is the first well-controlled study of this duration and degree of dietary control in

Table 1—*Screening characteristics*

n	17
Sex (M/F)	14/3
Ethnicity (Caucasian/African-American)	9/8
Age (years)	56 ± 3 (37–70)
Duration of type 2 diabetes (years)	7 ± (1–16)
Weight (kg)	102.3 ± 5.2 (69.5–151.5)
Height (cm)	175 ± 2 (157–196)
BMI (kg/m^2)	33.1 ± 1.4 (25.1–44.9)
HbA_{1c} (%)	8.8 ± 0.4 (6.1–11.8)
Microalbumin (μg/ml)	83 ± 17 (22–311)*
Oral antidiabetic agent/diet (yes/no)	16/1
Sulfonylureas	9
Biguanides	3
Biguanides + sulfonylureas	4
ACE inhibitor (yes/no)	8/9
ACE-1	6
ARB	1
ARB or ACE-1 + β-blocker	1
Systolic blood pressure (mmHg)	151 ± 4 (111–177)*
Diastolic blood pressure (mmHg)	85 ± 2 (73–94)*
Smoke (yes/no)	3/14
Lipid medications (yes/no)	4/13
Gemfibrazole	1
Gemfibrazole + niacin	1
HMG-CoA reductase inhibitors	2

Data are means ± SE (range) or *n*. *To meet recruitment goals, microalbumin and blood pressure exclusion criteria were broadened slightly. HMG, hydroxymethylglutaryl.

individuals with type 2 diabetes and microalbuminuria.

RESEARCH DESIGN AND METHODS

The study was approved by the local institutional review board, and subjects gave informed consent before study initiation. A total of 23 subjects with type 2 diabetes and microalbuminuria (albumin excretion rate [AER] >30 and <300 μg/ml) were recruited to participate in the study. Exclusion criteria included therapy with exogenous insulin, blood pressure >160/90 mmHg, age <35 or >75 years, and unwillingness to follow a standardized diet for an extended period of time. Six subjects were dropped from the study: one male and three female subjects for noncompliance with the diet and two females who did not tolerate phlebotomy. The only significant difference between the dropouts and the completers is sex. Screening characteristics of the 17 who completed the study are shown in Table 1.

Experimental design

After screening, the order of diets for subjects was randomized, using a computer-generated set of random numbers, to two 6-week periods using a crossover study design, with a 4-week wash-out period (usual diet) separating the study diets. One of the 6-week periods consisted of all PP meals, and the other contained meals with mainly AP. A 1-week run-in period provided standardized initial intake of food (from the hospital food service) for all participants. This was followed by a 36-h study on a general clinical research center (GCRC) unit to obtain baseline data before the initiation of the first diet period. For each 6-week diet, subjects received all food from the GCRC kitchen but ate meals at home. At the end of the 6-week period, subjects repeated the 36-h study on the GCRC unit. After the 4-week washout period, the process was repeated using the alternative diet.

Diets

Diets provided weight maintenance (based on 3-day food records and indirect calorimetry) to meet nationally recognized nutrition goals (18,19), and they were nutritionally equivalent (Table 2). Macronutrients were designated to be percentages of daily calories (e.g., 30% of calories as fat, 17% of calories as protein). Nutrient calculations were performed using Minnesota Nutrition Data System software (food database version 12A, nutrient database version 27, November 1996; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN), and they were confirmed by laboratory analyses (Covance Laboratories, Madison, WI). Major protein foods during the AP phase of the study included beef, poultry, fish, and milk; during the PP phase, they included tofu (Mori NU brand; Morinaga Nutritional Foods), textured vegetable protein and soy milk (Archer Daniel Midlands), and legumes. During the PP phase, ~62% of the protein was soy based, whereas none of the PP during the AP phase was soy based.

Foods for the 4-day menu cycles were prepared, weighed, and frozen in reheatable containers by the GCRC kitchen staff. Staples (bread, cereal, and juices) and fresh fruits were provided prepackaged. If body weight deviated by >0.9 kg in 1 week, subjects were provided with or asked to delete snacks containing a scaled version of the day's menu nutrients. Each subject was allowed 1 "free" day every 2 weeks during each 6-week period, not to be taken during the sixth week of the study.

Compliance was monitored by daily log sheets indicating foods and amounts to eat, weekly phone follow-up from the GCRC dietitians, and weekly food pickup, weight monitoring, and 24-h urine collection (urea nitrogen, cross-checked with calculated protein intake).

GCRC protocol

After being admitted to the GCRC, subjects fasted overnight. Intravenous lines were placed, and fasting blood for HbA_{1c}, amino acids, and the lipid profile was drawn at 0600 h the next morning. At 0630 h, primed-continuous infusion of inulin and paraminohippurate (PAH) was begun, lasting until 1130 h. Blood was sampled from the arm opposite the infusion site. Plasma samples were collected for analyses from 15 min before to 3 h after each meal, in half-hour increments for insulin and glucose and in hourly increments for triglyceride area under curve (AUC). Foods eaten during the day (0830, 1300, and 1800 h) were the same as those eaten during the run-in or the just-completed diet period (PP or AP).

Table 2—*Matching nutrients from foods for a 2,500-kcal diet: average of 4 days*

Nutrients	Plant	Animal
Protein [g (% kcal)]	107 (17)	106 (17)
Animal (g)	0	64
Plant (g)	107	43
Carbohydrate [g (% kcal)]	331 (53)	332 (53)
Sugars (g)	108	120
Starches (g)	172	163
Dietary fiber (g)	39	39
Soluble (g)	13	12
Insoluble (g)	26	26
Fat [g (% kcal)]	83 (30)	84 (30)
SFA [g (% kcal)]	21 (7.6)	21 (7.6)
MUFA [g (% kcal)]	31 (11.2)	31 (11.2)
PUFA [g (% kcal)]	26 (9.4)	25 (9)
Cholesterol (mg)	300*	312
Calcium (mg)	935†	820†
Sodium (mg)	1,638†	1,599†

*Cholesterol powder; †calcium tablets and salt packets were provided to meet goals of >1,000 and <2,400 mg, respectively. MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Inulin and PAH protocol

The inulin/PAH infusion protocol followed previously published methods (13,20). Blanks for inulin and PAH were obtained after the first hour and before the loading dose and maintenance infusion. The loading dose was based on initial screening weight and contained 25 mg/kg inulin (Laevosan-Gesellschaft, Linz, Austria) and 10 mg/kg PAH (Sigma, St. Louis, MO). Based on the subject's creatinine clearance (from screening or last assessment), estimated by the Cockcroft and Gault method (21), the concentration of both inulin and PAH in the maintenance infusate were adjusted to provide a clearance rate of 0.125 and 0.083 mg · ml^{-1} · min^{-1}, respectively, when infused continuously at a rate of 1.0 ml/min. Six timed urine collections (at 1 h, four 30-min periods, and then 1 h) were obtained by spontaneous voiding. Plasma samples were drawn in the middle of the collection periods. Breakfast during this challenge included juice, cereal, toast, margarine, and soy milk (PP) or reduced-fat cow's milk (AP).

Biochemical analyses

Biochemical and hormonal measurements were carried out in the analytical laboratory of the Indiana University Diabetes Research and Training Center (DRTC). All measures except for human insulin and bedside glucose measures were performed on the Cobas Mira S instrument using reagents obtained from Roche Diagnostics. The following methods were used: inulin (22), PAH (23), microalbumin (immunoturbidmetric precipitation using SPQ reagents from DiaSorin, intra- and interassay coefficients of variation [CVs] <3.5 and 5.7%, respectively), HbA_{1c} (immunoturbidmetric precipitation method, intra- and interassay CVs <2.5%, normal range 4.6–6.1%), total cholesterol (24), HDL cholesterol (EDTA plasma specimens and dextran sulfate [50,000 molecular weight] and magnesium microprecipitant step), triglycerides (25), urinary and serum creatinine (modified kinetic version of the Jaffe reaction), urinary urea nitrogen and plasma urea nitrogen (coupled enzymatic procedure of Talke and Schubert), plasma glucose concentrations (glucose analyzer; Yellow Springs Instruments, Yellow Springs, OH), human insulin (double-antibody assay [26], sensitivity of assay 0.08 ng/ml, intra-assay variance <4%, interassay CV <15% for control values <0.6 ng/ml and <6% for control values >1.15 ng/ml), and plasma amino acids (buffer ion-exchange chromatography with ninhydrin detection, intra-assay CV <5%). Weekly 24-h urine collections were used to follow creatinine clearance and compliance with the amount of protein in the diet. Urine urea nitrogen and an estimated nonurea nitrogen excretion of 0.031 g · kg^{-1} · day^{-1} were used to estimate dietary protein intake (27).

Statistical analysis

Data are presented as the means ± SE. Comparisons between variables measured once on each diet, such as weight change, were performed using a paired *t* test. Outcome variables were analyzed by three-way repeated-measures ANOVA using transformations when necessary to normalize the data. The grouping factor was the order of diets (AP first or PP first), and the repeated measures were time (start and end of each diet) and diet (AP and PP). The interaction term between diet and time from this analysis indicates whether the change between baseline and 6 weeks is different for the two diets. The inulin and PAH clearance results from the last two 30-min urine collections were averaged, and the mean values, corrected for body surface area, were used to represent glomerular filtration rate (GFR) and renal plasma flow (RPF), respectively, and are expressed as the value per 1.73 m^2 body surface area. Area under the response curve above baseline was calculated using the trapezoidal method. $P < 0.05$ was considered to be statistically significant. Our sample of 17 individuals provides 80% power to detect a difference between diets of 0.72 SDs using a paired *t* test, with a nominal significance level of 0.05. This comparison is equivalent to the interaction between diet treatment and change over time between 6 weeks and baseline for each study period.

RESULTS — One subject's primary care practitioner discontinued glyburide (5 mg) during the third week of AP in an AP-PP sequence. There were no other self-reported changes in activity level or medications during the study.

Diet

Each individual was provided 17% of total daily calories as protein, with the average protein intake being 1.20 g · kg^{-1} · day^{-1} for PP and 1.19 g · kg^{-1} · day^{-1} for AP. Daily protein intake from estimated dietary protein in the day's meals versus calculated protein from urinary nitrogen excretion did not differ between provided and consumed protein for either diet (117 vs. 110 g/day for PP; 115 vs. 115 g/day for AP). There was a small but not statistically significant weight loss by the end of each diet period: PP 2.6 ± 0.4 kg and AP 1.7 ±

Table 3—*Results*

	Measurements (n = 17)				
	Baseline plant protein	6 weeks' plant protein	Baseline animal protein	6 weeks' animal protein	Between-diet P value*
RPF (ml · min^{-1} · 1.73 m^{-2})	276 ± 25	298 ± 30	361 ± 43†	312 ± 28	0.21
GFR (ml · min^{-1} · 1.73 m^{-2})	100 ± 7	108 ± 8	116 ± 9	118 ± 6	0.63
AER (μg/min)	68 ± 39	49 ± 26	53 ± 29	62 ± 28	0.11
Total cholesterol (mmol/l)	4.75 ± 0.19	4.34 ± 0.18‡	4.75 ± 0.23	4.34 ± 0.22‡	0.88
Triglyceride 12.5-h AUC (mg% · h)	3,147 ± 494	2,839 ± 463	3,091 ± 531	2,727 ± 440	0.99
HDL cholesterol (mmol/l)	0.89 ± 0.07	0.93 ± 0.07	0.96 ± 0.09	0.90 ± 0.07	0.09
HbA_{1c} (%)	8.1 ± 0.4	7.5 ± 0.3‡	7.9 ± 0.4	7.4 ± 0.3‡	0.75
Glucose 10.5-h AUC (mg% · h)	2,442 ± 229	2,075 ± 135	2,179 ± 156	2,061 ± 166	0.12
Insulin 10.5-h AUC (ng/ml)	15.0 ± 2.8	17.0 ± 3.5	19.1 ± 3.3	19.0 ± 3.8	0.44
Systolic blood pressure (mmHg)	145 ± 4	141 ± 3	145 ± 3	140 ± 4	0.90
Diastolic blood pressure (mmHg)	83 ± 2	80 ± 2§	82 ± 2	78 ± 2§	0.75
Valine (mmol/l)	234.7 ± 11.4	224.1 ± 7.8	243.3 ± 9.2	242.6 ± 11.2	0.55
Lysine (mmol/l)	178.1 ± 15.2	160.6 ± 8.6	181.4 ± 8.8	175.5 ± 12.4	0.55

Data are means ± SE. *Significance of interaction term between diet and time (baseline versus 6 weeks) from three-way repeated-measures ANOVA. †Subject 01 had a significantly elevated RPF during the baseline for animal protein versus plant protein. Differences between baselines are not significant with data from subject 01 excluded. Furthermore, differences in RPF between diets at 6 weeks with subject 01 excluded increased P values from 0.21 to 0.72. ‡$P < 0.01$ vs. baseline; §$P < 0.02$ vs. baseline.

0.8 kg, representing 2.5 and 1.2% loss of body weight, respectively. There were no significant differences between diets with respect to 21 plasma amino acids (see Table 3 for representative data).

Outcome parameters

Calculation of RPF and GFR from data in the period preceding breakfast did not differ from postmeal measurements, and the effects of breakfast ingestion were not apparent. There were no significant differences in the change from baseline to 6 weeks between diets for any of the renal variables (GFR, RPF, and AER), the lipid variables (total cholesterol, HDL cholesterol, and triglyceride AUC), the glycemic variables (HbA_{1c}, glucose AUC, and insulin AUC), or blood pressure (Table 3). We also found no significant differences for other glucose measurements (fasting, prelunch, predinner, or 2-h postbreakfast, -lunch, or -dinner) (data not shown). Some variables showed improvement on both diets. There was a significant decrease in total cholesterol after both diets (4.75 to 4.34 mmol/l, both PP and AP; $P < 0.01$); subjects also showed a significant decrease in HbA_{1c} after both diets (PP 8.1 to 7.5%, $P < 0.01$; AP 7.9 to 7.4%, $P < 0.01$), and diastolic blood pressure was significantly lower after both diets (PP 83 to 80 mmHg, $P < 0.02$; AP 82 to 78 mmHg, $P < 0.02$) (Table 3). We could not detect differences in dietary effects in renal function, regardless of whether subjects were treated with ACE inhibitors. Baseline RPF for AP was significantly greater than PP, which can be explained by the significant elevation of RPF for subject 01 (see Table 3). There was a significant difference between baseline glucose AUC for PP versus AP, explainable in part by subject 01, whose glucose was significantly higher on PP. Exclusion of subject 01 results in differences between the two baselines that are less (PP 2,259 ± 146 mg% · h; AP 2,102 ± 145 mg% · h) but still significantly different ($P = 0.008$). With subject 01 excluded, the difference between diets for glucose AUC is still not significant ($P = 0.57$).

CONCLUSIONS — Previous reports that the protein source of a diet may affect renal function and albuminuria were of short duration, not controlled, and/or did not assess compliance. In contrast to previous studies, we used prepared standardized diets consistent with national nutritional recommendations, a group of patients with type 2 diabetes at high risk for kidney disease who achieved weight maintenance, and extended study periods so that longer-term effects on lipids and glycemia could be observed.

At the end of each period, we found no significant difference in renal outcomes from eating PP versus AP meals for people with type 2 diabetes and microalbuminuria. RPF rates and GFRs as calculated from inulin and PAH clearances (Table 3) did not differ significantly from baseline nor were there demonstrable effects on albumin excretion. Previous studies that demonstrated renal effects of protein in the diet used differing populations of subjects. Nakamura et al. (14) found, in acute feeding studies, that individuals with type 1 or type 2 diabetes and microalbuminuria did not have a significant change in GFR during 3 h after eating tuna fish or bean curd (tofu). In nondiabetic individuals and individuals with diabetes and normoalbuminuria, there was a significant increase in GFR after tuna fish but not after tofu (12). In a study lasting 4 weeks using normoalbuminuric subjects with type 1 diabetes, Kontessis et al. (13) found that GFR, RPF, and median urinary albumin excretion were significantly lower with PP compared with AP diets. It is possible that renal function can be improved in subjects with normoalbuminuria but not in subjects with microalbuminuria. It also may be that PP diets such as ours, where a majority of protein is soy-based and has a protein digestibility–corrected amino acid score (PDCAAS) comparable to beef and very near milk and egg white (28), provide renal responses similar to AP, whereas diets with a majority of protein with lower PDCAAS scores provide lower GFR, RPF, and AER. Kontessis et al. found serum va-

line and lysine to be higher with their AP diet than with their PP diet, but we found no significant difference between the diets for any of the amino acids. Unfortunately, details of the Kontessis et al. diets were not provided, so we cannot compare the studies further in this respect. Jibani et al. (29) found improved renal function while their subjects were on a mainly PP diet (8 weeks); however, protein amount was reduced substantially below current dietary recommendations.

We found that total cholesterol levels, HbA_{1c}, and diastolic blood pressure improved significantly during each diet. The cholesterol decrease is not surprising in the case of the PP diet because evidence exists concerning the cholesterol-lowering effect of soy protein (15–17), and the PP in our study was, on average, 62% soy protein. Interestingly, cholesterol improved significantly when subjects ate the AP diet as well. This might be attributable to the nutritional guidelines followed in providing these diets to the subjects or to tightly controlling the nutritional components within the study design. Alternatively, the improvement in both groups might be due to a slight decrease in caloric intake, resulting in a modest weight loss, rather than a particular change in dietary composition.

A criticism of outpatient dietary studies of this nature has been that diets were not tightly controlled. Rather than giving free-living subjects diet advice and collecting food records, we designed the diets to be nutritionally comparable and provided all foods to the subjects. Our diets were designed using defined macronutrient percentages of calories in order to hold this parameter constant while ensuring weight maintenance. Dietary counseling, emphasizing compliance, was provided when patients returned for new packets of food. Although complete assurance that diets were strictly followed cannot be given, a comparison of calculated dietary protein intake versus urine calculated protein intake indicated that our subjects complied with the prescribed amount of protein.

The protein in our study diets was not restricted and was typical of the average American intake of 14–18% of kilocalories as protein (30,31). The amount of daily protein in our study (both meal plans) averaged 1.2 g/kg body wt, and, in contrast to a previous study (32), our AP was from mixed animal sources. Although it is possible that reducing the amount of protein to 0.8–1.0 $g \cdot kg^{-1} \cdot day^{-1}$ regardless of source of protein might provide renal benefit (33–36) in people with type 2 diabetes and microalbuminuria, it appears that the source of dietary protein (plant versus animal) in amounts typically consumed does not make a difference.

An argument can be made that the lack of differences between diets reflects low power rather than no true difference. Changes in GFR, RPF, AER, and HbA_{1c} over the 6-week diet periods were compared for AP and PP to assess whether lack of power could explain the negative results. We had 80% power to detect differences between diet effects in GFR of 34 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, RPF of 148 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, AER of 41 μg/min, and HbA_{1c} of 0.72%. The actual changes seen were smaller and not clinically meaningful. Finally, lack of response at 6 weeks does not eliminate the possibility of a group difference for longer-term changes in protein composition.

There appears to be no clear advantage to recommending PP over AP to improve renal function or lipid and glycemic parameters in people who have type 2 diabetes and microalbuminuria.

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