

Association of a Reduction in Central Obesity and Phosphorus Intake With Changes in Urinary Albumin Excretion: The PREMIER Study

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Background: Excess adiposity and dietary factors may be important determinants of urinary albumin excretion (UAE).

Study Design: Observational analysis of PREMIER, a randomized trial designed to lower blood pressure using behavioral interventions (counseling on weight loss, healthy diet, and exercise).

Setting & Participants: 481 participants with normal kidney function who provided adequate 24-hour urine collections at baseline and 6 months.

Predictors: Change in waist circumference; 24-hour urine sodium, potassium, and phosphorus excretion; and protein intake estimated from urea nitrogen.

Outcomes & Measurements: The primary outcome was change in log-transformed 24-hour UAE over 6 months.

Results: After 6 months, the proportion of individuals with UAE ≥ 10 mg/d decreased from 18.7% to 12.7% ($P < 0.001$). Changes in mean waist circumference (-4.2 ± 6.6 [SD] cm), 24-hour excretion of sodium (-28.2 ± 71.7 mmol/d), potassium ($+8.4 \pm 27.8$ mmol/d), phosphorus (-27.7 ± 314.1 mg/d), and protein intake (-1.7 ± 19.4 g/d) were observed. After adjustment for relevant covariates, the following variables were associated significantly with reduction in $\ln(\text{UAE})$ in separate models: decrease in waist circumference ($P = 0.001$), decrease in 24-hour urine phosphorus excretion ($P < 0.001$), and decrease in protein intake ($P = 0.01$). In a multivariable model including these 3 predictors, decreases in waist circumference ($P = 0.002$) and 24-hour urine phosphorus excretion ($P = 0.03$), but not change in protein intake ($P = 0.5$), remained associated significantly with reduction in $\ln(\text{UAE})$. These associations remained significant even after adjustment for changes in blood pressure and insulin resistance. Baseline UAE and metabolic syndrome modified the relationship of waist circumference with $\ln(\text{UAE})$; specifically, individuals with higher UAE and baseline metabolic syndrome experienced greater reductions in $\ln(\text{UAE})$ from decreases in waist circumference.

Limitations: Observational study with potential for confounding.

Conclusions: In adults with normal kidney function, decreases in waist circumference and 24-hour urine phosphorus excretion are associated with reductions in UAE. These findings support the rationale for clinical trials to determine whether reducing dietary phosphorus intake or waist circumference could prevent chronic kidney disease or slow its progression.

Am J Kidney Dis. 62(5):900-907. © 2013 by the National Kidney Foundation, Inc.

INDEX WORDS: Weight loss; waist circumference; protein; phosphorus; urinary albumin excretion.

Elevated levels of urinary albumin excretion (UAE) are associated with increased risk of cardiovascular events, end-stage renal disease, and mortality even at levels as low as 10 mg/d.¹⁻⁵ Cohort studies of individuals with diabetes or vascular disease have shown that reductions in UAE are associated with decreased risk of cardiovascular outcomes,⁶ kidney

disease outcomes, and mortality.⁷ Potentially modifiable lifestyle factors that may affect UAE include excess adiposity⁸⁻¹² and diet.¹²⁻¹⁴ In a few small trials, weight-loss interventions reduced proteinuria and albuminuria; however, most of these studies did not assess changes in diet, including protein and phosphorus intake.^{11,15-19} Hence, it is uncertain whether the benefit of these inter-

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Received January 4, 2013. Accepted in revised form April 25, 2013. Originally published online July 1, 2013.

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0272-6386/\$36.00

<http://dx.doi.org/10.1053/j.ajkd.2013.04.022>

ventions resulted from weight loss or changes in nutrient intake. Only one study of 30 individuals with overt proteinuria reported changes in 24-hour urine urea nitrogen excretion (no significant change during the intervention) and found that a mean weight loss of 4.1% resulted in a mean decrease in proteinuria of 31.2%.²⁰ Furthermore, little is known about the impact of weight loss on UAE in individuals without overt kidney disease.

Diet may play an important role in UAE because dietary patterns characterized by high intake of red meat, saturated fats, and sweets have been associated with incident microalbuminuria.^{12,13} Although studies of protein restriction in individuals with chronic kidney disease (CKD) have suggested potential benefits on slowing the progression of CKD,²¹ potential risks of high protein intake in persons with normal kidney function remain uncertain.²²⁻²⁴ One dietary factor intrinsically linked to protein is phosphorus, which at high levels of consumption can cause kidney injury in animal CKD models (independent of protein).²⁵ Although serum phosphorus level has been found to be associated with low-grade albuminuria,²⁶ cardiovascular events, and mortality,^{27,28} little is known about risk associated with 24-hour urine phosphorus excretion, which may more adequately reflect dietary intake.²⁹

The goal of this study was to examine whether changes in central obesity and dietary factors, estimated from 24-hour urine collections, were associated with changes in UAE using data from a randomized controlled trial of dietary intervention in patients with prehypertension or stage I hypertension.

METHODS

Study Population

The PREMIER Study is a completed 18-month multicenter randomized trial that was designed to test the effect of 2 behavioral interventions on blood pressure (BP) in adults with prehypertension or stage I hypertension (systolic BP, 120-159 mm Hg; diastolic BP, 80-95 mm Hg). Participants were eligible if they were not taking antihypertensive agents and had systolic BP of 120-159 mm Hg or diastolic BP of 80-95 mm Hg. Exclusion criteria included use of BP medications, weight-loss or steroid medications, diabetes, decreased kidney function (estimated glomerular filtration rate <60 mL/min using the Cockcroft-Gault equation), history of a cardiovascular event, congestive heart failure, angina, cancer diagnosis or treatment in the past 2 years, consumption of more than 21 alcoholic drinks per week, and pregnancy. More detailed information about the study methods and main results have been published.³⁰

Eligible participants were randomly assigned to 1 of 3 groups: (1) an "established" group that received behavioral counseling on achieving weight loss of at least 15 lb at 6 months (for those with body mass index ≥ 25 kg/m²), engaging in 180 or more minutes per week of moderate-intensity physical activity, and consuming ≤ 100 mEq/d of dietary sodium; (2) an "established-plus-Dietary Approaches to Stop Hypertension (DASH)" group that received the same recommendations as the established group and counseling on the DASH dietary pattern; and (3) an "advice-only" comparison group that received a single 30-minute individual advice

session at the time of randomization with verbal and written instructions on weight loss, increasing physical activity, sodium reduction, and the DASH dietary pattern. Both the established and established-plus-DASH groups received group counseling weekly for the first 8 weeks, then biweekly through 6 months, that emphasized reduced total caloric intake and increased physical activity. The established group did not have goals for fruit, vegetable, and dairy intake; goals for saturated fat and total intake were set at $\leq 10\%$ and $\leq 30\%$ of energy intake, respectively. The established-plus-DASH group received additional instruction on following the DASH dietary pattern, which emphasized increased consumption of fruits and vegetables (9-12 servings daily), low-fat dairy products (2-3 servings daily), and reduced intake of saturated ($\leq 7\%$ of energy) and total fats ($\leq 25\%$ of energy).

Measurements

Baseline and 6-month measurements were obtained by staff who were masked to randomization assignment. BP measurements were obtained by trained certified individuals using a random-zero sphygmomanometer following a standardized protocol.⁹ All baseline BP measurements were obtained before randomization. BP at baseline and 6 months was defined as an average of 6-8 readings.

Twenty-four-hour urine collections were obtained at the baseline and 6-month visits. Collections with urine volume <500 mL or collection period less than 22 or more than 26 hours were repeated. Urinary sodium, potassium, phosphorus, urea nitrogen, and creatinine were measured in a central laboratory on a Hitachi 917 analyzer using Roche reagents. Albumin was measured on urine samples that were stored at -70°C for 3-5 years before analysis using a Tina-Quant (Roche) albumin assay. All urine laboratory values were standardized to 24-hour measurements. Dietary protein intake was estimated using the Maroni equation³¹⁻³⁴: estimated protein intake = [urinary urea nitrogen + (weight in kg \times 0.031 g nitrogen/kg/d)] \times 6.25.

Blood samples for measurement of glucose, insulin, and lipids were obtained by venipuncture in the morning after an overnight fast. Weight was measured to the nearest 0.1 kg twice at each study visit and averaged, using a calibrated scale with individuals in light indoor clothing and no shoes. Height was measured using a wall-mounted stadiometer. Waist circumference was measured using a tape according to a standardized protocol at baseline and 6 months.

Metabolic syndrome was defined by National Cholesterol Education Program (NCEP) criteria, which required 3 or more of the following: waist circumference >102 cm (men) or >88 cm (women); triglyceride level ≥ 150 mg/dL; high-density lipoprotein cholesterol level <40 mg/dL (men) or <50 mg/dL (women); BP $\geq 130/\geq 85$ mm Hg; and fasting glucose ≥ 110 mg/dL.³⁵ Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula: (glucose \times insulin)/405.³⁶ Supplement use was measured by 2 unannounced 24-hour dietary recalls conducted by telephone interviews (1 on a weekday and the other on a weekend day) only during the baseline visit.

Analysis

Unpaired *t* tests or Pearson χ^2 tests were used to compare continuous and categorical baseline characteristics between individuals with elevated UAE (≥ 10 mg/d) and those without elevated UAE. Median UAE and elevated UAE status at 6 months were compared to the baseline examination using paired *t* test and McNemar test. UAE was natural log transformed due to its skewed distribution and expressed as $\ln(\text{UAE})$ in longitudinal analyses examining associations between changes in waist circumference and dietary biomarkers with change in $\ln(\text{UAE})$. To minimize the influence of over- and undercollection of urine on this analysis, we

only included individuals with 24-hour urine creatinine coefficients of variation (CVs) <25%, which is the upper limit of the intraindividual CV found in previous studies.³⁷ This substantially improved correlation between the baseline and 6-month 24-hour urine creatinine measurements from 0.65 to 0.85.

Covariates including age, sex, race, cohort (participants were recruited in 4 waves), site, current smoking, treatment group assignment, baseline systolic BP, ln(UAE), and metabolic syndrome were considered in our base model, which was created using backwards stepwise regression, retaining variables with $P < 0.1$. We then created separate models adding change in waist circumference and each dietary measure (estimated protein intake and 24-hour urinary sodium, potassium, sodium to potassium ratio, and phosphorus) individually to the base model. We used waist circumference rather than weight because waist circumference better reflects central adiposity.³⁸ Covariates were standardized in these models to facilitate relative comparisons among regression coefficients. Beta coefficients then were back-transformed and presented as percentage of change in UAE associated with a 1-SD change in the corresponding predictor variable.

We then created multivariable models adding significant predictors ($P < 0.05$) to the base model, which included age, race, site, current smoking, baseline systolic BP, and ln(UAE): multivariable model 1: base model plus change in waist circumference, change in protein intake, and change in 24-hour urine phosphorus excretion; multivariable model 2: base model plus change in waist circumference and change in protein intake; and multivariable model 3: base model plus change in waist circumference and change in 24-hour urine phosphorus excretion. These latter 2 models were constructed because changes in protein intake and 24-hour urine phosphorus excretion were correlated strongly ($r = 0.58$; $P < 0.001$). To test for mediators, we included change in systolic BP and change in HOMA-IR to multivariable model 1. We also tested for effect modification by baseline systolic BP, baseline UAE, and baseline metabolic syndrome by adding relevant interaction terms to multivariable model 1.

Sensitivity analyses were performed using different inclusion criteria: (1) including those with 24-hour urine creatinine CV <40% (instead of 25%), and (2) including individuals with 24-hour urine collections within 30% of expected creatinine values (for men, 22.1 mg/kg; women, 17.2 mg/kg).^{34,39} We also repeated analyses adjusting for self-reported baseline use of calcium and vitamin D supplements. For all analyses, we used complete case analysis, only including participants with complete data for each model using Stata, version 11.1 (StataCorp LP).

RESULTS

Population Characteristics

A total of 810 participants were enrolled in the PREMIER trial, and 598 individuals provided complete 24-hour urine samples at baseline and at the 6-month visit. After exclusion of individuals who had 24-hour urine creatinine CV $\geq 25\%$ ($n = 95$) and individuals missing data for 24-hour urine dietary markers ($n = 16$) or waist circumference ($n = 6$), 481 participants were included in our analyses. A higher proportion of African Americans (42% vs 31%; $P = 0.03$) were excluded due to urine collections with CVs $\geq 25\%$; otherwise, there were no other significant differences between those with adequate and inadequate urine collections. Table 1 lists baseline characteristics by elevated UAE status (≥ 10 mg/d). Individu-

Table 1. Baseline Characteristics by Presence or Absence of Elevated UAE

	Elevated UAE (n = 90)	Normal UAE (n = 391)	P
Age (y)	50.9 ± 8.6	51.0 ± 8.5	0.9
Female sex	57%	62%	0.4
African American	42%	29%	0.02
BMI (kg/m ²)	34.7 ± 6.2	32.5 ± 5.6	0.002
Waist circumference (cm)	114.0 ± 17.6	106.9 ± 14.5	<0.001
SBP (mm Hg)	138.6 ± 9.3	133.9 ± 9.6	<0.001
DBP (mm Hg)	85.5 ± 4.3	84.5 ± 4.1	0.04
Hypertension	51%	34%	0.002
Glucose (mg/dL)	102.4 ± 16.5	99.0 ± 13.9	0.05
Insulin (μU/mL)	17.8 ± 11.3	13.9 ± 9.7	0.001
LDL cholesterol (mg/dL)	136.2 ± 30.9	135.9 ± 34.8	0.9
HOMA-IR	4.7 ± 4.0	3.6 ± 3.6	0.01
Current smoking	9%	3%	0.01
Metabolic syndrome	61%	51%	0.07
24-h UAE (mg/d)	22.0 [13.7-45.2]	3.2 [2.1-5.0]	<0.001
Estimated protein intake ^a (g/d)	95.7 ± 27.3	90.2 ± 24.4	0.06
Urine Na:K ratio	3.2 ± 1.3	2.7 ± 1.2	0.003
24-h urine Na (mmol/d)	198.0 ± 78.3	169.4 ± 69.1	<0.001
24-h urine K (mmol/d)	65.9 ± 22.4	67.5 ± 24.5	0.6
24-h urine P (mg/d)	1007.8 ± 372.4	914.1 ± 325.6	0.02

Note: Elevated UAE is ≥ 10 mg/d. Values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: glucose in mg/dL to mmol/L, $\times 0.05551$; LDL cholesterol in mg/dL to mmol/L, $\times 0.02586$.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; K, potassium; LDL, low-density lipoprotein; Na, sodium; P, phosphorus; SBP, systolic blood pressure; UAE, urinary albumin excretion.

^aEstimated protein intake = (urinary urea nitrogen + 0.031 g nitrogen/kg body weight) $\times 6.25$.

als with elevated UAE were more likely to be African American, obese, and current smokers and have hypertension. They also had higher mean waist circumference, systolic and diastolic BPs, insulin resistance, 24-hour urine sodium excretion, sodium/potassium ratios, and 24-hour urine phosphorus excretion (Table 1).

Changes in UAE and Measures of Obesity and Diet After 6 Months

After 6 months, median UAE decreased from 4.0 (interquartile range, 2.3-7.4) to 3.0 (interquartile range, 1.9-5.5; $P < 0.001$) with no significant differences between treatment groups. Overall, the proportion of individuals with elevated UAE ≥ 10 mg/d decreased

Table 2. Cross-Tabulation of Baseline and 6-Month UAE Categories

Baseline UAE	6-Month UAE		
	<10 mg/d	10-29.9 mg/d	≥30 mg/d
<10 mg/d	379 (78.8) ^a	11 (2.3) ^b	1 (0.2) ^b
10-29.9 mg/d	37 (7.7) ^c	18 (3.7) ^a	4 (0.8) ^b
≥30 mg/d	4 (0.8) ^c	11 (2.3) ^c	16 (3.3) ^a

Note: N = 481. Values are given as number (percentage).

Abbreviation: UAE, urinary albumin excretion.

^aNo change in UAE category.

^bWorsening in UAE category.

^cImprovement in UAE category.

from 18.7% to 12.7% ($P < 0.001$), and findings were similar using a UAE cutoff of ≥ 30 mg/d (6.4% to 4.4%; $P = 0.03$). When defined in categories of UAE < 10 , 10-29.9, and ≥ 30 mg/d, 52 individuals had improvements in UAE category while 16 individuals changed to worse UAE categories after 6 months (Table 2). Over 6 months, waist circumference changed by a mean of -4.2 ± 6.6 (SD) cm (Table 3). Changes in mean 24-hour urinary sodium (-28.2 ± 71.7 mmol/d), potassium (8.4 ± 27.8 mmol/d), and phosphorus (-27.7 ± 314.1 mg/d) excretion and protein intake (-1.7 ± 19.4 g/d) also were observed.

Associations Between Changes in Obesity and Dietary Measures With Change in ln(UAE)

Table 4 shows percentage changes in UAE for every 1-SD decrease in predictors in an analysis adjusted for age, site, African American race, current smoking, baseline systolic BP, and baseline ln(UAE). In individual models, every 1-SD reduction (6.6 cm) in waist circumference was associated with a -10.9% change (95% confidence interval [CI], -16.6% to -5.2% ; $P = 0.001$) in UAE; every 1-SD reduction in 24-hour urine phosphorus (314 mg/d) and protein intake (19 g/d) was associated with -10.9% (95% CI, -16.4% to -4.9% ; $P < 0.001$) and -8.1% (95% CI, -13.9% to -2.0% ; $P = 0.01$) changes in UAE, respectively, in these individual models. Changes in 24-hour urine sodium, potassium, and sodium/potassium ratio were not associated significantly with changes in UAE (Table 4).

In multivariable model 1, decreases in waist circumference (-9.9% change in UAE per 1-SD decrease; 95% CI, -15.6% to -3.8% ; $P = 0.002$) and 24-hour urine phosphorus (-8.2% change in UAE per 1-SD decrease; 95% CI, -15.2% to -0.6% ; $P = 0.03$) remained significantly associated with change in UAE, whereas decrease in estimated protein intake was not (Table 5). The association between decrease in 24-hour urine phosphorus and change in UAE was slightly

stronger (-9.8% change in UAE per 1-SD decrease; 95% CI, -15.4% to -3.8% ; $P = 0.002$) in multivariable model 2, which does not include change in protein intake ($r = 0.58$; $P < 0.001$ for correlation with 24-hour urine phosphorus). Decrease in protein intake was associated significantly with a -7.7% change in UAE per 1-SD decrease (95% CI, -13.4% to -1.5% ; $P = 0.02$) in multivariable model 3, which does not include change in 24-hour urine phosphorus (Table 3). Thus, the association between protein intake and UAE was largely explained by 24-hour urine phosphorus, whereas the association between 24-hour urine phosphorus and UAE was not explained solely by protein intake. When changes in systolic BP or insulin resistance were added to multivariable model 1, decreases in waist circumference and 24-hour urine phosphorus remained significantly associated with reductions in UAE.

In tests for interaction, we found that the effect of decreased waist circumference on change in UAE was modified by baseline metabolic syndrome ($P = 0.01$) and baseline UAE ($P = 0.02$), but not baseline systolic BP ($P = 0.5$; Fig 1). In subgroup analyses adjusted for the same covariates as multivariable model 1, individuals in the highest tertile of baseline UAE (≥ 5.5 mg/d) had a -16.4% (95% CI, -25.1% to -6.8% ; $P = 0.001$) change in UAE for every 1-SD decrease in waist circumference compared to -6.9% (95% CI, -15.7% to 2.8% ; $P = 0.2$) for the middle tertile (2.7-5.4 mg/d) and -4.9% (95% CI, -15.6% to 7.1% ; $P = 0.4$) for the lowest tertile (< 2.7 mg/d) of baseline UAE. Similarly, individuals who had metabolic syndrome at baseline had a -17.2% (95% CI, -23.9% to -9.9% ; $P < 0.001$) change in UAE for every 1-SD decrease in waist circumference, whereas no association ($P = 0.8$) was observed for individuals without metabolic syndrome. Baseline metabolic syndrome, baseline UAE, and baseline systolic BP did

Table 3. Changes in Obesity and Dietary Measures Over 6 Months

Measure	Change
Waist circumference (cm)	-4.2 ± 6.6
Weight (kg)	-4.3 ± 5.4
24-h urine Na (mmol/d)	-28.2 ± 71.7
24-h urine K (mmol/d)	$+8.4 \pm 27.8$
24-h urine P (mg/d)	-27.7 ± 314.1
Urine Na:K ratio	-0.58 ± 1.31
Estimated protein intake (g/d) ^a	-1.7 ± 19.4

Note: Values are given as mean \pm standard deviation.

Abbreviations: K, potassium; Na, sodium; P, phosphorus.

^aEstimated protein intake = (urinary urea nitrogen + 0.031 g nitrogen/kg body weight) \times 6.25.

Table 4. Changes in UAE Associated With Decreases in Waist Circumference and Dietary Measures

Decrease	Individual Models		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
	ΔUAE (95% CI)	P	ΔUAE (95% CI)	P	ΔUAE (95% CI)	P	ΔUAE (95% CI)	P
Waist circumference (per 6.6 cm)	-10.9 (-16.6 to -5.2)	0.001	-9.9 (-15.6 to -3.8)	0.002	-9.9 (-15.4 to -3.8)	0.002	-10.6 (-16.3 to -4.6)	0.001
24-h urine P (per 314.1 mg/d)	-10.9 (-16.4 to -4.9)	<0.001	-8.2 (-15.2 to -0.6)	0.03	-9.8 (-15.4 to -3.8)	0.002		
Protein intake (per 19.4 g/d)	-8.1 (-13.9 to -2.0)	0.01	-2.9 (-10.3 to 5.0)	0.5			-7.7 (-13.4 to -1.5)	0.02
24-h urine Na (per 71.7 mmol/d)	-4.7 (-10.7 to 1.7)	0.1						
24-h urine K (per 27.8 mmol/d)	-2.3 (-8.5 to 4.4)	0.5						
Na:K ratio (per 1.3 mmol/mmol)	-1.5 (-7.8 to 5.1)	0.6						

Note: N = 481. Each model was adjusted for age, site, African American race, current smoking, baseline systolic blood pressure, and ln(UAE). Covariates were standardized in these models to facilitate relative comparisons between regression coefficients. Beta coefficients were then back-transformed and are presented as percent change in UAE associated with a 1-SD decrease in the corresponding predictor variable.

Abbreviations and definitions: CI, confidence interval, ΔUAE, change in UAE; K, potassium; Na, sodium; P, phosphorus; UAE, urinary albumin excretion.

not modify the effect of changes in 24-hour urine phosphorus or protein intake on UAE.

Sensitivity analyses using different inclusion criteria (24-hour urine creatinine CV <40%; 24-hour urine creatinine values within 30% of expected sex-specific values^{34,39}) showed similar effect sizes and associations as our primary analysis, as did analyses in which we adjusted for baseline calcium and vitamin D supplement use (data not shown).

DISCUSSION

In this cohort of mostly overweight and obese individuals with prehypertension or stage I hypertension and normal kidney function, we found that reductions in waist circumference and 24-hour urine phosphorus excretion were associated significantly with decreases in UAE. Our findings suggest that reducing central adiposity and phosphorus intake could be an important strategy in reducing UAE. In our study, the association between change in waist circumference and UAE was greatest in those with baseline metabolic syndrome and higher baseline UAE. This latter finding is consistent with a meta-analysis of 5 controlled and 8 uncontrolled trials (n = 528 participants) evaluating the effect of weight loss on UAE and proteinuria.¹¹ Unlike most of these previous studies, our study was strengthened by having repeated 24-hour urine sodium, urea nitrogen, and phosphorus measurements. Thus, we were able to examine the impact of changes in diet as well as changes in central obesity on UAE.

Table 5. Multivariable Model 1 Adjusted for Potential Mediators

Decrease	ΔUAE (95% CI)	P
Waist circumference (per 6.6 cm)	-10.5 (-16.6 to -4.0)	0.002
24-h urine P (per 314.1 mg/d)	-8.6 (-15.6 to -1.0)	0.03
Protein intake (per 19.4 g/d)	-2.9% (-10.4 to 5.1)	0.5
SBP (per 9.2 mm Hg)	+1.7 (-5.3 to 9.3)	0.6
HOMA-IR (per 3.2 U)	+3.3 (-3.2 to 10.3)	0.3

Note: n = 473. Potential mediators are changes in SBP and HOMA-IR. Adjusted for age, site, African American race, baseline SBP, current smoking, and baseline ln(UAE). Covariates were standardized in these models to facilitate relative comparisons between regression coefficients. Beta coefficients were then back-transformed and are presented as percent change in UAE associated with a 1-SD decrease in the corresponding predictor variable.

Abbreviations and definitions: CI, confidence interval; ΔUAE, change in UAE; HOMA-IR, homeostasis model assessment of insulin resistance; P, phosphorus; SBP, systolic blood pressure; UAE, urinary albumin excretion.

phorus excretion were associated significantly with decreases in UAE. Our findings suggest that reducing central adiposity and phosphorus intake could be an important strategy in reducing UAE. In our study, the association between change in waist circumference and UAE was greatest in those with baseline metabolic syndrome and higher baseline UAE. This latter finding is consistent with a meta-analysis of 5 controlled and 8 uncontrolled trials (n = 528 participants) evaluating the effect of weight loss on UAE and proteinuria.¹¹ Unlike most of these previous studies, our study was strengthened by having repeated 24-hour urine sodium, urea nitrogen, and phosphorus measurements. Thus, we were able to examine the impact of changes in diet as well as changes in central obesity on UAE.

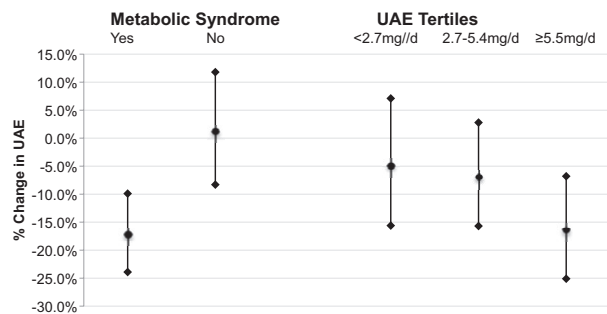


Figure 1. Effect of decreased waist circumference on urine albumin excretion (UAE) was modified by baseline metabolic syndrome and baseline UAE. Changes in UAE (95% confidence interval) associated with a 1-SD decrease (6.6 cm) in waist circumference stratified by baseline metabolic syndrome and UAE tertile are shown. All models adjusted for age, site, African American race, baseline systolic blood pressure, current smoking, baseline ln(UAE), changes in protein intake, and 24-hour urine phosphorus excretion. P < 0.05 for both interactions (baseline metabolic syndrome and baseline UAE as a continuous variable) on change in waist circumference.

The significant association we observed between changes in 24-hour urine phosphorus and UAE is novel and needs to be confirmed in other studies. These findings could reflect changes in total phosphorus intake, the sources of phosphorus being consumed, or less likely, changes in gut absorption or bone metabolism. In a normal physiologic state, 24-hour urine phosphorus should approximate gut absorption of phosphorus.^{29,40} However, the bioavailability of phosphorus can be affected by vitamin D and calcium supplements,^{41,42} as well as the source of phosphorus. For example, inorganic phosphorus salts are believed to have much higher bioavailability (90%-100%) than naturally occurring forms of phosphorus (40%-60%),⁴³⁻⁴⁵ and food additives have been estimated to contribute up to 30% of the phosphorus consumed in the US diet.⁴³ Phosphorus derived from animal protein typically is more bioavailable than vegetable protein because ~75% of plant protein exists as phytate, which is not readily digestible by humans.⁴⁶ Feeding studies have shown that there is lower 24-hour urinary phosphorus excretion while eating a diet with equivalent amounts of phosphorus from vegetable protein compared to animal protein, although no stool collections were done in these studies to confirm that this was due to differences in gut absorption.^{45,47} Thus, changes in 24-hour urine phosphorus excretion could be due to changes in the proportions of phosphorus derived from food processing, animal, and vegetable sources.

Cross-sectional studies have shown that UAE is highest in omnivores and lowest in vegans,⁴⁸ and crossover studies of individuals with normal kidney function⁴⁹ and individuals with diabetic nephropathy⁵⁰ have found lower rates of UAE while on vegetable protein diets compared with animal protein diets. Whether high protein intake of any type can cause long-term harm in individuals with normal kidney function remains unclear.^{23,24,33} A secondary analysis of OmniHeart (Optimal Macronutrient Intake Trial to Prevent Heart Disease), a randomized crossover feeding trial testing the effects of different macronutrient profiles on BP and lipid levels, found that a high-protein diet (25% total calories) increased estimated glomerular filtration rate independent of changes in BP compared with the other 2 diets with lower protein (15% total calories).²⁴ In a randomized trial comparing a prescribed low-carbohydrate high-protein weight-loss diet to a prescribed low-fat weight-loss diet, creatinine clearance was increased significantly at 3 months and 1 year (when adherence likely was greatest) in the low-carbohydrate high-protein diet group compared to the low-fat diet group.²² However, the long-term effects of glomerular hyperfiltration related to high protein intake are unknown;

studying the effects of diet on hard kidney disease or cardiovascular outcomes in a trial would require many years of follow-up or a high-risk population. Secondary analyses of the MDRD (Modification of Diet in Renal Disease) Study and a meta-analysis of dietary protein restriction studies suggest that restricting dietary protein intake may slow glomerular filtration rate decline in individuals with CKD.^{51,52}

Although a direct causal link between excess dietary phosphorus intake and UAE remains speculative, *in vitro* and *in vivo* studies in animals and humans provide some supportive evidence that excess dietary phosphorus could have a detrimental effect on the endothelium. Bovine aortic endothelial cells exposed to higher phosphorus concentrations have been shown to have increased reactive oxygen species production and decreased nitric oxide production.⁵³ These authors also reported that healthy volunteers who consumed a meal with 1,200 mg of phosphorus (800 mg as sodium phosphate supplement) developed postprandial impaired flow-mediated dilatation, which correlated inversely with serum phosphorus levels.⁵³ Observational studies have found that fasting serum phosphorus levels are associated with increased mortality even in individuals without CKD,²⁷ and the phosphaturic hormone fibroblast growth factor 23 (FGF-23) is associated with albuminuria, CKD progression,⁵⁴ incident heart failure, and all-cause mortality.⁵⁵ However, self-reported dietary phosphorus intake is associated weakly with fasting serum phosphorus levels, making it difficult to extrapolate adverse associations with serum phosphorus to dietary phosphorus intake.⁵⁶

High-phosphorus diets have been shown in animal models of CKD to cause renal injury (independent of protein intake).²⁵ Studies of reducing phosphorus intake in humans have been largely confounded by concomitant reductions in protein intake.²¹ However, one nonrandomized study of protein restriction in proteinuric patients with CKD found an interaction between 24-hour urine phosphorus excretion and the antiproteinuric effect of a very low-protein diet. Individuals in this study who attained lower 24-hour urine phosphorus excretion while on the very low-protein diet (0.3 g/kg supplemented with keto-analogues) experienced greater reductions in proteinuria (*P* for interaction <0.001),⁵⁷ providing some support for our findings.

Our study has a few limitations. First, this is an observational analysis of PREMIER, which was not originally designed to study the effects of behavioral interventions on UAE. Because multiple lifestyle factors changed simultaneously during the study, we cannot be certain that the observed associations were directly causal. We found no effect of the behavioral

interventions on UAE, possibly because the advice-only group also lost weight and had the most negative change in protein intake of the 3 groups. Second, we included only 59% of individuals originally randomly assigned in PREMIER, which mainly reflects the difficulty collecting repeated 24-hour urine collections. Third, participants had normal kidney function and most had baseline UAE <10 mg/d, above which seems to confer risk of cardiovascular disease and mortality.¹⁻⁵ Although reduction in albuminuria is associated with decreased risk of kidney and cardiovascular disease,^{6,7} the effect of changes in UAE in this low range are unknown. Last, we adjusted for baseline supplement use in sensitivity analyses, but did not have information for changes in levels of parathyroid hormone, vitamin D, or FGF-23. Although we cannot definitively exclude the possibility that changes in 24-hour urine phosphorus excretion were due in part to changes in phosphorus metabolism rather than dietary intake, we believe this possibility is unlikely in individuals with normal kidney function. Strengths of our study include repeated dietary measurements based on 24-hour urine dietary biomarkers in a well-characterized cohort and the wide generalizability of our study because individuals with prehypertension or stage I hypertension make up approximately two-thirds of the US population.

In conclusion, our findings suggest that reducing excess adiposity and phosphorus intake may be important in lowering UAE. More research is needed to understand determinants of phosphorus absorption and excretion and whether excessive dietary phosphorus intake could be harmful to individuals with normal kidney function.

ACKNOWLEDGEMENTS

We thank the PREMIER participants for their dedication; Gayle Meltesen, Alan Bauck, and Dave Gibson for assistance in obtaining the laboratory data; and Gayane Yenokyan for reviewing an early draft.

Support: Dr Chang was supported by the National Institute of Diabetes and Digestive and Kidney Diseases grant T32DK007732.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

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