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Original Investigation

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 ± 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(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(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(UAE); specifically, individuals with higher UAE and baseline metabolic syndrome experienced greater reductions in ln(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.

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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 adiposity[8-12] 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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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/m^2), 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 equation[31-34]: 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(UAE) in longitudinal analyses examining associations between changes in waist circumference and dietary biomarkers with change in ln(UAE). To minimize the influence of over- and undercollection of urine on this analysis, we