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Plant Protein Intake Is Associated with Fibroblast Growth Factor 23 and Serum Bicarbonate in Patients with CKD: The Chronic Renal Insufficiency Cohort Study

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Abstract

Background—Protein from plant, as opposed to animal, sources may be preferred in chronic kidney disease (CKD), due to lower bioavailability of phosphate and lower nonvolatile acid load.

Study Design—Observational cross-sectional study.

Setting & Participants—2938 participants with chronic kidney disease and information on dietary intake at the baseline visit in the Chronic Renal Insufficiency Cohort Study.

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Predictors—Percentage of total protein from plant sources (% plant protein) was determined by scoring individual food items from the National Cancer Institute Diet History Questionnaire (DHQ).

Outcomes—Metabolic parameters, including serum phosphate, bicarbonate (HCO_3), potassium, and albumin, plasma fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), and hemoglobin.

Measurements—We modeled the association between % plant protein and metabolic parameters using linear regression. Models were adjusted for age, sex, race, diabetes, body mass index, eGFR, income, smoking, total energy intake, total protein intake, 24 hour urinary sodium, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and use of diuretics.

Results—Higher % plant protein was associated with lower FGF23 (p=0.05) and higher HCO_3 (p=0.01), but not with serum phosphate or PTH (p=0.9 and 0.5, respectively). Higher % plant protein was not associated with higher serum potassium (p=0.2), lower serum albumin (p=0.2) or lower hemoglobin (p=0.3). The associations of % plant protein with FGF23 and HCO_3 did not differ by diabetes status, sex, race, CKD stage (2/3 vs. 4/5) or total protein intake (≤ 0.8 g/kg/d vs. >0.8 g/kg/d) (p-interaction > 0.10 for each).

Limitations—Cross-sectional study; Determination of % plant protein using the DHQ has not been validated.

Conclusions—Consumption of a higher percentage of protein from plant sources may lower FGF23 and raise HCO_3 in patients with CKD.

Keywords

chronic kidney disease; nutrition; mineral metabolism; acidosis

Introduction

High dietary protein intake may adversely affect metabolic parameters in patients with chronic kidney disease (CKD) due to high loads of phosphate and nonvolatile acid [1–3]. Although reduced overall protein intake may slow CKD progression and improve metabolic parameters in patients with CKD, this may be difficult to achieve and sustain in practice [4–7]. In addition, there is concern among nephrologists that low protein diets may place patients at risk for protein energy malnutrition, a strong risk factor for death in patients as they approach end stage renal disease (ESRD) [8–10].

Protein derived from plant sources, as compared with animal sources, may have less adverse impact on metabolic risk factors in CKD [11, 12]. Phosphate from plant-based proteins is complexed in the form of phytic acid, which is less digestible in humans and thus, is less bioavailable, than animal-based proteins [11, 13]. A recent, small feeding study of 9 patients with CKD demonstrated that consuming a vegetarian, as opposed to a meat-based diet, resulted in reduced levels of serum phosphate and fibroblast growth factor 23 (FGF23) [12]. These findings require confirmation in a larger, more diverse patient population consuming a range of diets. Additionally, sulfate containing amino acids, which contribute directly to nonvolatile acid load, are more abundant in animal-based, as opposed to plant-based proteins [14]. For this reason higher relative consumption of plant-based proteins may lower the nonvolatile acid load, and may improve serum bicarbonate levels, but this has not been previously studied.

In this study, we evaluated the association between the percentage of protein intake from plant sources and metabolic risk factors for adverse outcomes in CKD, such as serum

phosphate, FGF23, parathyroid hormone (PTH), and serum bicarbonate in a large, diverse cohort of patients with CKD consuming their usual diets.

Methods

Study Population

The Chronic Renal Insufficiency Cohort (CRIC) study is a prospective cohort study which enrolled 3612 adult participants (ages 21 to 74 years) with mild to moderate CKD (eGFR 20 to 70 mL/min/1.73 m^2) across seven clinical centers in the United States between 2003 and 2006. Exclusion criteria included institutionalization, inability to give informed consent, pregnancy, polycystic kidney disease, previous treatment with dialysis for greater than 1 month, and other severe medical conditions (New York Heart Association class III or IV heart failure, cirrhosis, HIV/AIDS, previous organ or bone marrow transplant, immunotherapy for renal disease or vasculitis within past 6 months, previous chemotherapy for systemic cancer in last 2 years, previous multiple myeloma or renal carcinoma), as previously described [15]. To increase representation of Hispanics, an additional 327 participants were enrolled from a single center between January 2006 and October 2008 as part of an ancillary study (HCRIC). Of all CRIC and HCRIC participants, 2938 with a dietary assessment available at study baseline were included in this analysis. This study was purely observational in nature. Participants did not undergo any dietary modification or receive dietary advice from the study staff as a component of CRIC. The study protocol was approved by all participating centers and participants provided written informed consent.

Data Collection

Dietary assessment was performed at the first study visit using a previously validated food frequency questionnaire, the National Cancer Institute Diet History Questionnaire (DHQ). Dietary intakes were estimated from participant responses using Diet*Calc software [16]. To determine the relative contribution of plant and animal protein sources to total protein intake, 255 foods from the DHQ were evaluated by two independent investigators (JJS, CAMA). The percentage of animal protein in a given food item was estimated by referring to common recipes or dominant national brands, in the case of pre-packaged foods. Disagreement between reviewers was resolved through consensus. The percentage of animal protein attributed to the food item was then multiplied by the total protein content of the food in grams to determine the total animal protein content in grams. The remaining protein was assigned as the total plant protein content. Estimated daily animal and plant protein intakes were determined for each participant and expressed as a percentage of total daily protein intake.

Laboratory parameters were measured at the first study visit in a central laboratory. Plasma PTH was measured using a total intact assay (Scantibodies, Santee, CA). Plasma FGF23 was measured using a second generation C-terminal assay (Immutopics, San Clemente, CA; intra-assay coefficient of variation <5%). Routine laboratories including serum creatinine, bicarbonate, potassium, phosphate, and albumin, hemoglobin and urinary sodium, potassium and phosphate were measured using standard clinical assays. Glomerular filtration rate was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17].

Sociodemographics, medical history, and body mass index were assessed at study baseline. Diabetes was defined as fasting glucose ≥ 126 mg/dL and/or the use of insulin or oral hypoglycemic medications. Active vitamin D sterols included calcitriol, doxercalciferol and paricalcitol. Phosphate binding medications included calcium as well as non-calcium based

binders. Alkali supplements included compounds containing calcium citrate, sodium bicarbonate, sodium citrate, and potassium citrate.

Statistical Analysis

The distributions of the exposure variable (i.e. percentage of protein from plant sources) and all outcome variables (serum phosphate, plasma FGF23, 24 hour urine phosphate, PTH, serum bicarbonate, serum albumin, serum potassium and hemoglobin) were assessed for normality and outliers. FGF23 and PTH were log transformed to approximate a normal distribution. The percentage of protein from plant sources was categorized in quintiles. Characteristics of the study population were compared across quintiles of the percentage of protein from plant sources using ANOVA (continuous variables) or Chi-square test (categorical variables).

The association between the percentage of protein from plant sources and all outcome variables was modeled using linear regression with the percentage of protein from plant sources treated as both a continuous and categorical variable. Models were adjusted for potential confounders identified *a priori* including age, sex, race, diabetes, body mass index, eGFR, income, smoking, total energy intake, total protein intake, 24 hour urinary sodium, use of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and use of diuretics. Pre-specified interactions were explored between the percentage of protein from plant sources and diabetic status, sex, race, CKD stage (2 and 3 vs. 4 and 5) and total dietary protein intake (≤ 0.8 g/kg/d vs. >0.8 g/kg/d) using stratified models and formally tested by putting interaction terms in the model. As a sensitivity analysis these associations were also tested among a subpopulation excluding participants who were using active vitamin D, phosphate binding agents or alkali supplements.

All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Overall, the study population consisted of 45% diabetics, the mean age was 58 years (range 21 to 75 years), and the median eGFR was 44 mL/min/1.73 m^2 (interquartile range 34 to 55 mL/min/1.73 m^2). Fifteen percent of participants had stage 2 CKD, 67% stage 3 CKD, 17% stage 4 CKD and 0.1% stage 5 CKD. Median total protein intake in the study population was 63.7 g/day (interquartile range 45.4 to 88.0 g/day) with median of 0.7 g/kg/day after scaling to body weight (interquartile range 0.5 to 1.0 g/kg/day). Median intake of protein from animal sources was 41.8 g/day (interquartile range 28.0 to 61.1 g/day) and from plant sources was 20.7 g/day (interquartile range 14.9 to 28.8 g/day), resulting in a median percentage of total protein from plant sources (percent plant protein) of 33% (interquartile range 26 to 41%).

Characteristics of the study population stratified by quintiles of percent plant protein are presented in Table 1. Quintiles of percent plant protein were associated with many demographic variables, but were not strongly associated with either comorbid diseases, such as diabetes (p=0.12), cardiovascular disease (p=0.75), or hypertension (p=0.19), or with severity of CKD based on eGFR (p=0.64). Percent plant protein intake was associated with greater use of phosphate binders and active vitamin D sterols, although use of these medications was low in this cohort with only 7.4% using phosphate binders and 3.4% using active vitamin D overall.

Higher percent plant protein was strongly associated with other dietary intake variables including higher percentage of calories from carbohydrate, lower percentage of calories from protein, fat, and saturated fat, and lower intake of total calories, sodium and phosphate.

Adjustment for total energy intake substantially attenuated the difference across quintiles for many correlated nutrients, such as sodium and phosphate (Table 2).

In unadjusted analyses, higher percent plant protein were strongly associated with 24 hour urinary phosphate (Table 3; p<0.001). Percent plant protein was no longer associated with 24 hour urinary phosphate after adjustment for demographics, total energy intake and total protein intake (p=0.24). Higher percent plant protein was not associated with serum phosphate, FGF23, or PTH in univariate analyses (Table 3). There was a marginal graded association between higher percent plant protein and higher serum bicarbonate (p=0.07). Table 4 presents associations between percent plant protein and metabolic parameters after adjustment for age, sex, race, diabetes, body mass index, eGFR, income, smoking, total energy intake, total protein intake, 24 hour urinary sodium, use of ACE inhibitors/ARBs, and use of diuretics. Higher percent plant protein intake was associated with lower FGF23 (p=0.05) and higher serum bicarbonate (p=0.01), but not with serum phosphate or PTH (p=0.9 and 0.5, respectively). The associations of percent plant protein with FGF23 (Figure 1) and serum bicarbonate (Figure 2) did not differ by diabetes status, sex, race, CKD stage (2 and 3 vs. 4 and 5) or total dietary protein intake (≤ 0.8 g/kg/d vs. >0.8 g/kg/d) (p-interaction > 0.10 for each). Results were similar in a sensitivity analysis excluding participants on alkali supplements, phosphate binders and active vitamin D sterols (n=2608; supplemental table 1), although the association between percent plant protein and FGF23 was no longer significant (p=0.07) due to a loss of statistical power. There was no association of higher percent plant protein with adverse metabolic consequences such as higher serum potassium (p=0.2), lower serum albumin (p=0.2) or lower hemoglobin (p=0.3).

Discussion

In this multicenter, multi-ethnic study of participants across the full spectrum of CKD, we found that a greater percentage of dietary protein intake from plant sources was associated with better metabolic parameters, including higher serum bicarbonate and lower FGF23. FGF23 is a circulating hormone which increases the fractional excretion of phosphate in the urine and inhibits 1-alpha hydroxylase activity, thereby maintaining phosphate homeostasis in the setting of decreased GFR [18, 19]. Circulating levels of FGF23 become elevated earlier in CKD than serum phosphate, suggesting it may be a more sensitive biomarker of abnormal phosphate metabolism and a possible inciting factor in the development of secondary hyperparathyroidism [20–22]. Critically, recent observational studies report that FGF23 is among the most potent risk factors for death among patients with CKD, making it an attractive target for preventive strategies in this patient population [23].

Previous physiologic studies have demonstrated that changes in FGF23 can be induced by altering phosphate intake [24–28]. Importantly, many of these studies utilized inorganic phosphate supplements, a highly bioavailable source of phosphate, to induce phosphate loading. This may have resulted in differences in bioavailable phosphate between feeding periods which are more dramatic than differences between whole food diets. Other studies which have modulated phosphate intake using whole food diets have shown conflicting results [29, 30]. Recently, a feeding study in 9 patients with CKD demonstrated that consuming a vegetarian diet compared with a meat based diet for 7 days lowered FGF23 [12]. Our results build on these prior findings by observing that even if not strictly vegetarian, higher intake of plant-based compared with animal-based protein is associated with lower FGF23. Consistent with these prior experimental studies, our findings suggest that a diet with greater predominance of plant-based protein may lower FGF23, a potent risk factor for mortality in CKD.

Although we observed that the percentage of plant protein intake was associated with FGF23 levels, we did not observe an association with serum phosphate. Similar results have been seen in some feeding studies demonstrating that low phosphate diets can lower FGF23 without affecting serum phosphate [24]. This is likely due to tight physiologic regulation of serum phosphate by FGF23 and potentially other phosphotonins [31]. In this study, urinary phosphate excretion was strongly associated with percent plant protein in univariate analyses, but not after adjustment for energy and total protein intake. Given our hypothesis that bioavailable phosphate is lower on a plant-based diet, this finding was unexpected. In this study we used the DHQ to ascertain habitual dietary intake over one year. In contrast, 24 hour urinary phosphate represents dietary intake over a period of days which may be only weakly correlated with habitual intake due to day to day variation in diet. Differences in the period of assessment using a food frequency questionnaire (i.e. long term habitual intake) versus a urinary biomarker (i.e. short term intake) may explain the lack of robust association between 24 hour urinary phosphate and plant protein intake.

Another key finding of this study was the association between greater percentage of protein from plant sources and higher serum bicarbonate levels. Previous observational studies have shown that serum bicarbonate levels associate with the nonvolatile acid load of the diet (i.e. net endogenous acid production) which is determined in part by total dietary protein intake [32, 2, 33]. This study builds on those findings and suggests that a higher intake of protein from plant, compared with animal sources, may further raise serum bicarbonate, presumably due to the lower sulfate content of plant-based proteins [14]. This finding has clear clinical relevance in CKD given recent observational and experimental studies demonstrating that higher serum bicarbonate levels may lower risk for CKD progression and mortality [34–38].

In addition to its potential benefits on phosphate and acid-base homeostatsis, a higher intake of plant-based foods has theoretical risks in patients with kidney disease due to a high potassium content [39] and inhibition of iron absorption by phytic acid [40]. In this study we did not observe associations between a higher intake of protein from plant sources and serum potassium or hemoglobin. It is important to note that we did not have information on the use of iron supplements, or indices of iron stores, such as ferritin or transferrin saturation, making it difficult to fully exclude an adverse association with iron absorption. We also did not observe an association between a greater percentage of protein from plant sources and lower serum albumin, a serologic marker of malnutrition.

Although we noted associations between higher relative intake of plant-based protein and more favorable levels of both FGF23 and serum bicarbonate, we acknowledge that the magnitude of the associations observed in this study were small. We believe the true associations between these factors may be underestimated in this study due to the relatively crude nature of dietary assessment in large population-based studies, and the use of only single measures of outcome variables, which may vary over time. Food frequency questionnaires are known to underestimate true dietary protein intake and correlate moderately with gold standard measures of dietary protein, such as weighed dietary records and dietary biomarkers [41]. The CRIC study did not include a dietary validation, therefore we were unable to calibrate for measurement error, as frequently performed in studies of dietary intake [42]. In addition, the observed interquartile range of percentage of protein from plant sources was 26% to 41%, values comparable to previously reported studies [43, 44]. Within the range of the observed data, the magnitude of these associations was relatively small, however the magnitude of effect may be much larger if our study population had included more participants with a greater predominance of plant-based protein (i.e. 90% protein from plant sources).

Our study had a number of limitations to consider. The food frequency questionnaire that we used in this study, has not been validated in a population with CKD. Additionally, the method we used to allocate protein sources has not been previously validated. We considered protein from a variety of plant sources together in this study, although intestinal phosphate absorption and nonvolatile acid load may differ between different types of plant foods, such as soy and grains. The biological quality of protein also differs between plants and is generally lower among plant protein compared with animal protein[45]. We did not observe an association between plant protein intake and the nutritional marker, serum albumin, however we cannot conclude from this study that there is no adverse impact of a plant-based diet on nutritional status in CKD and this area warrants further investigation. Finally, this is an observational, cross-sectional study, and it limits our ability to make causal inferences about the dietary pattern and the more favorable metabolic profile.

Despite these limitations, this study has many strengths including a large, diverse population of patients across the spectrum of CKD. We used standardized questionnaires for the assessment of habitual dietary intake from which we derived our key exposure variable, as well as several critical confounding variables including total energy intake and total protein intake. Additionally, the study includes comprehensive assessment of other confounding variables including comorbidity, medication usage and other dietary biomarkers (i.e. 24 hour urinary sodium).

In conclusion, we have observed lower levels of FGF23 and higher levels of serum bicarbonate among patients with CKD consuming a greater percentage of dietary protein from plant sources. These relationships were similar across subgroups defined by severity of CKD, diabetic status, race and level of overall protein intake. To our knowledge, this is the first study to document these associations across a range of observed dietary intakes and in a large, diverse patient population. This study suggests that serum bicarbonate and FGF23, both risk factors for morbidity and mortality in CKD, are potentially modifiable by dietary strategies which favor plant-based protein sources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Practical Application

We observed that patients with chronic kidney disease consuming a higher percentage of protein from plant sources had lower levels of fibroblast growth factor 23 and higher serum bicarbonate. Our results indicate that a diet based on plant foods may have metabolic benefits in patients with chronic kidney disease, but the safety of this dietary pattern and impact on nutritional status still need to be determined.

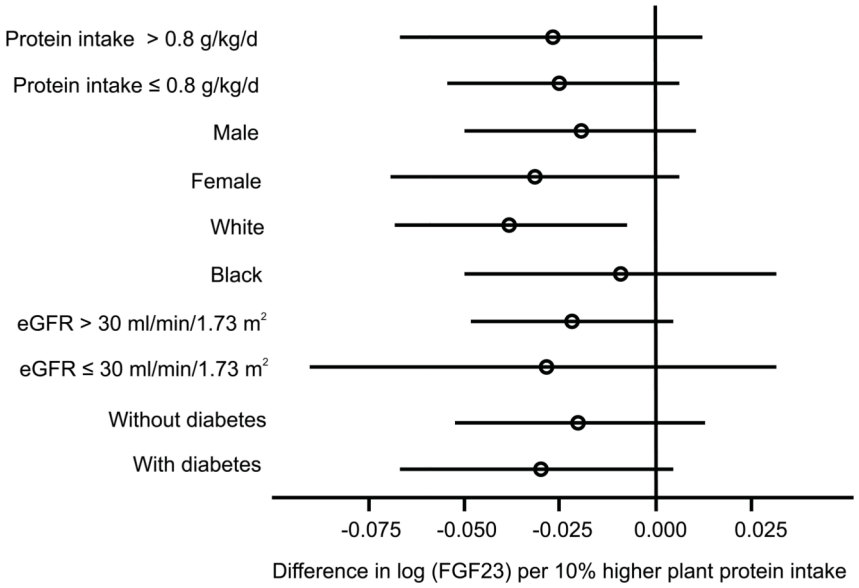

Figure 1.

Forest plot of difference in log fibroblast growth factor 23 (log FGF23) per 10% higher percentage of protein from plant sources across patient subgroups. Circles represent point estimate and bars represent 95% confidence intervals.

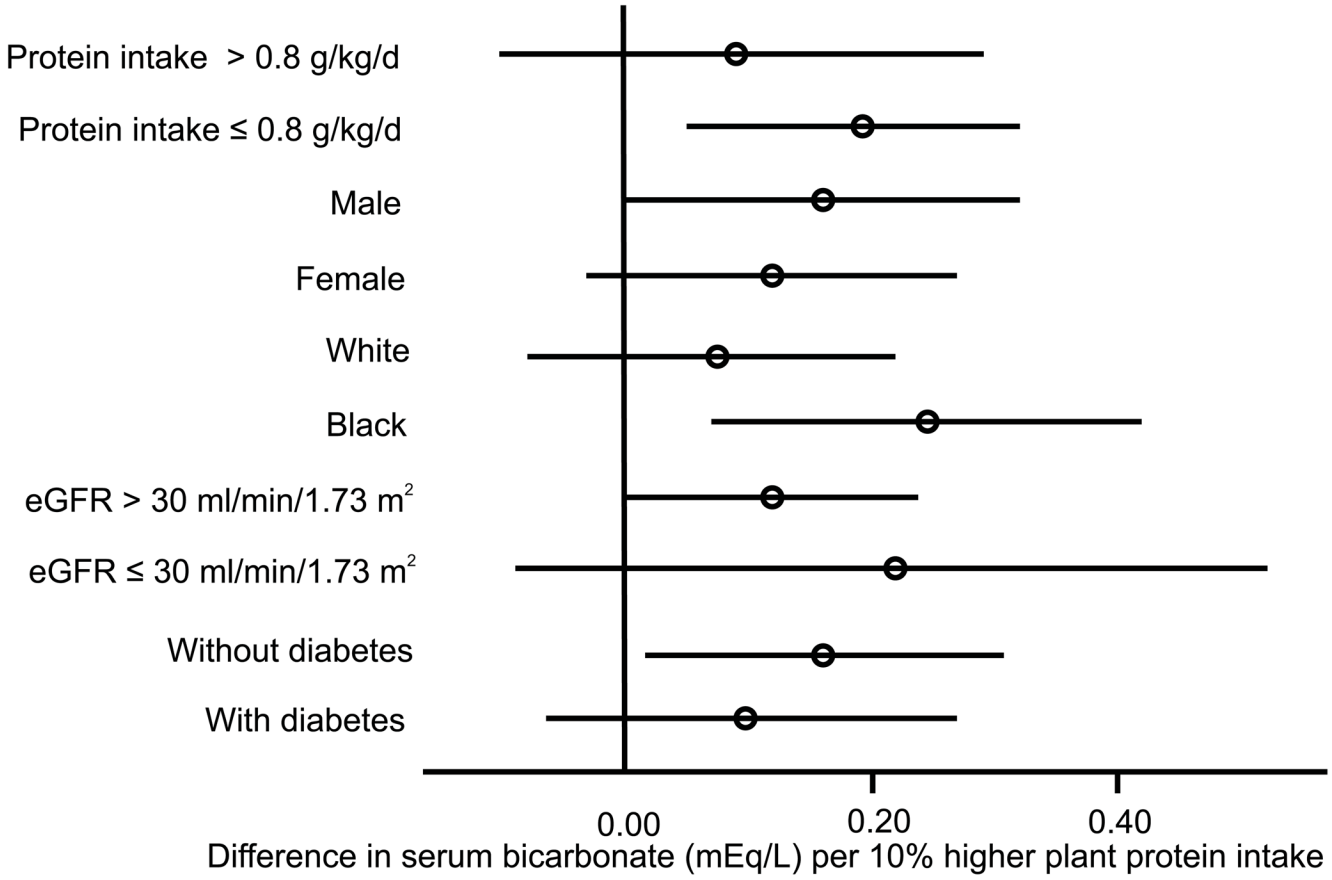

Figure 2.
Forest plot of difference in serum bicarbonate per 10% higher percentage of protein from plant sources across patient subgroups. Circles represent point estimate and bars represent 95% confidence intervals.

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Table 1

Characteristics of study population stratified by quintiles of percentage of total protein intake from plant sources (n=2938)

	Quintiles of Percent Plant Protein					
	1	2	3	4	5	
Characteristic	**<24%**	**24–29%**	**30–35%**	**36–44%**	**>44%**	
Mean ± SD or n (%)	**(n=587)**	**(n=588)**	**(n=588)**	**(n=587)**	**(n=588)**	**P-value**
Demographics						
Age (years)	56.5 ± 11.3	57.8 ± 11.1	58.5 ± 11.3	59.5 ± 9.9	59.6 ± 10.9	<0.001
Female sex	232 (39.5%)	272 (46.3%)	263 (44.7%)	302 (51.4%)	321 (54.6%)	<0.001
Race/ethnicity						<0.001
Non-hispanic white	279 (47.5%)	313 (53.2%)	309 (52.6%)	293 (49.9%)	254 (43.2%)	
Non-hispanic black	257 (43.8%)	248 (42.2%)	228 (38.8%)	248 (42.2%)	249 (42.3%)	
Hispanic	39 (6.6%)	17 (2.9%)	27 (4.6%)	22 (3.7%)	30 (5.1%)	
Other	12 (2.0%)	10 (1.7%)	24 (4.1%)	24 (4.1%)	55 (9.4%)	
Income †						0.02
$20,000 or under	152 (25.9%)	148 (25.2%)	137 (23.3%)	149 (25.4%)	173 (29.4%)	
$20,001– $50,000	146 (24.9%)	152 (25.9%)	145 (24.7%)	144 (24.5%)	152 (25.9%)	
$50,000 – $100,000	124 (21.1%)	117 (19.9%)	144 (24.5%)	137 (23.3%)	105 (17.9%)	
More than $100,000	84 (14.3%)	86 (14.6%)	60 (10.2%)	67 (11.4%)	53 (9.0%)	
Clinical characteristics						
Diabetes	278 (47.4%)	271 (46.1%)	261 (44.4%)	267 (45.5%)	236 (40.1%)	0.12
Cardiovascular disease	199 (33.9%)	188 (32.0%)	184 (31.3%)	202 (34.4%)	189 (32.1%)	0.75
Hypertension	516 (87.9%)	505 (85.9%)	494 (84.0%)	494 (84.2%)	491 (83.5%)	0.19
Body mass index (kg/m^2)	33.2 ± 8.0	32.8 ± 8.2	31.8 ± 7.3	31.9 ± 7.7	30.0 ± 7.3	<0.001
Estimated GFR (mL/min/1.73m^2)	45.6 ± 14.7	45.1 ± 15.5	44.7 ± 15.5	45.3 ± 14.7	44.4 ± 14.7	0.64
Medications						
ACE inhibitors/ARB	411 (70.5%)	422 (72.1%)	401 (68.7%)	390 (66.7%)	385 (65.8%)	0.11
Diuretics	350 (60.0%)	376 (64.3%)	333 (57.0%)	335 (57.3%)	333 (56.9%)	0.05
Active vitamin D sterols	14 (2.4%)	17 (2.9%)	12 (2.1%)	28 (4.8%)	29 (5.0%)	0.01

	Quintiles of Percent Plant Protein					
	1	2	3	4	5	
Characteristic	**<24%**	**24–29%**	**30–35%**	**36–44%**	**>44%**	
Mean ± SD or n (%)	**(n=587)**	**(n=588)**	**(n=588)**	**(n=587)**	**(n=588)**	**P-value**
Phosphate binders	37 (6.3%)	34 (5.8%)	38 (6.5%)	50 (8.5%)	58 (9.9%)	0.04
Alkali supplements	18 (3.1%)	10 (1.7%)	11 (1.9%)	16 (2.7%)	19 (3.2%)	0.33

[†]Column percent does not total 100 due to participant non-response

GFR = glomerular filtration rate; ACE inhibitors = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker

Table 2

Macro- and micro-nutrient intakes by quintiles of percentage of total protein intake from plant sources

	Quintiles of Percent Plant Protein					
	1	2	3	4	5	
Characteristic	<24%	24–29%	30–35%	36–44%	>44%	
Mean ± SD or n (%)	(n=587)	(n=588)	(n=588)	(n=587)	(n=588)	P-value
Dietary measures from DHQ						
Total energy (kcal)	1909 ± 893	1891 ± 797	1843 ± 804	1837 ± 854	1713 ± 763	<0.001
% kcal from carbohydrate	43 ± 9	48 ± 9	50 ± 9	53 ± 9	58 ± 11	<0.001
% kcal from protein	19 ± 4	16 ± 3	15 ± 3	15 ± 3	13 ± 3	<0.001
% kcal from fat	37 ± 7	36 ± 7	35 ± 7	33 ± 8	30 ± 9	<0.001
% kcal from saturated fat	12 ± 3	11 ± 3	11 ± 3	10 ± 3	8 ± 3	<0.001
Sodium intake (mg)	3127 ± 1519	3054 ± 1416	2930 ± 1359	2892 ± 1469	2507 ± 1255	<0.001
Potassium intake (mg)	2964 ± 1417	3034 ± 1281	2985 ± 1311	3133 ± 1410	3003 ± 1411	0.24
Phosphate intake (mg)	1289 ± 621	1224 ± 534	1142± 495	1129 ± 534	991 ± 439	<0.001
Sodium intake (mg/1000 kcal)	1659 ± 348	1624 ± 320	1605 ± 311	1584 ± 325	1492 ± 408	<0.001
Potassium intake (mg/1000 kcal)	1609 ±441	1650 ± 403	1668 ± 423	1773 ± 482	1817 ± 545	<0.001
Phosphate intake (mg/1000 kcal)	690 ± 158	655 ± 127	632 ± 131	624 ± 130	589 ± 132	<0.001
Dietary biomarkers (unadjusted)						
24 hour urinary sodium (mg)	4107 ± 1942	3863 ± 1887	3703 ± 1772	3638 ± 1581	3422 ± 1662	<0.001
24 hour urinary potassium (mg)	2303 ± 1198	2187 ± 998	2129 ± 966	2251 ± 1052	2164 ± 1004	0.04
24 hour urinary phosphate (mg)	849±370	812 ±364	768 ±347	752 ±318	697 ±331	<0.001
Dietary biomarkers (adjusted for energy intake)						
24 hour urinary sodium (mg)	3774 ± 321	3767 ± 287	3750 ± 289	3748 ± 308	3703 ± 275	<0.001
24 hour urinary potassium (mg)	2218 ±131	2215 ± 117	2208 ± 118	2207 ± 125	2189 ± 112	<0.001
24 hour urinary phosphate (mg)	781 ± 65	780 ± 58	776 ± 59	776 ± 62	767 ± 56	<0.001

Table 3

Unadjusted mean values (± standard deviation) of metabolic parameters by quintiles of percent plant protein

	1 <24% (n=587)	2 24–29% (n=588)	3 30–35% (n=588)	4 36–44% (n=587)	5 >44% (n=588)	p-trend
Serum phosphate (mg/dL)	3.67 ± 0.66	3.73 ± 0.64	3.69 ± 0.65	3.69 ± 0.61	3.69 ± 0.66	0.69
FGF23 (RU/mL) †	138 (92, 239)	144 (95, 247)	143 (94, 224)	139 (95, 232)	134 (88, 215)	0.60
24 urinary phosphate (mg)	849 ± 369.96	812 ± 363.71	768 ± 347.17	752 ± 318.22	697 ± 331.06	<0.001
iPTH (pg/mL) †	53 (34, 87)	54 (33, 90)	51 (33, 83)	53 (34, 84)	52 (35, 84)	0.83
Serum bicarbonate (mEq/L)	24.47 ± 3.17	24.50 ± 3.05	24.50 ± 3.07	24.85 ± 3.22	24.82 ± 3.19	0.07

† Median (interquartile range)

FGF23 = fibroblast growth factor 23; iPTH = intact parathyroid hormone

Table 4

Adjusted* difference (95% confidence interval) in metabolic parameters by quintiles of percent plant protein intake

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Continuous per 10% increase in % plant protein	p-value‡
Serum phosphate (mg/dL)	Ref	0.048 (−0.021, 0.117)	0.021 (−0.051, 0.092)	0.010 (−0.063, 0.083)	0.018 (−0.061, 0.096)	−0.002 (−0.023, 0.020)	0.89
Log FGF23 (RU/mL)	Ref	−0.005 (−0.082, 0.072)	−0.001 (−0.080, 0.078)	−0.027 (−0.108, 0.054)	−0.057 (−0.144, 0.029)	−0.024 (−0.047, −0.000)	0.05
24 urinary phosphate (mg)	Ref	11.12 (−20.95, 43.18)	−10.90 (−43.96, 22.16)	−4.80 (−38.67, 29.07)	−5.45 (−41.64, 30.73)	−4.31 (−14.15, 5.54)	0.39
Log iPTH (pg/mL)	Ref	−0.003 (−0.074, 0.068)	−0.024 (−0.097, 0.050)	−0.005 (−0.079, 0.070)	0.016 (−0.064, 0.096)	0.008 (−0.014, 0.030)	0.46
Serum bicarbonate (mEq/L)	Ref	0.013 (−0.341, 0.368)	0.033 (−0.332, 0.399)	0.230 (−0.144, 0.605)	0.297 (−0.103, 0.698)	0.141 (0.032, 0.251)	0.01

*all models adjusted for age, sex, race, diabetes, body mass index, eGFR, income, smoking, total energy, total protein, 24 hour urinary sodium, use of ACE inhibitors/ARBs, use of diuretics

†p<0.05

‡p-value from continuous model

FGF23 = fibroblast growth factor 23; iPTH = intact parathyroid hormone